CLINICAL TRIAL PROTOCOL

A Randomized, Open-Label, Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Short Title: A Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in R/R DLBCL

Protocol Number:	GCT3013-05
Trial Name:	EPCORE™ DLBCL-1
Sponsor Name:	Genmab*
Collaborator Name:	AbbVie
Regulatory Agency Identifier Number(s)	IND No.: 135659; EU CT No: 2023-504830-23; National Clinical Trial No.: NCT07226752
IMP:	Epcoritamab (GEN3013; DuoBody®-CD3xCD20)
Development Phase:	Phase 3
Protocol Approver**	Name: PPD, MD Title: PPD
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** This protocol was approved via electronic signature on the approval page appended to the document.

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Sponsor information for all other countries, including China	Genmab US, Inc. 777 Scudders Mill Road Plainsboro, NJ 08536 United States of America

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7 CN-2, version 6.0	01 August 2025
Amendment 7 CN-1, version 5.0	09 December 2024
Amendment 7, version 9.0	22 November 2024
Amendment 6, version 8.0	30 April 2024
Amendment 5, version 7.0	11 September 2023
Amendment 4 CN-1, version 4.0	14 July 2023
Amendment 4, version 6.0	09 June 2023
Amendment 3 CN-1, version 3.0	28 November 2022
Amendment 3, version 5.0	05 October 2022
Amendment 2 CN-1, version 2.0	12 May 2022
Amendment 2, version 4.0	13 January 2022
Amendment 1 CN-1, version 1.0	15 June 2021
Amendment 1, version 3.0	19 February 2021
Amendment 1, version 2.0 (not submitted)	19 February 2021
Original Protocol, version 1.0	14 July 2020

Amendment 7_CN-2 (01 August 2025)

Primary Rationale for the Amendment: to revise from dual primary endpoints of OS and PFS to a single primary endpoint of OS per Health Authority feedback.

The amendment changes are summarized below. As applicable, changes included in the Summary of Changes table are incorporated in the Trial Synopsis, as appropriate. Section numbers are as per Amendment 7_CN-2.

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints; Section 4.2 Trial Design Rationale; Section 11.1 Statistical Hypotheses Section 11.2 Sample Size Determination; Section 11.5 Efficacy Analyses; Section 11.5.2.1 Chinese subjects only; Section 11.5.2.2 Comparison of Chinese subjects vs. non-Chinese subjects and Asian subjects vs. Non-Asian subjects; Section 11.8 Biomarker Analyses;	Removed all mentions of PFS as a dual primary endpoint, and revised to OS as the single primary endpoint.	Per discussion with Health Authority (CDE).
Section 11.5.2.2 Comparison of Chinese subjects vs. non-Chinese subjects and Asian subjects vs. Non-Asian subjects	Inserted sentence clarifying that results of the Chinese vs. non-Chinese comparisons will be summarized separately from the clinical study report.	Clarification of statistical reporting plan.
Section 11.8.1 Biomarker Analyses for the Chinese Cohort	Inserted sentence stating that MRD analysis will not be performed for the Chinese cohort.	Clarification of existing process.

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STATEMENT OF COMPLIANCE

GCP Compliance

This trial will be conducted in compliance with the International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), and applicable regulatory requirements.

Confidentiality Statement

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASBMT	American Society for Blood and Marrow Transplantation
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
B-NHL	B-cell non-Hodgkin lymphoma
BR	bendamustine and rituximab
C	Cycle
CAR-T	chimeric antigen receptor T-cell
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTIS	Clinical Trials Information System
CTLS	clinical tumor lysis syndrome
D	Day
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DNA	deoxynucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EC20	concentration at which 20% of the maximum effect is observed
EC50	concentration at which 50% of the maximum effect is observed
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FL	follicular lymphoma
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GemOx	gemcitabine and oxaliplatin
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high-dose therapy
HGBCL	high-grade B-cell lymphoma

HIV	human immunodeficiency virus
IB	investigator's brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
Ig	immunoglobulin
IGRA	interferon gamma release assay
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IPI	International Prognostic Index
IR	indeterminate response
IRB	institutional review board
IRC	independent review committee
IV	intravenous(ly)
LDH	lactate dehydrogenase
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
mAb	monoclonal antibody
MOA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic/pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PSA	prostate specific antigen
PT	prothrombin time
QTcF	corrected QT interval by Fridericia's formula
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab, cisplatin, cytarabine, and dexamethasone
R-GemOx	rituximab, gemcitabine, and oxaliplatin
R-IPI	Revised International Prognostic Index
RMO	Responsible Medical Officer
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SCT	stem cell transplant
SD	stable disease
SLL	small lymphocytic leukemia
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent adverse event
TASQ	Treatment Administration Satisfaction Questionnaire
TFR	tumor flare reaction
TLS	tumor lysis syndrome
TTNT	time to next anti-lymphoma therapy
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization

TRIAL SYNOPSIS

<table>
<tr><td>Title</td><td>A Randomized, Open-label, Phase 3 Trial of Epcoritamab vs Investigator’s Choice Chemotherapy in Relapsed/Refractory Diffuse Large B-cell Lymphoma</td></tr>
<tr><td>Short Title</td><td>A Phase 3 Trial of Epcoritamab vs Investigator’s Choice Chemotherapy in R/R DLBCL</td></tr>
<tr><td>Clinical Phase</td><td>Phase 3</td></tr>
<tr><td>Purpose and Rationale</td><td>Most patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) will be cured with first-line combination immuno-chemotherapy, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). However, 30-40% of patients will relapse or have refractory (R/R) disease. The cure rate for such patients with standard salvage therapy, even when followed by consolidation with high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT), is <10%. Chimeric antigen receptor T-cell (CAR-T) therapies are inaccessible for most patients and yield durable responses in a minority of patients. Polatuzumab vedotin was recently granted accelerated approval by the FDA in third-line in combination with bendamustine-rituximab (BR), as well as conditional approval in the EU in combination with BR for patients with R/R DLBCL who are not candidates for stem cell transplant. However, in addition to being unavailable in many regions, this combination with chemotherapy presents risk of numerous toxicities in these heavily pre-treated patients. Novel therapies for patients with DLBCL failing multiple lines of therapy are needed.
Epcoritamab is a humanized, IgG1-bispecific antibody targeting CD3+ T-cells and CD20+ B-cells; the mechanism of action is engagement of T cells as effector cells to induce killing of CD20-expressing B cells and tumor cells. CD20 is a clinically validated target for treatment of B-cell malignancies. Pre-clinical findings include:
• In vitro, epcoritamab induced potent activation and cytotoxic activity of CD4+ and CD8+ T-cells in the presence of CD20-expressing cells, independent of the T-cell receptor-encoded specificity of the T-cell.
• Ex vivo, epcoritamab induced potent cytotoxicity in tumor cells derived from patients with DLBCL and follicular lymphoma (FL), irrespective of prior treatment with anti-CD20 monoclonal antibodies.
• Epcoritamab induces durable B-cell depletions in the peripheral blood and deeper depletion of B cells in lymphoid organs compared with rituximab.
Preliminary safety and efficacy data indicate the potential for epcoritamab to substantially improve clinical outcomes with a manageable safety profile in subjects with multiple R/R DLBCL (GCT3013-01 trial; NCT03625037).
The primary objective of this trial is to evaluate the efficacy of epcoritamab compared to investigator’s choice of chemotherapy in subjects with R/R DLBCL, who have failed or are ineligible for HDT-ASCT.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
<table>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• Compare the clinical efficacy of epcoritamab to standard of care (SOC) (rituximab, gemcitabine, and oxaliplatin [R-GemOx] or bendamustine and rituximab [BR])</td><td>• Overall survival (OS)</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• Compare other measures of epcoritamab efficacy to SOC</td><td>• Progression-free survival (PFS) determined by Lugano criteria per independent review committee (IRC) assessment and investigator assessment
• Overall response rate (ORR) determined by Lugano criteria per IRC assessment and investigator assessment
• Complete response (CR) rate determined by Lugano criteria per IRC assessment and investigator assessment</td></tr>
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		• Duration of response (DOR) determined by Lugano criteria per IRC assessment and investigator assessment • Time to response (TTR) determined by Lugano criteria per IRC assessment and investigator assessment • Rate and duration of minimal residual disease (MRD) negative status[a] • PFS determined by Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) per IRC assessment • ORR determined by LYRIC per IRC assessment • CR rate determined by LYRIC per IRC assessment • DOR determined by LYRIC per IRC assessment • TTR determined by LYRIC per IRC assessment • Time to next anti-lymphoma therapy (TTNT)
	• Compare safety and tolerability of epcoritamab to SOC	• Incidence and severity of adverse events (AEs) • Incidence and severity of changes in laboratory values • Incidence of dose interruptions and delays
	• Evaluate immunogenicity	• Anti-epcoritamab antibody response
	• To compare patient-reported outcomes (PROs) related to lymphoma symptoms between epcoritamab and SOC	• Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym)
	Other	
	• Evaluate pharmacodynamic markers linked to efficacy and mechanism of action of epcoritamab	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy)[b] •
	• Assess potential biomarkers predictive of clinical response to epcoritamab[a]	• Circulating tumor DNA[a] • DNA mutation status and gene profile[a]
	• To assess impact of lymphoma symptoms and its treatment on health status	• Changes in EQ-5D-3L for health states of interest
	[a] Not applicable for the Chinese Cohort. [b] For the Chinese cohort only pharmacodynamic markers in blood samples are assessed.	
Trial Design	This is an open-label, randomized (1:1), global, Phase 3 trial of epcoritamab versus pre-specified investigator's choice of chemotherapy in subjects with R/R DLBCL who failed or are ineligible for ASCT. Eligible subjects will be randomized to either epcoritamab or investigator's choice of R-GemOx or BR; prior to randomization, the investigator must select and document reason for the intended choice of chemotherapy (which the subject will receive if randomized to the investigator choice); no change in chemotherapy is permitted for an individual subject during the active treatment phase of the trial. Randomization will be stratified by number of prior lines of therapy (1 vs >1), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0-1 vs. 2), prior ASCT (yes vs. no)[a], and prior CAR-T (yes vs. no)[a]. Approximately 480 subjects outside of China (240 in each arm) and a cohort of approximately 72 Chinese subjects (36 in each arm) will be enrolled in the trial with a primary endpoint of OS. The global primary analysis will be performed when approximately 330 OS events (ie, deaths) have accumulated. An independent data monitoring committee (IDMC) will assess safety (global and Chinese cohorts) and efficacy (Chinese cohort only) data during the trial, according to the IDMC Charter.	
Population	Approximately 480 subjects aged 18 years or older with R/R DLBCL who failed a previous ASCT or are ineligible for ASCT at screening will be enrolled. The number of subjects with	

	only 1 prior therapy will be capped at approximately 120 subjects (approximately 25% of total enrollment).
Key Inclusion Criteria	• Must be at least 18 years of age; • Subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that the purpose of the trial and the procedures required for the trial are understood, and indicating that the subject is willing to participate in the trial prior to initiating any other trial-related assessments or procedures; • ECOG PS score of 0-2; • One of the confirmed histologies below with CD20-positivity: o DLBCL, NOS (according to the WHO 2016 classification), including de novo or histologically transformed from follicular lymphoma (FL); o "Double-hit" or "triple-hit" DLBCL (technically classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 translocations), including de novo or histologically transformed from FL ◦ Note: other double-/triple-hit lymphomas and those classified in WHO 2016 as HGBCL, NOS are not eligible; o FL Grade 3B; o T-cell/histiocyte-rich large B-cell lymphoma; • CD20-positivity at representative (previous or current) tumor biopsy based on the pathology report; • Relapsed or refractory disease and previously treated with at least 1 line of systemic antineoplastic therapy including anti-CD20 mAb-containing combination chemotherapy since lymphoma diagnosis (ie, having received R-CHOP or an equivalent regimen that would be considered adequate first-line treatment for DLBCL); o Relapsed disease is defined as disease that has recurred ≥6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy or progressed within 6 months (<6 months) of completion of therapy; • Failed previous HDT-ASCT or not eligible for HDT-ASCT at screening. If ineligible for HDT-ASCT, the decision must have been based on age, performance status, comorbidity, and/or insufficient response to prior treatment; • Has measurable disease: o A fluorodeoxyglucose-positron emission tomography (FDG-PET) scan demonstrating positive lesion(s) compatible with computed tomography (CT)- or magnetic resonance imaging (MRI)-defined anatomical tumor sites; o ≥1 measurable nodal lesion (long axis >1.5 cm and short axis >1.0 cm) and/or ≥1 measurable extranodal lesion (long axis >1.0 cm) on CT scan or MRI; • Absolute neutrophil count ≥1.0 × 10^9/L (growth factor permitted); • Platelet count ≥75 × 10^9/L (or >50 × 10^9/L if bone marrow involvement or splenomegaly); • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level ≤3 times the upper limit of normal (× ULN), unless enzyme elevation is due to a non-hepatic origin or lymphoma involvement of the liver and ALT and AST levels are ≤5 × ULN; • Total bilirubin level ≤2 × ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin or lymphoma involvement of the liver and total bilirubin is ≤5 × ULN; • Estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2 as calculated by Cockcroft-Gault; • Prothrombin time (PT)/international normalized ratio (INR)/activated partial thromboplastin time (aPTT) ≤1.5 × ULN, unless receiving anticoagulation; • Life expectancy >2 months on SOC treatment.
Key Exclusion Criteria	• Primary central nervous system (CNS) tumor or known CNS involvement as assessed by brain MRI at screening or by CT and lumbar puncture (if MRI contraindicated); • Any prior therapy with a bispecific antibody targeting CD3 and CD20 • History of severe allergic or anaphylactic reactions to anti-CD20 antibody therapy; • Contraindication to any component of SOC regimen selected prior to randomization; • Major surgery within 4 weeks prior to randomization; • Chemotherapy and other non-investigational antineoplastic agents (except CD20 mAbs) within 4 weeks or 5 half-lives (whichever is shorter) prior to randomization;

	• Any investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to randomization; • ASCT within 100 days of randomization; • Treatment with CAR-T therapy within 100 days prior to randomization; • Receiving immunosuppressive therapy, including more than the equivalent of 20 mg of prednisolone daily, unless for control of lymphoma or intermittent prophylaxis/treatment of allergic reactions; • Seizure disorder requiring anti-epileptic therapy; • Vaccination with live vaccines within 28 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not allowed; • Clinically significant cardiovascular disease, including: o Myocardial infarction within 1 year prior to randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV) cardiac arrhythmia (CTCAE Version 5.0 Grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities; o Stroke within 6 months prior to randomization; • Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec; • Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results; • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection requiring systemic treatment at time of randomization; • Known history of seropositivity for human immunodeficiency virus (HIV) infection; • Active hepatitis B virus (HBV) (DNA polymerase chain reaction [PCR]-positive) or hepatitis C (RNA PCR-positive infection). Subjects with evidence of prior HBV but who are PCR-negative are permitted in the trial but should receive prophylactic antiviral therapy. Subjects who received treatment for hepatitis C that was intended to eradicate the virus may participate if hepatitis C RNA levels are undetectable. • Has known past or current malignancy other than inclusion diagnosis, except for: o Cervical carcinoma of Stage 1B or less; o Non-invasive basal cell or squamous cell skin carcinoma; o Non-invasive, superficial bladder cancer; o Prostate cancer with a current prostate specific antigen (PSA) level <0.1 ng/mL; o Any curable cancer with a complete response of >2 years duration; • Has known or suspected allergies, hypersensitivity, or intolerance to epcoritamab or its excipients (refer to the Investigator's Brochure for more information); • Contraindication to all uric acid lowering agents; • A woman of childbearing potential with a positive serum or urine pregnancy test at screening. Female subjects must also agree not to breastfeed during the entire trial and until 12 months after the last administration of study drug; • Clinically significant liver disease, including active hepatitis, current alcohol abuse, or cirrhosis; • Active tuberculosis or history of treatment for active tuberculosis within the past 12 months; Note: For subjects with positive interferon gamma release assay (IGRA), active pulmonary tuberculosis must be excluded with clinical evaluation and radiologic imaging. Subjects with positive IGRA and no evidence of active disease may be enrolled after treatment for latent tuberculosis infection (recommendation isoniazid monotherapy for total of 6 months) has been initiated; • Receiving immunostimulatory agent; • Prior allogeneic hematopoietic stem cell transplantation.

Trial Treatment	In the epcoritamab arm, treatment will be administered as subcutaneous (SC) injections using a step-up dosing method: priming dose at 0.16 mg on Cycle 1 Day 1, followed by intermediate dose at 0.8 mg on Cycle 1 Day 8, and then full doses at 48 mg on Cycle 1 Day 15 and Cycle 1 Day 22. Each treatment cycle is 28 days. Full doses (48 mg) will be then given on Days 1, 8, 15, 22 of Cycles 2 and 3, Days 1 and 15 of Cycles 4-9, and Day 1 of cycles thereafter (Cycle 10+), with treatment until progressive disease or unacceptable toxicity. Prophylaxis for cytokine release syndrome (CRS) will consist of corticosteroids. Dosing Schedule: Epcoritamab arm (28-day cycles) • Cycle 1: Epcoritamab 0.16 mg SC on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22 • Cycles 2-3: Epcoritamab 48 mg SC on Days 1, 8, 15, and 22 • Cycles 4-9: Epcoritamab 48 mg SC on Days 1 and 15 • Cycles 10+: Epcoritamab 48 mg SC on Day 1 Investigator's choice will be one of the following: • BR: rituximab 375 mg/m2 IV on Day 1 and bendamustine 90 mg/m2 IV on Days 1 and 2 of each 21-day cycle for up to 6 cycles • R-GemOx: rituximab 375 mg/m2 IV on Days 1 and 15 and gemcitabine 1000 mg/m2 IV followed by oxaliplatin 100 mg/m^2 IV on Days 2 and 16 of each 28-day cycle for up to 4 cycles (8 total doses of R-GemOx). Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.
Statistics	The trial is designed to have 90% power at a 2-sided 5% alpha level to claim significant improvement in OS when the true hazard ratio (HR) is 0.7, and subjects are randomized 1:1 to epcoritamab or control. A Chinese cohort comprising approximately 72 subjects will be analyzed and reported separately. The global primary analysis will be performed when approximately 330 deaths have accumulated.
GCP Compliance	This trial will be conducted in compliance with International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), and applicable regulatory requirements.

[a] Not applicable for the Chinese Cohort.
[b] For the Chinese cohort only pharmacodynamic markers in blood samples are assessed.

1 VISIT ASSESSMENT SCHEDULES

The overall visit assessments schedules are provided in Table 1-1, Table 1-2, Table 1-3, and Table 1-4. Supplemental visit assessment schedules for PK, cytokine (soluble factors), immunophenotyping (enumeration of circulating T, B and NK cells), immunogenicity (ADA), and TLS are provided in Table 1-5, Table 1-6, and Table 1-7.

1.1 Epcoritamab Monotherapy

Table 1-1 Epcoritamab Monotherapy (28-Day Cycles)

Cycle(s) (each cycle is 28 days)	Protocol Section	Screening	QW Dosing[21]				Q2W Dosing[21]				Q4W Dosing[21]	Unsched	End of Tx[20]	Safety Follow-up[2, 20]	Subsequent Post-treatment Follow-up[19, 20]	Survival Follow-up[3, 20]	End of Trial
			Cycles 1-3				Cycles 4-5		Cycles 6-9		Cycles 10 +						
Day		D-21 to -1	D1[1]	D8	D15	D22	D1	D15	D1	D15	D1		asap after last dose	60d after last dose	Q4W until PD or start of new systemic anti-cancer tx	Q60d	
Visit Window														+14d	±14d	±14d	
Informed consent (must be obtained prior to any trial related activity)	13.2.4	X															
Eligibility Criteria	5	X															
Demographics	9.1.1	X															
Medical History[8]	9.1.3	X															
Disease status and subtype	9.1.2	X															
Height	9.3.3	X															
Body Weight	9.3.3	X	X		X		X	X	X		X	X	X	X	X		
Complete physical examination	9.3.1	X											X	X			
Limited physical examination	9.3.1		C1[4]												X		
Lymph node examination	9.3.1	X	X				X		X		X	X	X		X		
Neurological Evaluation (ICANS)[5]	9.3.2	X	X	X	X	X	X	X	X		X	X	X	X			
Vital signs[6]	9.3.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	9.3.5	X	X				X		X		X	X	X				
MRI/CT scan (brain) and lumbar puncture[7]	9.2.2.1	X															
ECOG PS	9.3.6	X	X				X		X		X	X	X	X	X		
Constitutional Symptoms (ie, B Symptoms)	9.3.7	X	X		X		X		X		X	X	X	X	X		
Adverse Events	10	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Previous and concomitant medications	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Cycle(s) (each cycle is 28 days)	Protocol Section	Screening	QW Dosing[21]				Q2W Dosing[21]				Q4W Dosing[21]	Unsched	End of Tx[20]	Safety Follow-up[2, 20]	Subsequent Post-treatment Follow-up[19, 20]	Survival Follow-up[3, 20]	End of Trial
			Cycles 1-3				Cycles 4-5		Cycles 6-9		Cycles 10 +						
Day		D-21 to -1	D1[1]	D8	D15	D22	D1	D15	D1	D15	D1		asap after last dose	60d after last dose	Q4W until PD or start of new systemic anti-cancer tx	Q60d	
Visit Window														+14d	±14d	±14d	
Concomitant procedures	9.1.5		X	X	X	X	X	X	X	X			X	X	X		
Prior cancer therapy and surgery	9.1.6	X															
STUDY TREATMENT ADMINISTRATION																	
Hospitalization[9]	4				C1												
Premedications	6.2		X[10]	X[10]	X[10]	X[10]											
CRS prophylaxis	6.2		X[11]	X[11]	X[11]	X[11]											
Epcoritamab administration	6.3.1		X	X	X	X	X	X	X	X	X						
TUMOR ASSESSMENT(S)																	
PET-CT scan[12] and response assessment	9.2.2.1	X[12]	Every 6 weeks (+7 days) for the first 24 weeks, every 12 weeks (+7 days) through week 48, and then every 24 weeks (±2 weeks) thereafter until disease progression, start of new systemic anti-cancer therapy, withdrawal from trial, or death, whichever comes first[12]														
Bone marrow biopsy and aspirate[13]	9.2.2.2	X[13]		At time of CR or as clinically indicated[13]													
LOCAL LABORATORY ASSESSMENTS																	
Hematology	9.4	X	X		X		X	X	X		X	X	X	X	X		
Biochemistry	9.4	X	X		X		X	X	X		X	X	X	X	X		
Coagulation	9.4	X	X		X		X	X	X		X	X	X	X	X		
Immunoglobulins (IgA, IgG, IgM)	9.4	X	X				X	X	X		X	X	X	X	X		
Urinalysis	9.4	X	X				X		X		X	X	X	X			
Beta2-microglobulin	9.4	X															
Tuberculosis test[25]	9.4	X															
Pregnancy Test (serum)[14]	9.4	X															
Pregnancy Test (urine or serum)[14]	9.4		X				X		X		X	X	X	X			
HBV and HCV serology	9.4	X											X[15]	X[15]			
CMV and EBV PCR	9.4	X[16]	X[16]						X[16]		X[16]		X[16]	X[16]			
HIV serology[26]	9.4	X															
TLS monitoring	9.4		See Table 1-7														

Cycle(s) (each cycle is 28 days)	Protocol Section	Screening	QW Dosing[21]				Q2W Dosing[21]				Q4W Dosing[21]	Unsched	End of Tx[20]	Safety Follow-up[2, 20]	Subsequent Post-treatment Follow-up[19, 20]	Survival Follow-up[3, 20]	End of Trial
			Cycles 1-3				Cycles 4-5		Cycles 6-9		Cycles 10 +						
Day		D-21 to -1	D1[1]	D8	D15	D22	D1	D15	D1	D15	D1		asap after last dose	60d after last dose	Q4W until PD or start of new systemic anti-cancer tx	Q60d	
Visit Window														+14d	±14d	±14d	
CENTRAL LABORATORY ASSESSMENTS																	
Samples for PK, ADA, pharmacodynamics, and biomarkers	9.5, 9.6, and 9.7		See Table 1-5 for assessments and time points														
PATIENT REPORTED OUTCOMES[17]																	
FACT-Lym	9.8.1		X				X		X		X		X	X	X[18]		
EQ-5D-3L	9.8.2		X				X		X		X		X	X	X[18]		
TASQ IV	9.8.3	X															
TASQ SC	9.8.3		D1 of C4, C8, C12, C16, C20, and C24														
END OF TREATMENT																	
New anti-cancer therapy																X	
Survival Status	8.6, 8.7															X	
End of trial information																	X

ADA=anti-drug antibody; asap=as soon as possible; ASTCT=American Society for Transplantation and Cellular Therapy; BCG=Bacillus Calmette–Guérin; C=cycle; CMV=cytomegalovirus; CR=complete response; CRS=cytokine release syndrome; CT=computerized tomography; D/d=day; d=days; EBV=Epstein-Barr virus; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FACT-Lym=Functional Assessment of Cancer Therapy – Lymphoma; ICANS=immune effector cell-associated neurotoxicity syndrome; HBV=hepatitis B; HCV=hepatitis C; Ig=immunoglobulin; IV=intravenous; M=months; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PET-CT=positron emission tomography-computed tomography; PK=pharmacokinetic; QW=every week; Q2W=every other week; Q4W=every 4 weeks; Q60d=every 60 days; SC=subcutaneous; TASQ=Treatment Administration Satisfaction Questionnaire; Tx=treatment; Unsched=unscheduled; W=week.

1. Baseline is defined as the available data from the latest recorded measurement made before the first epcoritamab administration.
2. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 60 days (+14 days) after the last dose of epcoritamab. If the subject initiates new anti-cancer therapy within 60 days of the last dose of epcoritamab, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
3. Survival status, second primary malignancy, and new anti-cancer treatment will be collected every 60 days (±14 days) counted from the safety follow-up visit (for subjects not moving into post-treatment follow-up) and from the last post-treatment follow-up visit (for subjects in post-treatment follow-up after the safety follow-up visit). Survival follow-up contact may be performed as a telephone call, email, or on-site visit. Refer to Sections 8.2 and 8.6 for continued collection of survival data for randomized subjects who withdraw from trial participation.
4. Limited physical exam on Day 1 of Cycle 1, and then as clinically indicated.
5. ICANS evaluation (based on ASTCT ICANS Consensus Grading per (Lee et al., 2019)) must also be performed in the presence of CRS-type symptoms or any neurological signs/symptoms.
6. Vital sign assessment must be conducted before dosing and 1 hr (±30 min) following each dose.
7. MRI/CT scan (brain) is required at screening and may be taken within 30 days before C1D1. A lumbar puncture should be obtained if clinically indicated (eg, suspected CNS involvement) and may be taken within 30 days before C1D1.

8. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
9. Hospitalized for at least 24 hours after the third administration of epcoritamab in Cycle 1. Additional or longer hospitalization should be per the investigator's discretion.
10. Premedication (antipyretic and antihistamine) should be administered 30 min to 2 hours before administration of Cycle 1 epcoritamab doses; premedications are optional for Cycle 2 and onward (see Table 6-1).
11. CRS prophylaxis consists of dexamethasone 15 mg (or alternative steroid equivalent) daily for Cycle 1 Days 1-4, 8-11, 15-18, and 22-25; for Cycle 2 onward, 4 consecutive days of corticosteroid CRS prophylaxis is required if ≥ grade 2 CRS occurs following the previous dose of epcoritamab, and should be continued until one full dose of epcoritamab is administered without subsequent occurrence of ≥ grade 2 CRS (see Table 6-1). The dose of corticosteroid used for CRS prophylaxis may be decreased to a minimum of 12 mg dexamethasone (or alternative steroid equivalent) at the discretion of the investigator if due to concern of tolerability. On epcoritamab dosing days, corticosteroid should be given 30 min to 2 hours prior to epcoritamab injection.
12. Combined PET-CT scan should be performed (or separate PET and CT/MRI, when combined PET-CT scan not available) and may be taken within 30 days before Day 1 of Cycle 1. All assessments will be determined from the first dose date and will follow the counting of calendar days and not the dosing cycles. Response assessments will be performed until disease progression (Section 8.3).
13. At screening, a bone marrow biopsy is required; a bone marrow biopsy obtained as routine standard of care may be used instead if taken up to 42 days before first dose of trial treatment. For subjects with bone marrow involvement at screening, a bone marrow biopsy and aspirate are required at the time of CR (aspirate is optional).
14. Pregnancy testing is only required for female subjects of childbearing potential (Appendix 10). For testing required on a dosing day, results must be available before dosing.
15. Subjects with positive serology or PCR at baseline or during the trial: PCR for HBV-DNA and/or PCR for HCV RNA to be performed.
16. CMV and EBV testing by PCR to be collected and submitted during screening. (Note: Test results may come after enrollment.) CMV and EBV PCR should be repeated every third cycle (ie, C3D1, C6D1, C9D1, etc.), at end of treatment, and at the safety follow-up visit.
17. It is strongly recommended that subjects complete PRO questionnaires prior to any other assessments and prior to seeing the investigator. PRO questionnaires must be completed before administration of trial drug.
18. FACT-Lym and EQ-5D-3L questionnaires to be completed during post-treatment follow-up until disease progression or start of a new systemic anti-cancer therapy.
19. Subjects discontinuing from treatment for other reasons than disease progression or initiation of new systemic anti-cancer therapy will move into subsequent post-treatment follow-up. First post-treatment follow-up visit should occur 4 weeks (±14 days) after the safety follow-up visit. Post-treatment follow-up visits should be performed every 4 weeks (±14 days) until progressive disease or start of new systemic anti-cancer therapy.
20. Two visits may be performed concurrently if the timing occurs within the designated window for each visit.
21. Every effort should be made to keep subjects on the planned dosing schedule. There must be minimum of 7 days between epcoritamab administrations. If the interval between epcoritamab doses exceeds certain length, repriming is required. Refer to Section 7.1 for details. If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).
22. Footnote removed per Amendment 1_CN-1.
23. Footnote removed per Amendment 1_CN-1.
24. Footnote removed per Amendment 1_CN-1.
25. Tuberculosis testing must be performed within 4 weeks prior to C1D1. Interferon gamma release assay (IGRA) is preferred. For subjects where another tuberculosis test (other than IGRA) has been performed: IGRA testing is required for subjects with documented BCG vaccine and a positive tuberculosis test result.
26. HIV testing is required at screening only if required per local health authorities or institutional standards.

Table 1-2 Epcoritamab Repriming Cycle[1]

	Day 1	Day 8	Day 15	Day 22
Body Weight	X		X	
Complete physical examination	X			
Lymph node examination	X			
Neurological Evaluation (ICANS)[2]	X	X	X	X
Vital signs[3]	X	X	X	X
12-Lead ECG	X			
ECOG Performance Status	X			
Constitutional Symptoms (ie, B Symptoms)	X		X	
Adverse Events	X	X	X	X
Previous and concomitant medications	X	X	X	X
Concomitant procedures	X	X	X	X
STUDY TREATMENT ADMINISTRATION				
Hospitalization[4]			X	
Premedications[5]	X	X	X	X
CRS prophylaxis[6]	X	X	X	X
Epcoritamab administration[8]	X	X	X	X
LOCAL LABORATORY ASSESSMENTS				
Hematology	X		X	
Biochemistry	X		X	
Coagulation	X		X	
Immunoglobulins (IgA, IgG, IgM)	X			
Urinalysis	X			
Pregnancy Test (urine or serum)[7]	X			
TLS monitoring	See Table 1-7			
CENTRAL LABORATORY ASSESSMENTS				
PK	X	X	X	X
ADA	X		X	
Immunophenotyping (TBNK by flow cytometry)	X			

ADA=anti-drug antibodies; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICANS=immune effector cell-associated neurotoxicity syndrome; Ig=immunoglobulin; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic; TLS=tumor lysis syndrome.

1. Once the full repriming cycle is completed, the subject should resume treatment with Day 1 of the next planned cycle (subsequent to the cycle during which the dosing was delayed); see Section 7.1.1.
2. ICANS evaluation (based on ASTCT ICANS Consensus Grading per (Lee et al., 2019)) must also be performed in the presence of CRS-type symptoms or any neurological signs/symptoms.
3. Vital sign assessment must be conducted before dosing and 1 hr (±30 min) following each dose.
4. Hospitalized for at least 24 hours after the third administration of epcoritamab in a repriming cycle. Additional or longer hospitalization should be per the investigator's discretion.
5. Premedication should be administered 30 min to 2 hours before administration of epcoritamab.
6. CRS prophylaxis consists of dexamethasone 15 mg (or alternative steroid equivalent) daily for Days 1-4, 8-11, 15-18, and 22-25 of a repriming cycle. The dose of corticosteroid used for CRS prophylaxis may be decreased to a minimum of 12 mg dexamethasone (or alternative steroid equivalent) at the discretion of the investigator if due to concern of tolerability. On epcoritamab dosing days, corticosteroid should be given 30 min to 2 hours prior to epcoritamab injection. See also in Section 6.2.
7. Pregnancy testing is only required for female subjects of childbearing potential (refer to Appendix 10). For testing required on a dosing day, results must be available before dosing.
8. Repriming Day 1=priming dose of 0.16 mg epcoritamab; Repriming Day 8=intermediate dose of 0.8 mg epcoritamab; Repriming Day 15=full dose of 48 mg epcoritamab; Repriming Day 22=full dose of 48 mg epcoritamab.

1.2 Investigator's Choice Immuno-chemotherapy: Bendamustine + Rituximab

Table 1-3 Bendamustine + Rituximab (21-Day Cycles)

Cycle(s) (each cycle is 21 days)	Protocol Section	Screening	Q3W Dosing[16] Cycles 1-6		End of Tx[21]	Unsched	Safety Follow-up Visit[2, 21]	Subsequent Post-treatment FU Visits[17, 21]	Survival Follow-up[3, 21]	End of Trial
Day		D-21 to -1	D1[1]	D2	asap after last dose		60d after last dose	Q4W until PD or start of new systemic anti-cancer tx	Q60d	
Visit Window							+14d	±14d	±14d	
Informed consent (must be obtained prior to any trial related activity)	13.2.4	X								
Eligibility criteria	5	X								
Demographics	9.1.1	X								
Medical history[8]	9.1.3	X								
Disease status and subtype	9.1.2	X								
Height	9.3.3	X								
Body weight	9.3.3	X	X		X	X	X	X		
Complete physical examination	9.3.1	X			X		X			
Limited physical examination	9.3.1		C1[4]					X		
Lymph node examination	9.3.1	X	X		X			X		
Neurological Evaluation (ICANS)[5]	9.3.2	X	X		X	X	X			
Vital signs[6]	9.3.4	X	X	X	X	X	X	X		
12-lead ECG	9.3.5	X	X		X	X				
MRI/CT scan (brain) and lumbar puncture[7]	9.2.2.1	X								
ECOG PS	9.3.6	X	X		X	X	X	X		
Constitutional symptoms (B symptoms)	9.3.7	X	X		X	X	X	X		
Adverse events	10	X[8]	X	X	X	X	X	X		
Previous and concomitant medications	9.1.4	X	X		X	X	X	X		
Concomitant procedures	9.1.5	X	X		X	X	X	X		
TRIAL TREATMENT ADMINISTRATION										
Premedications and prophylaxis	6.2.2		Refer to Section 6.2.2							
Rituximab	6.5		X							
Bendamustine	6.6		X	X						

Cycle(s) (each cycle is 21 days)	Protocol Section	Screening	Q3W Dosing[16] Cycles 1-6		End of Tx[21]	Unsched	Safety Follow-up Visit[2, 21]	Subsequent Post-treatment FU Visits[17, 21]	Survival Follow-up[3, 21]	End of Trial
Day		D-21 to -1	D1[1]	D2	asap after last dose		60d after last dose	Q4W until PD or start of new systemic anti-cancer tx	Q60d	
Visit Window							+14d	±14d	±14d	
TUMOR ASSESSMENTS										
PET-CT scan[9] and response assessment	9.2.2.1	X	Every 6 weeks (+7 days) for the first 24 weeks, every 12 weeks (+7 days) through week 48, and then every 24 weeks (±2 weeks) thereafter until disease progression, start of new systemic anti-cancer therapy, withdrawal from trial, or death, whichever comes first[9]							
Bone marrow biopsy and aspirate[10]	9.2.2.2	X	Bone marrow exam may be needed to confirm CR (see Section 9.2.2.2)[10]							
LOCAL LABORATORY ASSESSMENTS										
Hematology	9.4	X	X		X	X	X	X		
Biochemistry	9.4	X	X		X	X	X	X		
Coagulation	9.4	X	X		X	X	X	X		
Immunoglobulins (IgA, IgG, IgM)	9.4	X	X		X		X	X		
Urinalysis	9.4	X	X		X	X	X			
Beta2-microglobulin	9.4	X								
Tuberculosis test[23]	9.4	X								
Pregnancy test (serum)[11]	9.4	X								
Pregnancy test (urine or serum)[11]	9.4		X		X	X	X[12]			
HBV and HCV serology	9.4	X			X[13]		X[13]			
CMV and EBV PCR	9.4	X[14]	X[14]		X[14]		X[14]			
HIV serology[24]	9.4	X								
TLS monitoring	9.4		Table 1-7							
CENTRAL LABORATORY										
Samples for pharmacodynamics and biomarkers	9.7		See Table 1-6 for assessments and time points							
PATIENT REPORTED OUTCOMES[15]										
FACT-Lym	9.8.1		X		X		X	X[22]		
EQ-5D-3L	9.8.2		X		X		X	X[22]		
TASQ IV	9.8.3	X								
END OF TREATMENT										
New anti-cancer therapy and survival status	8.6, 8.7								X	
End of trial information										X

asap=as soon as possible; ASTCT=American Society for Transplantation and Cellular Therapy; BCG=Bacillus Calmette–Guérin; C=cycle; CMV=cytomegalovirus; CR=complete response; CRS=cytokine release syndrome; CT=computerized tomography; D/d=day; d=days; EBV=Epstein-Barr virus; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FACT-Lym=Functional Assessment of Cancer Therapy – Lymphoma; FU=follow-up; HBV=hepatitis B; HCV=hepatitis C; ICANS=immune effector cell-associated neurotoxicity syndrome; Ig=immunoglobulin; IGRA=interferon gamma release assay; IV=intravenous; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PD=progressive disease; PET-CT=positron emission tomography-computed tomography; PK=pharmacokinetic; Q3W=every 3 weeks; Q4W=every 4 weeks; Q60d=every 60 days; TASQ=Treatment Administration Satisfaction Questionnaire; TLS=tumor lysis syndrome; Tx=treatment; Unsched=unscheduled; W/Wk=week.

1. Baseline is defined as the available data from the latest documented measurement made before the first administration of trial treatment.
2. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 60 days (+14 days) after the last dose of trial treatment. If the subject initiates new anti-cancer therapy within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
3. Survival status, second primary malignancy, and new anti-cancer treatment will be collected every 60 days (± 14 days) counted from the safety follow-up visit (for subjects not moving into post-treatment follow-up) and from the last post-treatment follow-up visit (for subjects in post-treatment follow-up after the safety follow-up visit). Survival follow-up contact may be performed as a telephone call, email, or on-site visit. Refer to Sections 8.2 and 8.6 for continued collection of survival data for randomized subjects who withdraw from trial participation.
4. Limited physical exam on Day 1 of Cycle 1, and then as clinically indicated.
5. ICANS evaluation (based on ASTCT ICANS Consensus Grading per (Lee et al., 2019)) must also be performed in the presence of CRS-type symptoms or any neurological signs or symptoms.
6. Vital sign assessment must be conducted before dosing and 1 hr (±30 min) following administration.
7. MRI/CT scan (brain) is required at screening and may be taken within 30 days before C1D1. A lumbar puncture should be obtained if clinically indicated (eg, suspected CNS involvement) and may be taken within 30 days before C1D1.
8. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
9. Combined PET-CT scan should be performed (or separate PET and CT/MRI, when combined PET-CT scan not available) and may be taken within 30 days before Day 1 of Cycle 1. All assessments will be determined from the first dose date and will follow the counting of calendar days and not the dosing cycles. Response assessments will be performed until disease progression (Section 8.3).
10. At screening, a bone marrow biopsy is required; a bone marrow biopsy obtained as routine standard of care may be used instead if taken up to 42 days before first dose of trial treatment. For subjects with bone marrow involvement at screening, a bone marrow biopsy and aspirate are required at the time of CR (aspirate is optional).
11. Pregnancy testing is only required for female subjects of childbearing potential (refer to Appendix 10). For testing required on a dosing day, results must be available before dosing.
12. Until at least 60 days after the last dose of rituximab.
13. Subjects with positive serology or PCR at baseline or during the trial: PCR for HBV-DNA and/or PCR for HCV RNA to be performed.
14. CMV and EBV testing by PCR to be collected and submitted during screening. (Note: Test results may come after enrollment). CMV and EMV PCR should be repeated every third cycle (ie, C3D1, C6D1), at end of treatment, and at the safety follow-up visit.
15. It is strongly recommended that subjects complete PRO questionnaires prior to any other assessments and prior to seeing the investigator. PRO questionnaires must be completed before administration of trial drug.
16. Every effort should be made to keep subjects on the planned dosing schedule. If a bendamustine dose is delayed, then next bendamustine dose should be calculated from the previous dose of bendamustine in order to maintain the regular cycle interval of minimum 21 days (Section 6.5 and Section 6.6). If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).
17. Subjects discontinuing from treatment for other reasons than disease progression or initiation of new systemic anti-cancer therapy will move into subsequent post-treatment follow-up. First post-treatment follow-up visit should occur 4 weeks (±14 days) after the safety follow-up visit. Post-treatment follow-up visits should be performed every

4 weeks (±14 days) until progressive disease or start of new systemic anti-cancer therapy.

18. Footnote removed per Amendment 1_CN-1.
19. Footnote removed per Amendment 1_CN-1.
20. Footnote removed per Amendment 1_CN-1.
21. Two visits may be performed concurrently if the timing occurs within the designated window for each visit.
22. FACT-Lym and EQ-5D-3L questionnaires to be completed during Post-treatment Follow-up until disease progression or start of a new systemic anti-cancer therapy.
23. Tuberculosis testing must be performed within 4 weeks prior to C1D1. Interferon gamma release assay (IGRA) is preferred. For subjects where another tuberculosis test (other than IGRA) has been performed: IGRA testing is required for subjects with documented BCG vaccine and a positive tuberculosis test result.
24. HIV testing is required at screening only if required per local health authorities or institutional standards.

1.3 Investigator's Choice: R-GemOx

Table 1-4 Rituximab + Gemcitabine and Oxaliplatin (28-Day Cycles)

			Q2W Dosing[20]									
Cycle(s) (each cycle is 28 days)	**Protocol Section**	**Screening**	**Cycles 1-4**				**End of Tx[22]**	**Unsched**	**Safety Follow-up[2, 22]**	**Subsequent Post-treatment FU Visits[16, 22]**	**Survival Follow-up[3, 22]**	**End of Trial**
Day		**D-21 to -1**	**D1[1]**	**D2**	**D15**	**D16**	**asap after last dose**		**60d after last dose**	**Q4W until PD or start of new systemic anti-cancer tx**	**Q60d**	
Visit Window									**+14d**	**±14d**	**±14d**	
Informed consent (must be obtained prior to any trial related activity)	13.2.4	X										
Eligibility criteria	5	X										
Demographics	9.1.1	X										
Medical history	9.1.3	X										
Disease status and subtype	9.1.2	X										
Height	9.3.3	X										
Body weight	9.3.3	X	X		X		X	X	X	X		
Complete physical examination	9.3.1	X					X		X			
Limited physical examination	9.3.1		C1[4]							X		
Lymph node examination	9.3.1	X	X				X			X		
Neurological Evaluation (ICANS) [5]	9.3.2	X	X		X		X	X	X			
Vital signs[6]	9.3.4	X	X		X		X	X	X	X		
12-lead ECG	9.3.5	X	X				X	X				
MRI/CT scan (brain) and lumbar puncture[7]	9.2.2.1	X										
ECOG PS	9.3.6	X	X				X	X	X	X		
Constitutional symptoms (B symptoms)	9.3.7	X	X				X	X	X	X		
Adverse events	10	X[8]	X	X[25]	X	X[25]	X	X	X	X		
Previous and concomitant medications	9.1.4	X	X		X		X	X	X	X		
Concomitant procedures	9.1.5	X	X		X		X	X	X	X		
TRIAL TREATMENT ADMINISTRATION												
Premedications and prophylaxis	6.2.2		Refer to Section 6.2.2									
Gemcitabine	6.7			X[21]		X						
Oxaliplatin	6.7			X[21]		X						
Rituximab	6.5		X		X							

			Q2W Dosing[20]									
Cycle(s) (each cycle is 28 days)	**Protocol Section**	**Screening**	**Cycles 1-4**				**End of Tx[22]**	**Unsched**	**Safety Follow-up[2, 22]**	**Subsequent Post-treatment FU Visits[16, 22]**	**Survival Follow-up[3, 22]**	**End of Trial**
Day		**D-21 to -1**	**D1[1]**	**D2**	**D15**	**D16**	**asap after last dose**		**60d after last dose**	**Q4W until PD or start of new systemic anti-cancer tx**	**Q60d**	
Visit Window									**+14d**	**±14d**	**±14d**	
TUMOR ASSESSMENT												
FDG-PET/CT scan[9] and response assessment	9.2.2.1	X	Every 6 weeks (+7 days) for the first 24 weeks, every 12 weeks (+7 days) through week 48, and then every 24 weeks (±2 weeks) thereafter until disease progression, start of new systemic anti-cancer therapy, withdrawal from trial, or death, whichever comes first[9]									
Bone marrow biopsy and aspirate[10]	9.2.2.2	X	Bone marrow exam may be needed to confirm CR (see Section 9.2.2.2)[10]									
LOCAL LABORATORY ASSESSMENTS												
Hematology	9.4	X	X		X		X	X	X	X		
Biochemistry	9.4	X	X		X		X	X	X	X		
Coagulation	9.4	X	X		X		X	X	X	X		
Immunoglobulins (IgA, IgG, IgM)	9.4	X	X				X		X	X		
Beta2-microglobulin	9.4	X										
Tuberculosis test[24]	9.4	X										
Urinalysis	9.4	X	X				X	X	X			
Pregnancy test (serum)[14]	9.4	X										
Pregnancy test (urine or serum)[14]	9.4		X				X	X	X			
HBV and HCV serology	9.4	X					X[12]		X[12]			
HIV serology[26]	9.4	X										
CMV and EBV PCR	9.4	X[13]	X[13]				X[13]		X[13]			
TLS monitoring	9.4		Table 1-7									
CENTRAL LABORATORY ASSESSMENTS												
Samples for biomarker/ pharmacodynamics	9.7		See Table 1-5 for assessments and time points									
PATIENT REPORTED OUTCOMES[15]												
FACT-Lym	9.8.1		X				X		X	X[23]		
EQ-5D-3L	9.8.2		X				X		X	X[23]		
TASQ IV	9.8.3	X										
END OF TREATMENT												
New anti-cancer therapy and survival status	8.6, 8.7										X	
End of trial information												X

asap=as soon as possible; ASTCT=American Society for Transplantation and Cellular Therapy; BCG=Bacillus Calmette–Guérin; C=cycle; CMV=cytomegalovirus; CR=complete response; CRS=cytokine release syndrome; CT=computerized tomography; D/d=day; d=days; EBV=Epstein-Barr virus; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FACT-Lym=Functional Assessment of Cancer Therapy – Lymphoma; FU=follow-up; HBV=hepatitis B; HCV=hepatitis C; ICANS=immune effector cell-associated neurotoxicity syndrome; Ig=immunoglobulin; IGRA=interferon gamma release assay; IV=intravenous; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PD=progressive disease; PET-CT=positron emission tomography-computed tomography; PK=pharmacokinetic; Q2W=every other week; Q4W=every 4 weeks; Q60d=every 60 days; TASQ=Treatment Administration Satisfaction Questionnaire; TLS=tumor lysis syndrome; Tx=treatment; Unsched=unscheduled; W/Wk=week.

1. Baseline is defined as the available data from the latest documented measurement made before the first administration of trial treatment.
2. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 60 days (+14 days) after the last dose of trial treatment. If the subject initiates new anti-cancer therapy within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
3. Survival status, second primary malignancy, and new anti-cancer treatment will be collected every 60 days (± 14 days) counted from the safety follow-up visit (for subjects not moving into post-treatment follow-up) and from the last post-treatment follow-up visit (for subjects in post-treatment follow-up after the safety follow-up visit). Survival follow-up contact may be performed as a telephone call, email, or on-site visit. Refer to Sections 8.2 and 8.6 for continued collection of survival data for randomized subjects who withdraw from trial participation.
4. Limited physical exam on Day 1 of Cycle 1, and then as clinically indicated.
5. ICANS evaluation (based on ASTCT ICANS Consensus Grading per (Lee et al., 2019)) must also be performed in the presence of CRS-type symptoms or any neurological signs or symptoms.
6. Vital sign assessment must be conducted before dosing and 1 hr (±30 min) following completion of the dose.
7. MRI/CT scan (brain) is required at screening and may be taken within 30 days before C1D1. A lumbar puncture should be obtained if clinically indicated (eg, suspected CNS involvement) and may be taken within 30 days before C1D1.
8. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
9. Combined PET-CT scan should be performed (or separate PET and CT/MRI, when combined PET-CT scan not available) and may be taken within 30 days before Day 1 of Cycle 1. All assessments will be determined from the first dose date and will follow the counting of calendar days and not the dosing cycles. Response assessments will be performed until disease progression (Section 8.3).
10. At screening, a bone marrow biopsy is required; a bone marrow biopsy obtained as routine standard of care may be used instead if taken up to 42 days before first dose of trial treatment. For subjects with bone marrow involvement at screening, a bone marrow biopsy and aspirate are required at the time of CR (aspirate is optional).
11. Until at least 60 days after the last dose of rituximab.
12. Subjects with positive serology or PCR at baseline or during the trial: PCR for HBV-DNA and/or PCR for HCV RNA to be performed.
13. CMV and EBV testing by PCR to be collected and submitted during screening. (Note: Test results may come after enrollment). CMV and EMV PCR should be repeated at C3D1, end of treatment, and at the safety follow-up visit.
14. Pregnancy testing is only required for female subjects of childbearing potential (refer to Appendix 10). For testing required on a dosing day, results must be available before dosing.
15. It is strongly recommended that subjects complete PRO questionnaires prior to any other assessments and prior to seeing the investigator. PRO questionnaires must be completed before administration of trial drug
16. Subjects discontinuing from treatment for other reasons than disease progression or initiation of new systemic anti-cancer therapy will move into subsequent post-treatment follow-up. First post-treatment follow-up visit should occur 4 weeks (±14 days) after the safety follow-up visit. Post-treatment follow-up visits should be performed every 4 weeks (±14 days) until progressive disease or start of new systemic anti-cancer therapy.
17. Footnote removed per Amendment 1_CN-1.
18. Footnote removed per Amendment 1_CN-1.
19. Footnote removed per Amendment 1_CN-1.

20. Every effort should be made to keep subjects on the planned dosing schedule. If a GemOx dose is delayed, then next GemOx dose should be calculated from the previous dose of GemOx in order to maintain the regular chemotherapy interval of minimum 14 days (Section 6.5 and Section 6.7). If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).
21. Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.
22. Two visits may be performed concurrently if the timing occurs within the designated window for each visit.
23. FACT-Lym and EQ-5D-3L questionnaires to be completed during Post-treatment Follow-up until disease progression or start of a new systemic anti-cancer therapy.
24. Tuberculosis testing must be performed within 4 weeks prior to C1D1. Interferon gamma release assay (IGRA) is preferred. For subjects where another tuberculosis test (other than IGRA) has been performed: IGRA testing is required for subjects with documented BCG vaccine and a positive tuberculosis test result.
25. Adverse event collection if trial treatment is administered.
26. HIV testing is required at screening only if required per local health authorities or institutional standards.

1.4 Pharmacokinetics, Immunogenicity, Biomarker/Pharmacodynamics, and Tumor Lysis Syndrome

Table 1-5 Pharmacokinetics, Biomarker/Pharmacodynamics, Immunogenicity (ADA) – Epcoritamab and R-GemOx Arms

Cycle (28-day cycles)	Visit	Sampling time	Epcoritamab Only		Epcoritamab and R-GemOx	
			PK	ADA	Cytokine (Soluble factors)	Immunopheno-typing (TBNK by Flow Cytometry)
Cycle 1	Day 1	Predose	X	X	X	X
	Day 8	Predose	X			
	Day 15	Predose	X	X		
	Day 22	Predose	X			
Cycle 2	Day 1	Predose	X	X		
	Day 8	Predose	X			
	Day 15	Predose	X		X	X
	Day 22	Predose	X	X		
Cycle 3	Day 1	Predose	X	X		
	Day 8	Predose	X			
	Day 15	Predose	X			
	Day 22	Predose	X			
Cycles 4-9	Day 1	Predose	X	X		X[2]
	Day 15	Predose	X			
Cycle 10+	Day 1	Predose	X	X		
Unsched			X[1]		X	X
End of Tx	asap after last dose		X	X		X

ADA=anti-drug antibodies; asap=as soon as possible; PK=pharmacokinetic; R-GemOx=rituximab, gemcitabine, and oxaliplatin; Tx=treatment; Unsched=unscheduled.

1. Unscheduled PK samples will be taken (when feasible) at the time of development of any of the following events, or at the earliest possible convenience thereafter:
   - Dose interruption
     - At time of interruption, collect the unscheduled PK sample and clearly record the reason for this collection (ie, due to interruption)
     - At treatment restart
   - Disease response (ie, first evaluation of complete response or partial response)
   - Disease progression
2. Immunophenotyping sample collected on C4D1 only.

Table 1-6 Biomarker/Pharmacodynamics for BR Arm

Cycle (21-day cycles)	Visit	Sampling time	BR Arm	
			Cytokine (Soluble factors)	Immunopheno-typing (TBNK by Flow Cytometry)
Cycle 1	Day 1	Predose	X	X
Cycle 3	Day 1	Predose	X	X
Cycles 4-6	Day 1	Predose		X[1]
Unsched			X	X
End of Tx	asap after last dose			X

asap=as soon as possible; BR=bendamustine+rituximab; Tx=treatment; Unsched=unscheduled.

1. Immunophenotyping sample collected on C5D1 only.

Table 1-7 Tumor Lysis Sampling Schedule[1]

Treatment Administration	Sampling times
Cycle 1 Day 1 (all subjects)	24, 48, 72, and 96 hours post-dose (±6 hours at each time point)
Subsequent doses (high-risk subjects)[2]	24, 48, 72, and 96 hours post-dose (±6 hours at each time point)

1. Laboratory tests for TLS will be performed locally. Tumor lysis sample includes uric acid, potassium, inorganic phosphorus (phosphate), calcium, and creatinine. Refer to Appendix 8 for further details about TLS monitoring, classification, and management of TLS.
2. Refer to Section 7.2.3 for further details on risk assessment for TLS.

2 INTRODUCTION

2.1 Trial Rationale

Most patients with newly diagnosed DLBCL will be cured with first-line combination immuno-chemotherapy, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) (Coiffier et al., 2010; Sehn, 2007). However, 30% to 40% of patients will have R/R disease. The cure rate for such patients with standard salvage therapy, even when followed by consolidation with high-dose therapy-autologous stem cell transplant (HDT-ASCT), is <10%. For patients who have failed, or are ineligible for stem cell transplant (SCT), options are limited, and most patients will receive palliative chemotherapy with a regimen such as BR or GemOx. CAR-T therapies are inaccessible for most patients and yield durable responses in only a minority of patients. Polatuzumab vedotin was recently granted accelerated approval by the FDA in third-line in combination with BR, as well as conditional approval in the EU in combination with BR for patients with R/R DLBCL who are not candidates for SCT. However, in addition to being unavailable in many regions, this combination with chemotherapy presents risk of numerous toxicities in these heavily pre-treated patients. Novel therapies for patients with DLBCL failing multiple lines of therapy are needed.

Bispecific T-cell engaging antibodies represent a promising new class of disease-targeting agents shown to promote the activation of a subject's own immune system to attack and kill cancer cells. Epcoritamab (GEN3013; DuoBody®-CD3xCD20) is a bispecific antibody that binds to both CD3 expressed on T-cells and CD20 expressed on tumor and B cells and induces T-cell mediated killing of the CD20+ cells.

Epcoritamab is a humanized, IgG1 bispecific antibody targeting CD3+ T-cells and CD20+ B cells; the mechanism of action is engagement of T cells as effector cells to induce killing of CD20-expressing B cells and tumor cells. CD20 is a clinically validated target for treatment of B-cell malignancies. Pre-clinical findings include:

- In vitro, epcoritamab induced potent activation and cytotoxic activity of CD4+ and CD8+ T cells in the presence of CD20-expressing cells, independent of the T-cell receptor-encoded specificity of the T-cell.
- Ex vivo, epcoritamab induced potent cytotoxicity in tumor cells derived from patients with DLBCL and FL, irrespective of prior treatment with anti-CD20 monoclonal antibodies.
- Epcoritamab induces durable B-cell depletions in the peripheral blood and deeper depletion of B cells in lymphoid organs compared with rituximab.

Preliminary safety and efficacy data from the FIH epcoritamab trial (GCT3013-01 trial; NCT03625037) indicate the potential for epcoritamab to substantially improve clinical outcomes with a manageable safety profile in subjects with multiple R/R DLBCL.

The purpose of this phase 3 trial is to evaluate the efficacy and safety of epcoritamab compared to investigator's choice of chemotherapy in subjects with R/R DLBCL, who have failed or are ineligible for HDT-ASCT.

2.2 Background on B-Cell Non-Hodgkin Lymphoma

Malignant lymphomas represent a disease entity characterized by malignant transformation of the cells from lymphoid tissue. Lymphomas of B-cell origin constitute a diverse set of neoplasms within the larger context of NHL. DLBCL is the most common type of NHL accounting for approximately 30% to 40% of all NHL diagnoses, followed by FL (20% to 25% of all NHL diagnoses). The majority of the B-cell lymphomas express B-cell markers, such as CD19, CD20, CD22, and CD79b (Swerdlow et al., 2016).

The biologic heterogeneity of B-cell malignancies is reflected in the clinical course and outcome of individual diseases. Indolent diseases such as FL and CLL/SLL evolve slowly, with a median survival of 8 to 10 years. In contrast, more aggressive diseases such as DLBCL, if left untreated, have a median survival of 6 months. The median age at diagnosis for most patients with lymphoma is approximately 60 to 65 years (WHO, 2008).

Historically, therapy for B-cell lymphomas was mainly combination chemotherapy. The introduction of immunotherapy with the CD20-targeting mAb, rituximab, was one of the first immunotherapeutic approaches in cancer and the first mAb to be approved. Currently, most patients with B-cell lymphoma are treated with a CD20-targeting mAb, either alone or in combination with chemotherapy, as part of their first-line treatment. Many patients will also receive a CD20-targeting mAb in later lines of treatment. However, response rates tend to decrease and the DOR typically shortens with each successive line. In addition, some patients are refractory to or ineligible for available treatment.

2.2.1 Diffuse Large B-cell Lymphoma

The standard first-line therapy for DLBCL is R-CHOP. The cure rate of this combination for the overall population of newly-diagnosed DLBCL is between 60% and 70% (Sehn et al., 2007). Attempts to improve upon outcomes of first-line therapy, including intensification of dose and addition of other agents to intensify the regimen, have failed to provide sufficient evidence to alter SOC.

Risk factors impacting rates of CR to first-line treatment, disease relapse, and OS are included in the IPI or R-IPI (Appendix 6): age >60 years, ECOG >1 or Karnofsky performance status <60, LDH > ULN; extranodal disease >1 (2 or more), and disease Stage 3 or 4 (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993; Sehn et al., 2007). While patients in the good risk group (1-2 IPI factors) have a 4-year PFS of 80% following standard first-line R-CHOP, the 45% of patients in the poor risk group (3-5 IPI factors) only achieve a 4-year PFS and OS of 55% (Sehn et al., 2007).

Approximately 35% of patients with DLBCL are either primary refractory to or relapse following standard frontline chemoimmunotherapy. In this group, the only option for long-term survival is salvage chemotherapy, such as rituximab combined with DHAP (dexamethasone, cytarabine, and cisplatin), followed by HDT with ASCT (Philip et al., 1995). However, only half of patients with R/R DLBCL are eligible to receive HDT-ASCT, and among those who are transplant-eligible, some are insensitive to salvage therapy, precluding the ASCT procedure. Finally, a significant proportion of patients relapse following HDT-ASCT treatment, with approximately 45% progressing within 3 years (Gisselbrecht et al., 2010). Overall, less than 10% of patients with R/R DLBCL can expect cure with standard secondary therapies. For the patients who relapse after or are ineligible for HDT-ASCT, there are palliative treatment options, with the goal of achieving remission and prolonging survival. However, there is no consensus gold standard, and patients will normally be offered non-intensive (eg, R-GemOx, BR) or other palliative intervention (sequential single-agent chemotherapy, local radiation therapy for focal symptoms).

The recently approved CAR-T cell therapies demonstrate a durable response in only a small subset of patients (Locke et al., 2019; Schuster et al., 2019). However, access to this highly specialized intervention is limited. Thus, novel, effective, and widely available treatments are needed.

2.3 Introduction to Investigational Medicinal Product

Epcoritamab is a bispecific antibody targeting the T-cell antigen CD3 and the B-cell antigen CD20 (Engelberts et al., 2020). The MOA of epcoritamab is engagement of T-cells as effector cells to induce cytotoxicity of CD20-expressing B cells and tumor cells. This is a different MOA compared to that of chemotherapy or conventional CD20-targeting mAbs that induce cytotoxicity through Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity, and in some cases programmed cell death.

Epcoritamab is generated using Genmab's DuoBody® technology (Labrijn et al., 2013; Labrijn et al., 2014). DuoBody molecules are bispecific antibodies with a regular IgG1 structure and biochemical characteristics typical of human IgG1. Accordingly, DuoBody molecules show normal binding to the neonatal Fc receptor, resulting in the relatively long plasma half-life. The Fc domain of epcoritamab has been modified to silence Fc-mediated effector functions, ensuring that epcoritamab does not activate T-cells through IgG Fc receptor-mediated CD3 crosslinking.

2.3.1 Summary of Nonclinical Studies

A nonclinical pharmacology package demonstrating the potency and MOA of epcoritamab in models representing B-cell malignancies is available. Epcoritamab induced potent killing of CD20-expressing cells by both $CD4^+$ and $CD8^+$ T-cells in vitro, ex vivo, and in vivo. Epcoritamab was capable of inducing effective anti-tumor activity in the presence of circulating CD20 mAb that can compete for target binding in mouse models in vivo. Furthermore, epcoritamab induced T-cell-mediated cytotoxicity in biopsy samples taken from patients with DLBCL and FL who had been previously treated with a CD20 mAb. Activation and cytotoxic activity of T cells induced by epcoritamab were dependent on the simultaneous binding to both CD3-expressing T cells and CD20-expressing B cells or tumor cells. EC_{20} and EC_{50} values for epcoritamab-induced cytotoxicity towards B-cell lymphoma cell lines and endogenous B cells were in the low picomolar range, as determined in a flow cytometry assay (EC_{50}: 0.2-3.5 pM; EC_{20}: 0.02-0.98 pM).

A nonclinical safety package to support the FIH trial with epcoritamab is also available and consists of in vitro cross-species binding assessments, in vitro safety studies using human cells and tissues (cytokine release assay, cross-reactivity, hemolytic potential, and plasma compatibility assays), and in vivo studies in cynomolgus monkeys (including safety pharmacology and local tolerance evaluations). In the in vitro cross-species binding studies, cynomolgus monkey was identified as a relevant species for toxicologic evaluations.

In in vitro safety studies, epcoritamab was associated with cytokine release in a human whole blood model. Epcoritamab did not cause hemolysis of human whole blood and was compatible with human plasma. In in vivo safety studies performed in cynomolgus monkeys, epcoritamab was associated with adverse clinical signs (including mortality) and cytokine release primarily following the first dose, reversible hematologic alterations, reversible B-cell depletion in peripheral blood, and reversible decreased lymphoid cellularity in lymphoid tissues. There were no epcoritamab-related local tolerance findings following SC administration of epcoritamab in cynomolgus monkeys. Peak cytokine levels in monkeys at a comparable dose (mg/kg) were generally lower following SC administration relative to IV administration, but with comparable B-cell depletion. In addition, IV administration of epcoritamab preceded by a priming dose

resulted in lower levels of cytokine release. These results support the rationale for the SC route of administration and use of a priming dose in the clinical setting. For additional information related to the nonclinical studies for epcoritamab, please refer to the IB.

2.3.2 Summary of Clinical Trials

For information related to epcoritamab clinical trials, please refer to the IB.

2.4 Benefit-Risk Assessment

2.4.1 Potential Benefit

Subjects with R/R DLBCL may benefit from treatment with epcoritamab in terms of disease reduction or control (see the IB for preliminary efficacy results).

Similarly, subjects with R/R DLBCL may benefit from treatment with investigator's choice of R-GemOx or BR in terms of disease reduction or control (Mounier et al., 2013; Vacirca et al., 2014).

2.4.2 Potential Risks

The expected mode of action of epcoritamab is activation of the T-cells upon binding to CD3, simultaneously with CD20 binding, with release of perforin/granzymes and FAS ligand and lysis of the target CD20-expressing cell. CD20 is exclusively expressed on B cells, so eradication of cells other than B cells is not expected.

The main risks identified for epcoritamab are CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) (see Table 2-1).

Identification of potential risks, such as TLS, and the risk mitigation strategies are detailed for epcoritamab in Table 2-1.

Table 2-1 Potential Risks for Epcoritamab

Potential Risk	Risk Mitigation
CRS symptoms such as chills, fever, hypotension, and hypoxia	• The first dose is a priming dose, ie, a lower dose than subsequent doses; the second dose is an intermediated dose, ie, higher than the priming dose but lower than the subsequent full-dose levels (see Section 4.3) • Premedication is mandatory prior to the first 4 administrations and optional for later administrations (see Section 6.2) • Prophylactic corticosteroids are mandatory for 4 days for each of the first 4 weekly administrations; for subsequent administrations, prophylactic steroids are only necessary if CRS ≥ grade 2 occurred with the previous epcoritamab administration (see Section 6.2) • Hospitalization for CRS monitoring is mandatory for at least 24 hours following the third dose (first full dose) of epcoritamab administration only
ICANS	Monitoring of the neurologic and cognitive status of subjects to secure timely introduction of supportive care (see Section 9.3.2 and Appendix 9)
TLS	Laboratory monitoring; prophylaxis and management guidelines (see Appendix 8)

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TLS=tumor lysis syndrome.

The main risks associated with the immunochemotherapy regimens, R-GemOx and BR, are well-described in the literature for these widely used SOC treatments, and specific risks for the individual agents are discussed in the individual labels for the locally-approved compounds.

2.4.3 Conclusion

The purpose of the safety precautions and close monitoring in this trial is to facilitate a positive benefit-risk ratio for each subject. Subjects with R/R DLBCL may benefit from treatment with epcoritamab in terms of disease reduction, as epcoritamab has a different mode of action from chemotherapy and direct CD20-targeting monoclonal antibodies. It is expected that toxicities can be managed with standard supportive care. The potential benefit of therapy with epcoritamab is expected to outweigh the treatment-related risks. Treatment with investigator's choice immunochemotherapy regimens is according to local guidelines and represents standard of care treatment with established benefit-risk profiles.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 3-1. Please note that not all objectives and endpoints are applicable for the Chinese cohort (footnote a and b).

Table 3-1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• Compare the clinical efficacy of epcoritamab to SOC (R-GemOx or BR)	• OS
Secondary	
• Compare other measures of epcoritamab efficacy to SOC	• PFS determined by Lugano criteria per IRC assessment and investigator assessment • ORR determined by Lugano criteria per IRC assessment and investigator assessment • CR rate, determined by Lugano criteria per IRC assessment and investigator assessment • DOR determined by Lugano criteria per IRC assessment and investigator assessment • TTR determined by Lugano criteria per IRC assessment and investigator assessment • Rate and duration of MRD negative status[a] • PFS determined by LYRIC per IRC assessment • ORR determined by LYRIC per IRC assessment • CR rate determined by LYRIC per IRC assessment • DOR determined by LYRIC per IRC assessment • TTR determined by LYRIC per IRC assessment • TTNT
• Compare safety and tolerability of epcoritamab to SOC	• Incidence and severity of AEs • Incidence and severity of changes in laboratory values • Incidence of dose interruptions and delays
• Evaluate immunogenicity	• Anti-epcoritamab antibody response
• To compare PROs related to lymphoma symptoms between epcoritamab and SOC	• Changes in lymphoma symptoms as measured by the FACT-Lym
Other	
• Evaluate pharmacodynamic markers linked to efficacy and mechanism of action of epcoritamab	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy)[b]
• Assess potential biomarkers predictive of clinical response to epcoritamab[a]	• Circulating tumor DNA[a] • DNA mutation status and gene profile[a]
• To assess impact of lymphoma symptoms and its treatment on health status	• Changes in EQ-5D-3L for health states of interest

[a] Not applicable for the Chinese Cohort.
[b] For the Chinese cohort only pharmacodynamic markers in blood samples are assessed.
AE=adverse event; BR=bendamustine and rituximab; CR=complete response; DOR=duration of response; FACT-Lym=Functional Assessment of Cancer Therapy - Lymphoma; IRC=independent review committee; LYRIC=Lymphoma Response to Immunomodulatory Therapy Criteria; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; R-GemOx=rituximab, gemcitabine, and oxaliplatin; SOC=standard of care; TTNT=time to next anti-lymphoma therapy; TTR=time to response.

4 TRIAL DESIGN

4.1 Description of Trial Design

Specific trial design features for the Chinese cohort, including randomization details, are provided in Section 4.1.1.

This is a Phase 3, open-label, randomized, global trial of epcoritamab versus SOC (ie, pre-specified investigator's choice of R-GemOx or BR) in 480 subjects, plus a cohort of 72 Chinese subjects, aged 18 years or older with R/R DLBCL who failed a previous ASCT or are ineligible for ASCT at screening (as defined in the Inclusion/Exclusion Criteria, Section 5). The trial will consist of screening, treatment (Cycle 1 Day 1 until trial treatment discontinuation), safety follow-up, post-treatment follow-up (until disease progression), and survival follow-up. A diagram of the overall trial design is provided in Figure 1.

Subjects in the global trial will be randomized 1:1 to receive either epcoritamab (n=240) or investigator's choice of R-GemOx or BR (n=240). Prior to randomization, the investigator must select and document the intended choice of chemotherapy (which the subject will receive if randomized to the investigator's choice arm); no change in chemotherapy is permitted for a subject during the treatment phase of the trial. In addition, an enrollment cap will be implemented in the SOC arm so that at most 50% subjects will receive BR. Randomization will be stratified by number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs 2), prior ASCT (yes vs no), and prior CAR-T (yes vs no). There will also be a cap of approximately 120 subjects (approximately 25% of total enrollment) on the number of second-line subjects (ie, those with only 1 prior line of therapy) who may be enrolled.

Subjects randomized to receive epcoritamab will be administered epcoritamab as an SC injection in 4-week cycles (ie, 28 days) as below until one or more of the discontinuation criteria in Section 8.1 are met:

- Epcoritamab: 0.16 mg SC on Day 1 (priming dose), 0.8 mg SC on Day 8 (intermediate dose), 48 mg (full dose) SC on Days 15 and 22 of Cycle 1; 48 mg SC on Days 1, 8, 15, 22 of Cycles 2 and 3; 48 mg SC on Days 1 and 15 of Cycles 4 through 9; and 48 mg SC on Day 1 of Cycle 10 and onward.

Subjects randomized to SOC will be administered 1 of the 2 chemotherapy options below until completion of the maximum cycles or one or more of the discontinuation criteria in Section 8.1 are met:

- BR: rituximab 375 mg/m^2 IV on Day 1 and bendamustine 90 mg/m^2 IV on Days 1 and 2 of each 21-day cycle for up to 6 cycles (Sehn et al., 2017)
- R-GemOx: rituximab 375 mg/m^2 IV on Days 1 and 15 and gemcitabine 1000 mg/m^2 IV + oxaliplatin 100 mg/m^2 IV on Days 2 and 16 of each 28-day cycle for up to 4 cycles (Mounier et al., 2013). Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.

After the end of treatment visit, all subjects will have a safety follow-up visit (Section 8.4). After the safety follow-up visit:

- Subjects who discontinue treatment due to other reasons than disease progression or initiation of new systemic anti-cancer therapy will move into the post-treatment follow-up (Section 8.5), followed by survival follow-up (Section 8.6).

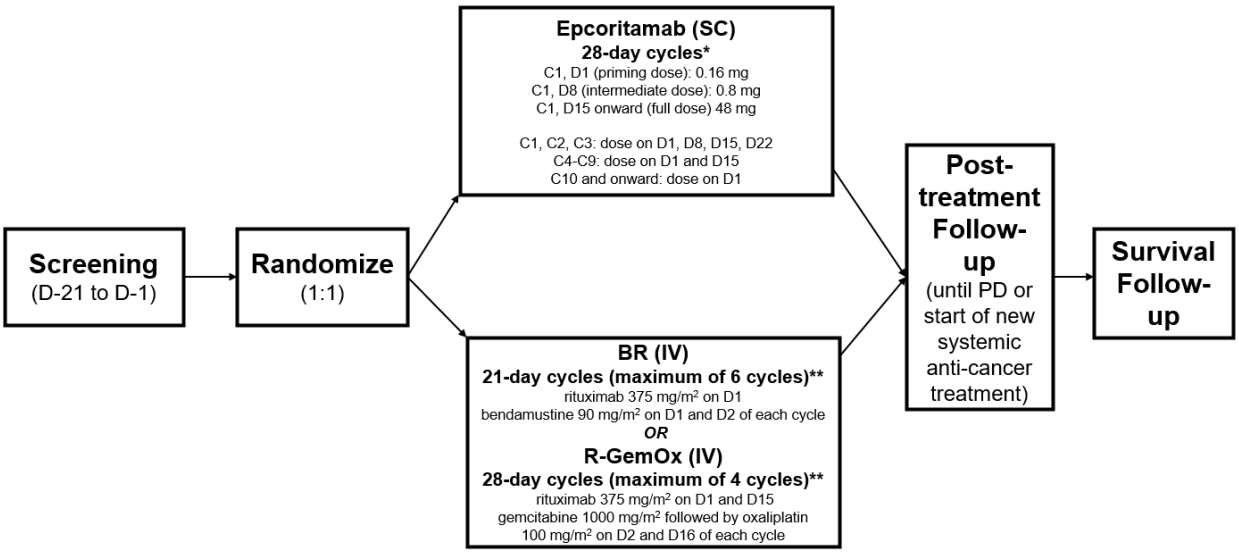
- Subjects who discontinue treatment due to disease progression or initiation of new systemic anti-cancer therapy will directly move into the survival follow-up (Section 8.6).

Trial assessments will be performed as detailed in the Visit Assessment Schedules in Section 1.

The primary analysis of the global trial will take place when approximately 330 OS events (ie, deaths) have accumulated. Once the primary analysis has been conducted, trial subjects may roll over to a maintenance/extension protocol for continued treatment and/or follow-up, as applicable.

An independent data monitoring committee (IDMC) will be established for this study to review safety results for the global trial; in addition, they will review cumulative safety data after 40 subjects (approximately 20 in the epcoritamab arm) have been treated for at least 1 cycle, and approximately every 4 months thereafter during the trial, according to the IDMC Charter (see Section 11.11 for additional details).

Figure 1 Overall Trial Design



C=cycle; D=Day; IV=intravenous; PD=progressive disease; SC=subcutaneous
*Until one or more of the discontinuation criteria in Section 8.1 are met
**Until completion of the maximum cycles or one or more of the discontinuation criteria in Section 8.1 are met

4.1.1 Specific Trial Design Features for the Chinese Cohort

Chinese subjects will be randomized 1:1 to receive either epcoritamab (n=36 approximately) or investigator's choice of R-GemOx or BR (n=36 approximately). Prior to randomization, the investigator must select and document the intended choice of chemotherapy (which the subject will receive if randomized to the investigator's choice arm); no change in chemotherapy is permitted for a subject during the treatment phase of the trial. In addition, an enrollment cap will be implemented in the SOC arm so that at maximum 50% of Chinese subjects on SOC will receive BR.

Randomization will be stratified by number of prior lines of therapy (1 vs >1) and ECOG PS (0-1 vs 2). There will also be a cap of 18 subjects (25% of total Chinese subjects) on the number of second-line subjects (ie, those with only 1 prior line of therapy) who may be enrolled.

Subjects randomized to receive epcoritamab will be administered epcoritamab as an SC injection in 4-week cycles (ie, 28 days) as below until one or more of the discontinuation criteria in Section 8.1 are met:

- Epcoritamab: 0.16 mg SC on Day 1 (priming dose), 0.8 mg SC on Day 8 (intermediate dose), 48 mg (full dose) SC on Days 15 and 22 of Cycle 1; 48 mg SC on Days 1, 8, 15, 22 of Cycles 2 and 3; 48 mg SC on Days 1 and 15 of Cycles 4 through 9; and 48 mg SC on Day 1 of Cycle 10 and onward.

Subjects randomized to SOC will be administered 1 of the 2 chemotherapy options below until completion of the maximum cycles or one or more of the discontinuation criteria in Section 8.1 are met:

- BR: rituximab 375 mg/m^2 IV on Day 1 and bendamustine 90 mg/m^2 IV on Days 1 and 2 of each 21-day cycle for up to 6 cycles (Sehn et al., 2017)
- R-GemOx: rituximab 375 mg/m^2 IV on Days 1 and 15 and gemcitabine 1000 mg/m^2 IV + oxaliplatin 100 mg/m^2 IV on Days 2 and 16 of each 28-day cycle for up to 4 cycles (Mounier et al., 2013). Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.

After the end of treatment visit, all subjects will have a safety follow-up visit (Section 8.4). After the safety follow-up visit:

- Subjects who discontinue treatment due to other reasons than disease progression or initiation of new systemic anti-cancer therapy will move into the post-treatment follow-up (Section 8.5), followed by survival follow-up (Section 8.6).
- Subjects who discontinue treatment due to disease progression or initiation of new systemic anti-cancer therapy will directly move into the survival follow-up (Section 8.6).

Trial assessments will be performed as detailed in the Visit Assessment Schedules in Section 1.

The primary analysis of the Chinese cohort will take place when approximately 50 deaths have accumulated in that cohort and once the global cohort has met the trigger for their primary analysis. No formal interim analysis is planned for the Chinese cohort.

An independent data monitoring committee (IDMC) established for this study will review efficacy and safety results from the Chinese cohort when all Chinese subjects have been enrolled and have completed two scans (unless imaging is considered completed before second scan); in addition, they will review cumulative safety data for the Chinese cohort at timepoints aligned with IDMC review of the global cohort (see Section 11.11 for additional details).

A decision to discontinue the Chinese cohort may be taken separately from the global study.

Once the global and China primary analyses have been conducted, Chinese trial subjects may roll over to a maintenance/extension protocol for continued treatment and/or follow-up, as applicable.

4.2 Trial Design Rationale

The comparator for epcoritamab monotherapy is investigator's choice of chemotherapy, with the investigator selecting either R-GemOx or BR for each subject, prior to randomization, as the SOC treatment that the subject will receive if randomized to the control arm (see additional details in Section 2.2.1). These options include the European Society for Medical Oncology recommendation for platinum- and/or gemcitabine-based regimens and are listed as suggested treatment regimens by National Comprehensive Cancer Network.

The primary endpoint of this study is OS, which is an objective gold standard endpoint of clinical benefit for oncology clinical trials. Given that epcoritamab is a subcutaneous injection given on a

different schedule from the multiple intravenous medications comprising the investigator's choice control, blinding of the subjects or the investigators to the study treatment is not possible.

4.3 Dose and Schedule Rationale

Based on data from the dose escalation part of the ongoing GCT3013-01 trial (refer to the IB), a priming dose of 0.16 mg and an intermediate dose of 0.8 mg, followed by full doses of 48 mg will be administered in GCT3013-05. For the Chinese cohort this is supported by data on this dose regimen obtained from Asian subjects (n=61 at the time of initial version of the China protocol) in GCT3013-01 and GCT3013-04. Further data in Chinese subjects will be collected from trial M21-103 (first subject in 1H-2022).

Rationale for Selection of Priming and Intermediate Dose Levels: With regard to timing of CRS onset, a total of 6 subjects were exposed to the RP2D priming dose of 0.16 mg; 1 subject (16.7%) experienced CRS (Grade 1) within the subsequent 7 days with an onset of a little more than 72 hours after epcoritamab administration. Eighteen subjects were exposed to the RP2D intermediate dose of 0.8 mg: 5 subjects (27.8%) experienced CRS within the subsequent 7 days, 4 subjects (22.2%) experienced the CRS event (grade 1) within 24 hours after epcoritamab administration, and 1 subject (5.6%) experienced CRS (grade 2) approximately after 72 hours. Four subjects were exposed to the RP2D of 48 mg at first and second full-dose administration during Cycle 1; 3 subjects (75%) experienced CRS (1 subject with Grade 1 and 2 subjects with Grade 2) $\leq$ 24 hours following the first full-dose administration. No subject experienced a CRS event within the subsequent 7 days following the second 48 mg full-dose administration. Based on the above observations following the administration of the 0.16 mg priming dose, the 0.80 mg intermediate dose, and the 48 mg full dose, a mandatory hospitalization for 24 hours following the first full dose will be implemented.

Rationale for Selection of Full Dose Level: The epcoritamab IB provides a summary of the available clinical data from the dose escalation part of the GCT3013-01 trial, including the 48 mg dose level, which is the selected RP2D for epcoritamab.

Rationale for Selection of the Dosing Schedule: The administration schedule in the current trial is the same that is used in the Phase 2 (expansion part) of GCT3013-01, ie, weekly in Cycles 1, 2, and 3; every 2 weeks in Cycles 4 through 9; and then every 4 weeks from Cycle 10 onward until one of the treatment discontinuation criteria are met (Section 8.1). As in GCT3013-01, premedication with a corticosteroid, antihistamine and antipyretic, and post-treatment CRS prophylaxis with a corticosteroid, are mandatory during Cycle 1.

The dosages and schedule of the R-GemOx or BR selected based on known efficacy and safety of these regimens; the dosages and schedules are consistent with standard of care.

4.4 End of Trial Definition

The end of trial is defined as the last date of data collection for the last subject in the trial globally.

In this trial, the end of trial will occur when the last subject dies or withdraws from the trial. However, the maximum trial duration is approximately 5 years after the last subject is randomized.

4.5 Estimated Trial Duration for an Individual Subject

While the estimated trial duration for an individual subject depends upon the treatment arm assigned, all subjects have a 21-day screening period, a treatment period, and a follow-up period that continues until death (unless end of trial criteria are met).

For subjects assigned to the investigator's choice arm, the treatment period is a maximum of 16 weeks (approximately 4 months) for R-GemOx, and 18 weeks (approximately 4.5 months) for BR.

For subjects assigned to the epcoritamab treatment arm, the treatment period maximally continues until disease progression (the timing of which will vary from subject to subject).

A subject is considered to have completed the trial if they complete all periods of the trial shown in the Schedule of Activities (Section 1).

4.6 Treatment Discontinuation

Treatment should continue until the subject meets one of the treatment discontinuation criteria (see Section 8.1).

4.7 Trial Termination

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a trial site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's guidance documents/trial plans, ICH GCP E6(R2), and applicable regulatory requirements.
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further IMP development

Subjects with a potential treatment benefit will be ensured continued access to trial drug under a protocol or as provided for by the country's local regulatory mechanism (Section 8.9). However, Genmab reserves the unilateral right, at its sole discretion, to determine whether to supply Genmab IMP(s) and by what mechanism, after termination of the trial and before the product(s) is/are available commercially.

5 TRIAL POPULATIONS

5.1 Inclusion Criteria

Each potential subject must fulfill all of the following criteria to be enrolled in the trial.

1. Criterion modified as per Amendment 1

1.1 Must be at least 18 years of age;

2. Subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that the purpose of the trial and the procedures required for the trial are understood, and indicating that the subject is willing to participate in the trial prior to initiating any other trial-related assessments or procedures;

3. ECOG PS score of 0-2;

4. Criterion modified as per Amendment 1

4.1 Criterion modified as per Amendment 2

4.2 One of the confirmed histologies below with CD20-positivity:

a) DLBCL, NOS (according to the WHO 2016 classification), including de novo or histologically transformed from FL

b) "Double-hit" or "triple-hit" DLBCL (technically classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 translocations), including de novo or histologically transformed from FL

- Note: other double-/triple-hit lymphomas and those classified in WHO 2016 as HGBCL, NOS are not eligible

c) FL Grade 3B

d) T-cell/histiocyte-rich large B-cell lymphoma;

5. Criterion modified as per Amendment 1

5.1 CD20-positivity at representative (previous or current) tumor biopsy based on the pathology report;

6. Criterion modified as per Amendment 1

6.1 Relapsed or refractory disease and previously treated with at least 1 line of systemic antineoplastic therapy including anti-CD20 mAb-containing combination chemotherapy since lymphoma diagnosis (ie, having received R-CHOP or an equivalent regimen that would be considered adequate first-line treatment for DLBCL);

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

7. Failed previous HDT-ASCT or not eligible for HDT-ASCT at screening. If ineligible for HDT-ASCT, the decision must have been based on age, performance status, comorbidity, and/or insufficient response to prior treatment;

8. Has measurable disease:

a. An FDG-PET scan demonstrating positive lesion(s) compatible with CT- or MRI-defined anatomical tumor sites

b. ≥1 measurable nodal lesion (long axis >1.5 cm and short axis >1.0 cm) and/or ≥1 measurable extranodal lesion (long axis >1.0 cm) on CT scan or MRI;

9. Absolute neutrophil count ≥1.0 × 10^9/L (growth factor permitted);

10. Criterion modified as per Amendment 2

10.1 Platelet count ≥75 × 10^9/L (or >50 × 10^9/L if bone marrow involvement or splenomegaly);

11. Criterion modified as per Amendment 1

11.1 Criterion modified as per Amendment 2

11.2 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level ≤3 times the upper limit of normal (× ULN), unless enzyme elevation is due to a non-hepatic origin or lymphoma involvement of the liver and ALT and AST levels are ≤5 × ULN;

12. Criterion modified as per Amendment 2

12.1 Total bilirubin level ≤2 × ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin or lymphoma involvement of the liver and total bilirubin is ≤5 × ULN;

13. Criterion modified as per Amendment 1

13.1 Criterion modified as per Amendment 2

13.2 Estimated GFR ≥50 mL/min/1.73 m^2 as calculated by Cockcroft-Gault (Appendix 1);

14. PT/INR/aPTT ≤1.5 × ULN, unless receiving anticoagulation;

15. A female subject with reproductive potential (Appendix 10) must agree to use adequate contraception during the trial, and for 12 months after the last administration of trial treatment. Adequate contraception is defined as highly effective methods of contraception (defined in Appendix 10);

- Note: If the reproductive potential changes after start of the trial (eg, female subject who is not heterosexually active becomes active, premenarchal female subject experiences menarche), a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in Appendix 10.

16. Criterion modified as per Amendment 1

16.1 A female subject of childbearing potential must have a negative serum (beta-hCG) pregnancy test at screening and a negative serum or urine pregnancy test before treatment administration on Day 1 of every cycle;

17. A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 12 months after the last administration of trial treatment;

18. Criterion modified as per Amendment 1

18.1 A male subject who is sexually active with a female of reproductive potential and has not had a vasectomy must agree to use a barrier method of birth control (ie, condom) and must agree not to donate sperm during the trial and for 12 months after receiving the last administration of trial treatment;

19. Life expectancy >2 months on SOC treatment.

5.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the trial.

1. Primary central nervous system (CNS) tumor or known CNS involvement as assessed by brain MRI at screening or by CT and lumbar puncture (if MRI contraindicated);
2. Any prior therapy with a bispecific antibody targeting CD3 and CD20;
3. History of severe allergic or anaphylactic reactions to anti-CD20 antibody therapy;
4. Criterion modified as per Amendment 1

4.1 Contraindication to any component of SOC regimen selected prior to randomization;

5. Criterion modified as per Amendment 1

5.1 Major surgery within 4 weeks prior to randomization;

6. Criterion modified as per Amendment 1

6.1 Chemotherapy and other non-investigational antineoplastic agents (except CD20 mAbs) within 4 weeks or 5 half-lives (whichever is shorter) prior to randomization;

7. Criterion modified as per Amendment 1

7.1 Any investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to randomization;

8. ASCT within 100 days of randomization;
9. Criterion modified as per Amendment 1

9.1 Treatment with CAR-T therapy within 100 days prior to randomization;

10. Criterion modified as per Amendment 1

10.1 Criterion modified as per Amendment 2

10.2 Receiving immunosuppressive therapy, including more than the equivalent of 20 mg of prednisolone daily, unless for control of lymphoma or intermittent prophylaxis/treatment of allergic reactions;

11. Seizure disorder requiring anti-epileptic therapy;
12. Criterion modified as per Amendment 1

12.1 Criterion modified as per Amendment 2

12.2 Vaccination with live vaccines within 28 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not allowed;

13. Criterion modified as per Amendment 1

13.1 Clinically significant cardiovascular disease, including:

   a. Myocardial infarction within 1 year prior to randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV) cardiac arrhythmia (CTCAE Version 5.0 Grade 2 or higher), or clinically significant ECG abnormalities;

   b. Stroke within 6 months prior to randomization;

14. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec;

15. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results;

16. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection requiring systemic treatment at time of randomization;

17. Criterion modified as per Amendment 1

17.1 Criterion modified as per Amendment 2

17.2 Known history of seropositivity for HIV infection. Note: HIV testing is required at screening only if required per local health authorities or institutional standards;

18. Active HBV (DNA PCR-positive) or hepatitis C (RNA PCR-positive infection). Subjects with evidence of prior HBV but who are PCR-negative are permitted in the trial but should receive prophylactic antiviral therapy. Subjects who received treatment for HCV that was intended to eradicate the virus may participate if hepatitis C RNA levels are undetectable.

19. Has known past or current malignancy other than inclusion diagnosis, except for:

   a. Cervical carcinoma of Stage 1B or less

   b. Non-invasive basal cell or squamous cell skin carcinoma

   c. Non-invasive, superficial bladder cancer

   d. Prostate cancer with a current PSA level <0.1 ng/mL

   e. Any curable cancer with a complete response of >2 years duration;

20. Has known or suspected allergies, hypersensitivity, or intolerance to epcoritamab or its excipients (refer to the IB for more information);

21. Contraindication to all uric acid lowering agents;

22. Criterion modified as per Amendment 1

22.1 A woman of childbearing potential with a positive serum or urine pregnancy test at screening. Female subjects must also agree not to breastfeed during the entire trial and until 12 months after the last administration of study drug;

23. Clinically significant liver disease, including active hepatitis, current alcohol abuse, or cirrhosis;

24. Criterion modified as per Amendment 1

24.1 Criterion modified as per Amendment 2

24.2 Active tuberculosis or history of treatment for active tuberculosis within the past 12 months;

Note: For subjects with positive interferon gamma release assay (IGRA), active pulmonary tuberculosis must be excluded with clinical evaluation and radiologic imaging. Subjects with positive IGRA and no evidence of active disease may be enrolled after treatment for latent tuberculosis infection (recommendation isoniazid monotherapy for total of 6 months) has been initiated;

25. Criterion deleted as per Amendment 1

26. Receiving immunostimulatory agent;

27. Prior allogeneic hematopoietic stem cell transplantation.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (see Section 5.1, Inclusion Criteria, and Section 5.2, Exclusion Criteria). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons), and any SAEs or AEs related to a trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be re-assessed at the rescreening visit.

Screen failures may be rescreened only once. Subjects are required to sign a new ICF if updates have been made since signing the most recent ICF.

6 TREATMENT

6.1 Treatment Assignment or Randomization

6.1.1 Subject Numbering

After signing the ICF, subjects will be assigned a unique subject identification number before undergoing any screening procedure(s).

6.1.2 Treatment Assignment (Randomization)

This is an open-label trial; therefore, blinding of treatment will not be performed.

Eligible subjects will be randomized to either epcoritamab or investigator's choice of SOC: R-GemOx or BR (ie, investigators will choose either R-GemOx or BR for each subject, prior to randomization, as the SOC treatment that the subject will receive if randomized to the SOC control arm). Once a chemotherapy option is selected for a subject, that is the only regimen that the subject can receive if randomized to investigator's choice arm, and no change in chemotherapy is permitted during the treatment phase of the trial.

Block randomization will be stratified by number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs 2), prior ASCT (yes vs no), and prior CAR-T (yes vs no). Randomization will be accomplished by a validated interactive response technology system. Randomization will be performed prior to Cycle 1 Day 1.

6.1.2.1 Treatment Assignment for the Chinese Cohort

The Chinese cohort consisting of approximately 72 subjects will be recruited and randomized 1:1 to receive epcoritamab or SOC. Block randomization will be stratified by number of prior lines of therapy (1 vs >1), and, ECOG PS (0-1 vs 2). Randomization will be accomplished by a validated interactive response technology system.

6.2 Premedication

6.2.1 Epcoritamab Arm: Premedication and CRS Prophylaxis

CRS prophylaxis with corticosteroids and premedication with antihistamines and antipyretics is mandatory as described in Table 6-1 and recommendations for hydration and antihypertensive management are provided in Section 6.3.1.

For each dose of epcoritamab in Cycle 1, 4 days of corticosteroids are mandatory to prevent/reduce severity of symptoms from potential CRS as described in Table 6-1. For administration of epcoritamab in Cycle 2 and beyond, CRS prophylaxis with corticosteroids is only necessary if grade ≥2 CRS occurred with the previous administration.

Corticosteroid administration can be either oral route or IV with recommended dose or equivalent (see Appendix 3).

Table 6-1 Prophylactic Corticosteroid and Premedication Administration

			Corticosteroids[2]	Antihistamines	Antipyretics
Cycle 1 and Repriming Cycles	1st epcoritamab administration (priming dose)	Day 01[1]	Dexamethasone 15 mg (or equivalent)[2]	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 02	Dexamethasone 15 mg (or equivalent)[2]		
		Day 03	Dexamethasone 15 mg (or equivalent)[2]		
		Day 04	Dexamethasone 15 mg (or equivalent)[2]		
	2nd epcoritamab administration (intermediate dose)	Day 08[1]	Dexamethasone 15 mg (or equivalent)[2]	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 09	Dexamethasone 15 mg (or equivalent)[2]		
		Day 10	Dexamethasone 15 mg (or equivalent)[2]		
		Day 11	Dexamethasone 15 mg (or equivalent)[2]		
	3rd epcoritamab administration (1st full dose)	Day 15[1]	Dexamethasone 15 mg (or equivalent)[2]	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 16	Dexamethasone 15 mg (or equivalent)[2]		
		Day 17	Dexamethasone 15 mg (or equivalent)[2]		
		Day 18	Dexamethasone 15 mg (or equivalent)[2]		
	4th epcoritamab administration (2nd full dose)	Day 22[1]	Dexamethasone 15 mg (or equivalent)[2]	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 23	Dexamethasone 15 mg (or equivalent)[2]		
		Day 24	Dexamethasone 15 mg (or equivalent)[2]		
		Day 25	Dexamethasone 15 mg (or equivalent)[2]		
Cycle 2 onward	5th epcoritamab administration (3rd full dose) onward	Day 1[1]	If CRS ≥ grade 2 occurs following the 4th epcoritamab administration, 4-day consecutive corticosteroids must also be repeated for CRS prophylaxis with each epcoritamab dose until 1 full dose is administered without subsequent occurrence of CRS grade ≥2.	Optional, based on whether prior injection reactions observed	Optional, based on whether prior injection reactions observed
		Day 2			
		Day 3			
		Day 4			

CRS=cytokine release syndrome; IV=intravenous(ly); PO=oral(ly).

1. 30 minutes to 2 hours prior to administration of epcoritamab.
2. Refer to Appendix 3 for corticosteroid dose equivalents. Minimum corticosteroid dose for cytokine release syndrome prophylaxis provided in table. The dose of corticosteroid used for CRS prophylaxis may be decreased to a minimum of 12 mg dexamethasone (or alternative steroid equivalent) at the discretion of the investigator if due to concern of tolerability. Maximum dose is at the investigator's discretion.

6.2.2 Chemotherapy Arms (Investigator's Choice): Premedication and Prophylaxis

The following are supportive therapies that are recommended for the chemotherapy arms:

- Premedication with acetaminophen (650 mg orally), diphenhydramine (50 to 100 mg IV or orally), and steroids, 30 to 60 minutes before starting each rituximab infusion, may attenuate infusion reactions.

6.2.3 All Arms: Central Nervous System Prophylaxis

CNS prophylaxis is allowed and recommended in accordance with local guidelines. CNS prophylaxis with IV methotrexate is not permitted in this trial.

6.3 Dosages and Administration

6.3.1 Epcoritamab

Subjects randomized to epcoritamab arm will be administered epcoritamab as an SC injection in 28-day cycles as below until one or more of the discontinuation criteria in Section 8.1 are met:

- Cycle 1: 0.16 mg SC on Day 1 (priming dose), 0.8 mg SC on Day 8 (intermediate dose), 48 mg (full dose) SC on Days 15 and 22 (once weekly)
- Cycles 2 and 3: 48 mg SC on Days 1, 8, 15, 22 (once weekly)
- Cycles 4 through 9: 48 mg SC on Days 1 and 15 (every 2 weeks)
- Cycle 10 onward: 48 mg SC on Day 1 (every 4 weeks)

Every effort should be made to keep subjects on the planned dosing schedule. There must be minimum of 7 days between epcoritamab administrations. Repriming is required if the interval between epcoritamab doses exceeds lengths defined in Section 7.1.

NOTE: Cycle and Day are nominal labels for dosing visits that represent when sequential doses are administered; they do not necessarily correlate with study day. For example, the Cycle 1, Day 15 visit always represents the first full dose of epcoritamab and may occur >7 days after Cycle 1, Day 8 if dose delay was indicated (eg, delay due to AEs).

NOTE: The 24-hour mandatory hospitalization always occurs following the first full dose of epcoritamab during Cycle 1 and any repriming cycle(s).

During the step-up dosing cycles, (ie, the first 4 administrations of epcoritamab [Cycle 1] and any repriming cycle), it is strongly recommended that subjects adhere to all of the following (unless medically contraindicated):

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

Please refer to mandatory corticosteroid, antipyretic and antihistamine prophylaxis in Table 6-1.

6.3.2 Investigator's Choice Immuno-Chemotherapy

Subjects randomized to investigator's choice chemotherapy arm will be administered 1 of the 2 chemotherapy options below until the regimen is completed or one or more of the discontinuation criteria in Section 8.1 are met:

- BR: rituximab 375 mg/m^2 IV on Day 1 and bendamustine 90 mg/m^2 IV on Days 1 and 2 of each 21-day cycle for up to 6 cycles (Sehn, 2007).
- R-GemOx: rituximab 375 mg/m^2 IV on Days 1 and 15 and gemcitabine 1000 mg/m^2 IV + oxaliplatin 100 mg/m^2 IV on Days 2 and 16 of each 28-day cycle for up to 4 cycles (8 total doses of R-GemOx) (Mounier et al., 2013). Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.

Trial treatment should be administered as described in Table 6-2 until one or more of the discontinuation criteria in Section 8.1 are met.

Guidelines for dosage modification and treatment interruption or discontinuation of all trial medications are provided in Section 7.

Table 6-2 Summary of Treatments Administered

	Epcoritamab	**Rituximab**	**Bendamustine**	**GemOx**
Dosage Formulation	Refer to epcoritamab Preparation and Administration Guide	Refer to local prescribing information	Refer to local prescribing information	Refer to local prescribing information
Dose (Refer to local guidelines for administration details for SOC, including recommended premedications)	***(see visit assessment schedules for details)*** ***Step-up Dosing:*** Priming dose: 0.16 mg Int. dose: 0.8 mg Full dose: 48 mg	375 mg/m^2 on Day 1 for BR arm 375 mg/m^2 on Day 1 and Day 15 for R-GemOx arm	*(for 21-day cycle)* 90 mg/m^2 on Day 1 and Day 2	*(for 28-day cycle)* **Gemcitabine** 1000 mg/m^2 (usually over at least 100 min) on Day 2* and Day 16* **Oxaliplatin** 100 mg/m^2 (usually over 2 hr) on Day 2* and Day 16*
Route of Administration	SC injection	IV	IV	IV

BR=bendamustine + rituximab; GemOx=gemcitabine + oxaliplatin; hr=hour(s); int=intermediate; IV=intravenous; min=minutes; R-GemOx=rituximab, gemcitabine, and oxaliplatin; SC=subcutaneous; SOC=standard of care.
*Rituximab, gemcitabine, and oxaliplatin may all be given on the same day (Days 1 and 15) if this is standard procedure at site.

Detailed dose modification guidance is provided in Section 7. Refer to Section 6.9 for information regarding concomitant therapy.

6.4 Epcoritamab Information

Epcoritamab is to be administered by SC injection, by qualified site personnel. Injection site is preferably in the lower part of abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during weekly administration.

6.4.1 Physical Description of Epcoritamab

Epcoritamab at 5 mg/mL or 60 mg/mL will be provided by the sponsor.

6.4.2 Packaging and Labeling

Epcoritamab at 5 mg/mL or 60 mg/mL will be provided by the sponsor. Epcoritamab labels will contain information to meet the applicable regulatory requirements. For further details see the IMP Preparation and Administration Guide.

6.4.3 Preparation, Handling, and Storage

Epcoritamab should be stored in a refrigerator at 2°C to 8°C.

Detailed dose preparation instructions including the important dilution steps will be provided in the IMP Preparation and Administration Guide.

6.5 Rituximab Information

Rituximab will be administered according to the standard preparation and infusion procedures at each investigational site. During the treatment period, rituximab must be administered to subjects in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and participants should be under close supervision of the investigator at all times. For the management of infusion-related reactions and anaphylaxis, refer to local prescribing information and institutional guidelines.

If a rituximab dose is delayed, the next rituximab dose should be calculated from the previous dose of rituximab in order to maintain the regular cycle interval of minimum 14 days or minimum 21 days depending on whether given as part of R-GemOx or BR, respectively.

See the IMP Preparation and Administration Guide for additional details on administration, storage, and handling.

6.6 Bendamustine Information

Bendamustine will be administered according to the standard preparation and infusion procedures at each investigational site. If a bendamustine dose is delayed, then next bendamustine dose should be calculated from the previous dose of bendamustine in order to maintain the regular cycle interval of minimum 21 days.

See the IMP Preparation and Administration Guide for additional details on administration, storage, and handling.

6.7 GemOx Information

GemOx will be administered according to the standard preparation and infusion procedures at each investigational site. If a GemOx dose is delayed, then the next GemOx dose should be calculated from the previous dose of GemOx in order to maintain the regular chemotherapy interval of minimum 14 days.

See the IMP Preparation and Administration Guide for additional details on administration, storage, and handling.

6.8 Compliance

All trial medication will be administered by site personnel to assure compliance with trial requirements.

6.9 Concomitant Medications and Therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care, according to local guidelines, except for those medications identified as "prohibited" (Section 6.9.3).

The subject must notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) he/she takes after the start of screening. All medications (other than trial treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered during the trial must be collected and documented. As relevant medical history, vaccination(s) >28 days prior to screening may also be collected.

Concomitant therapies/medications should also be documented beyond 60 days following study drug discontinuation if prescribed for new or worsening AEs. In addition, relevant vaccines should be documented until the start of survival follow-up.

The sponsor's RMO, or delegate, should be contacted if there are any questions regarding concomitant medication or prior therapy.

The trial site will ensure supportive medication is available for each subject, eg, premedication, antiviral medication, corticosteroids, and anti-cytokine therapy for AE management.

6.9.1 Permitted Concomitant Medications and Therapies

The following concomitant medication and therapies are permitted (if consistent with local guidelines) during the trial:

- SARS-CoV-2 not-live or not-live attenuated vaccines are generally permitted, including mRNA-based, protein-based, or non-replicating viral vector-based vaccines. Consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired.
- Local palliative radiotherapy or surgery to non-target lesions.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and ≥ grade 3 neutropenia, when clinically indicated or at the investigator's discretion. In case of recurring ≥ grade 3 neutropenia, use of growth factors is mandated
- Red blood cell and platelet transfusions, if clinically indicated
- Multivitamins, vitamin D, calcium, and supplements for prevention of weight loss
- Prescribed medicinal cannabinoids as palliative therapy
- Omeprazole 20 mg/day orally or equivalent therapy for peptic ulcer
- 5HT3 antagonists or equivalent anti-emetics
- Loperamide for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose regimen should be according to standard practice
- Bowel care is recommended to prevent constipation and should be administered per standard practice

6.9.2 Permitted Concomitant Therapy Requiring Caution and/or Action

Refer to the local prescribing information for details regarding permitted concomitant therapy requiring caution and/or action, specific to the components of the SOC regimens. Medication for handling CRS, ICANS, TLS/CTLS, and tumor flare reaction is permitted. Please refer to Section 7.1.1.1 for AE management guidelines and mitigation plans.

Rescue medication in terms of an antidote to reverse the action of epcoritamab is not available. Potential side effects of epcoritamab have to be treated symptomatically. Please refer to Section 7.1.1.1.1 for CRS dose modification and management guidance.

6.9.2.1 Antibiotic, Antiviral, and Antifungal Therapy

Prophylactic antibiotic, antiviral, and antifungal therapies are allowed. For subjects who are considered to have an increased risk for herpes and/or *Pneumocystis jirovecii* infections, prophylaxis is recommended, unless medically contraindicated. For subjects who are considered to have an increased risk for other infections, prophylactic therapy is recommended, unless medically contraindicated.

For subjects with a history of recurrent herpes virus infections, herpes infection during previous anti-lymphoma therapy, neutropenia (≥ grade 3) and/or low CD4+ cell counts (<200 cells/µL), prophylactic antiviral therapy is mandatory, eg, acyclovir 400 mg three times a day orally.

Prophylaxis against *Pneumocystis jirovecii*, eg, oral trimethoprim/sulfamethoxazole 80 mg/400 mg (or 160 mg/800 mg) every other day, is mandatory for subjects who are considered at increased risk, eg, subjects with low $CD4^+$ cell counts (<350 cells/µL).

Prophylactic treatment for *Pneumocystis carinii* pneumonia is mandatory according to local standards.

Cytomegalovirus reactivation during treatment should be treated according to local standards or available guidelines (O'Brien et al., 2006).

6.9.2.2 Growth Factors

The use of growth factors for neutropenia such as G-CSF will be allowed. In case of recurring grade ≥3 neutropenia, use of growth factors is mandated.

6.9.2.3 Immunizations

Physicians should review the subject's vaccination status and subject should be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating treatment and, if possible, vaccines administered at least 4 weeks prior to randomization.

6.9.2.4 Immunoglobulin Therapies

Immunoglobulins administered at doses on the order of 1 g/kg body weight have the potential to alter the clearance of other antibodies. Investigators should therefore be aware that the efficacy of antibody-based agents, including epcoritamab and rituximab, may be decreased when administering immunoglobulins at these doses, eg, for the treatment of immune thrombocytopenia, or other immune, inflammatory, or paraneoplastic conditions.

6.9.2.5 Herbal Preparations

Herbal preparations, related over-the-counter preparations containing herbal ingredients, and nutritional supplements (other than those prohibited, see Section 6.9.3) should be used with

caution, as purity of these supplements are not always ensured. Please record all ingredients of any preparation or supplement on the concomitant medication eCRF.

6.9.3 Prohibited Concomitant Therapy

The following medications are prohibited from first dose until 60 days after last dose of study drug unless otherwise specified:

- Any systemic anti-cancer therapy, eg, chemotherapy, immunotherapy, or experimental therapy, other than epcoritamab or the investigator's choice of chemotherapy until subject is in survival follow-up phase (ie, experienced disease progression or started new systemic anti-cancer therapy. Initiation of any of above therapies will move the subject directly into survival follow-up phase).

  Note: Any new systemic anti-cancer therapy should be documented.
- Immunosuppressive therapies, including corticosteroid, that exceed a total daily dose of 20 mg of prednisolone or equivalent unless for the management of AEs, symptom management of lymphoma or given as premedication or prophylaxis.
- Live attenuated vaccines beginning 28 days prior to randomization and for 3 months following the last dose of trial treatment. Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.
- Immunostimulatory agents.
- Investigational agents or interventional studies until subject is in the survival follow-up phase.
- Herbal preparations or related OTC preparations containing herbal ingredients, including rooibos tea, are not permitted during participation in the trial
- Chinese herbal medicine and Chinese patent medicine are not permitted during participation in the trial

Also refer to the local prescribing information for details regarding prohibited concomitant therapy specific to the components of the SOC regimens.

6.10 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of trial treatment in a drug accountability log. Accountability of trial treatments will be verified by the Clinical Research Associate during site visits and at the completion of the trial.

When drug accountability has been verified and a copy of the completed drug accountability log has been received by sponsor, the investigator will dispose all used and unused trial treatment and packaging in accordance with the guidance in the IMP Preparation and Administration Guide and local regulations.

6.11 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of subjects,

investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.11.1 Procedures

All initial technical complaints must be made to the sponsor by the trial-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an AE or SAE, the trial-site personnel must report the SAE to the sponsor according to the AE and SAE reporting process and timelines (Section 10) in addition to reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.11.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the contact information page(s), which will be provided as a separate document.

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

7.1 Dose Modification and Safety Stopping Criteria

7.1.1 Epcoritamab Dose Modification

Dose reduction: No dose reduction of epcoritamab on an individual subject level is allowed in this trial. Refer to Section 4.3 for dosing rationale.

Dose delay: If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).

A repriming cycle is necessary if dose is delayed at certain timepoints, as described below. A repriming cycle consists of a weekly schedule of a priming dose, intermediate dose, and 2 full doses. Refer to Table 1-2 for the repriming cycle Visit Assessment Schedule.

A repriming cycle should occur:

- If C1D8 is delayed more than 1 day (ie, C1D8 is planned to occur more than 8 days after C1D1).
- If C1D15 is delayed more than 7 days (ie, C1D15 is planned to occur more than 14 days after C1D8).
- For C1D22 onward, if the interval between the previous dose of epcoritamab and next planned dose exceeds 6 weeks.

During the repriming cycle, CRS prophylaxis must be resumed with 4 consecutive days of corticosteroids beginning at each epcoritamab dose, until at least 1 full dose of epcoritamab is administered without subsequent occurrence of CRS grade ≥2 (see Section 6.2.1).

Once the full repriming cycle is completed, the subject should resume treatment with Day 1 of the next planned cycle (subsequent to the cycle during which the dosing was delayed). For example, if the subject experiences a 7-week delay after C3D1, the subject should receive a repriming cycle, then continue treatment at C4D1.

7.1.1.1 Epcoritamab Dose Modification for Specific Adverse Events

7.1.1.1.1 Cytokine Release Syndrome

Table 7-1 Epcoritamab Dose Modification for Cytokine Release Syndrome

ASTCT Grade	Hold Treatment (Y/N)	Epcoritamab Dose Modification/Premedication
Grade 1	Y	Hold until resolution of CRS event. If CRS is combined with MAS/HLH, permanently discontinue epcoritamab.
Grade 2 and Grade 3	Y	Hold until resolution of CRS event. If grade 2 or higher CRS occurs with the second full dose or beyond, administer CRS prophylaxis with the next dose until an epcoritamab dose is given without subsequent CRS grade ≥2. If CRS is combined with MAS/HLH, permanently discontinue epcoritamab.
Grade 4	Y	Permanently discontinue epcoritamab.

ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; MAS/HLH=macrophage activation syndrome/hemophagocytic lymphohistiocytosis; N=no; Y=yes.

CRS should be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS (Lee et al., 2019).

Refer to Section 7.2.1 for guidelines for CRS management.

7.1.1.1.2 Tumor Lysis Syndrome

Refer to Section 7.1.5 for information about dose modification due to TLS.

7.1.1.1.3 Immune Effector Cell-Associated Neurotoxicity Syndrome

For grades 1 and 2 ICANS, hold epcoritamab until resolution. For grades 3 and 4 ICANS, permanently discontinue epcoritamab. Refer to Appendix 9 for guidelines for ICANS management.

7.1.1.1.4 All Other AEs Related to Epcoritamab

Table 7-2 Dose Modification for All Other Epcoritamab-Related AEs

CTCAE Grade	Hold Treatment (Y/N)	Epcoritamab Dose Modification
Grade 1	N	Continue epcoritamab
Grade 2	N	Continue epcoritamab
Grade 3	Y	First episode: Hold treatment until improvement to ≤ grade 2 or resolution to baseline. Second episode of the same AE considered related to epcoritamab: Hold treatment until improvement to ≤ grade 1 or resolution to baseline. Permanently discontinue if no improvement within 14 days.
Grade 4	Y	First episode: Hold treatment until improvement to ≤ grade 2 or resolution to baseline. Second episode of same AE considered related to epcoritamab: Permanently discontinue epcoritamab.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = no; Y = yes.

7.1.2 Rituximab Dose Modification Guidance and Safety Criteria

Dose reduction: There will be no dose reductions for rituximab.

Refer to Section 7.1.5 for information about dose modification due to TLS. For rituximab dose modification due to other AEs, see Table 7-3.

Table 7-3 Recommended Dose Modification for Rituximab

CTCAE Grade	Rituximab Dose Modification
Grade 3 related to rituximab, clinically significant and unmanageable	Hold dosing until the adverse event returns to baseline or resolves completely
Grade 4 (any)	Hold dosing until the adverse event returns to baseline or resolves completely

CTCAE=Common Terminology Criteria for Adverse Events.

Detailed safety information and dosing instructions for infusion reactions are provided in the local prescribing information.

7.1.3 Bendamustine Dose Modification Guidance and Safety Criteria

Dose delay: If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).

Refer to Section 7.1.5 for information about dose modification due to TLS.

Hematologic toxicity: Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L.

Table 7-4 Recommended Bendamustine Dose Modification for Hematologic Toxicity

CTCAE Grade	Bendamustine Dose Modification
Grade 4 (first episode)	Hold bendamustine. Once the blood counts have improved (ANC greater than or equal to 1×10^9/L, platelets greater than or equal to 75×10^9/L), reinitiate bendamustine at the discretion of the treating physician. Reduce dose to 60 mg/m^2 on Days 1 and 2 of each cycle.
Grade 4 (second episode)	Discontinue bendamustine.

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events.

Table 7-5 Recommended Bendamustine Dose Modification for Non-Hematologic Toxicity

CTCAE Grade	Bendamustine Dose Modification
Grade 2, clinically significant	Hold bendamustine. Once non-hematologic toxicity has recovered to less than or equal to Grade 1, reinitiate bendamustine at the discretion of the treating physician. In addition, consider dose reduction to 60 mg/m^2 on Days 1 and 2 of each cycle.
≥ Grade 3 (first episode)	Hold bendamustine. Once non-hematologic toxicity has recovered to less than or equal to Grade 1, reinitiate bendamustine at the discretion of the treating physician. Reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.
≥ Grade 3 (second episode of same AE)	Discontinue bendamustine.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.

Also refer to the local prescribing information for details regarding bendamustine safety information, including the safety precautions to be taken, ie, sperm preservation.

7.1.4 GemOx Dose Modification Guidance and Safety Criteria

Dose delay: If a dose is delayed for >4 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (the latter, as clinically indicated).

Refer to Section 7.1.5 for information about dose modification due to TLS.

Table 7-6 Recommended GemOx Dose Modification for Neuropathy (Worsening Compared with Baseline)

Neuropathy Type and Duration	GemOx Dose Modification
Paresthesia lasting 1 to 6 days after each administration	No dose reduction
Significant paresthesia (increase in severity from baseline) lasting 7 to 13 days after each administration	Reduce oxaliplatin dose to 75 mg/m^2
Abnormal results by neurologic examination or significant paresthesia lasting >14 days	Hold oxaliplatin. Once symptoms improve, restart oxaliplatin at a maximum dose of 75 mg/m^2 for the remainder of the treatment course
Pharyngolaryngeal dysesthesia	Prolong oxaliplatin infusion from 2 to 6 hours

GemOx=gemcitabine+oxaliplatin.

Refer to the local prescribing information for further details regarding gemcitabine. Also refer to the local prescribing information for further details regarding oxaliplatin safety information, including the safety precautions to be taken, ie, sperm preservation.

7.1.5 Dose Modification for Tumor Lysis Syndrome (All Arms)

In cases of TLS, hold trial treatment until the TLS has resolved.

TLS should be reported as an AE, using CTCAE grading, whereas CTLS should be reported as an AESI, using grading in Appendix 8.

Refer to Section 7.2.3 for guidelines about management of TLS.

7.2 Management of Specific Adverse Events

7.2.1 Cytokine Release Syndrome

For treatment of CRS, subjects must receive supportive care. The supportive care can include, but is not limited to the following:

- Infusion of saline
- Systemic corticosteroids, antihistamines, antipyretics
- Support for blood pressure (vasopressin, vasopressors)
- Support for low-flow and high-flow oxygen and positive pressure ventilation
- mAb against IL-6R, IL-6, or IL-1, eg, IV administration of tocilizumab, siltuximab and/or anakinra.

Blood product support, analgesics, skin, and mouth care, etc., should be according to local guidelines and the investigator's discretion.

Refer to Appendix 7 for further details about CRS management.

7.2.2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Refer to Appendix 9 for information about grading and management guidelines for ICANS.

7.2.3 Tumor Lysis Syndrome

Subjects who are considered to have an increased risk for TLS (see Appendix 8), eg, due to the type of lymphoma, the tumor burden (bulky disease and/or elevated LDH), renal impairment and/or elevated uric acid should be considered for hydration and prophylactic treatment with a uric acid lowering agent as well as frequent monitoring, according to local standards or available guidelines (Appendix 8) (Coiffier et al., 2008). If signs of TLS occur, supportive therapy, including rasburicase, may be used as clinically indicated at the investigator's discretion.

In addition, close monitoring of laboratory parameters to allow for early diagnosis of possible TLS is recommended at investigator discretion. For details, refer to Table 1-7 for the minimum sampling time points for tumor lysis.

Refer to Appendix 8 for further details about classification and management of laboratory and clinical TLS.

7.2.4 Tumor Flare Reaction

Subjects in this study should be monitored for tumor flare reaction (TFR). TFR is defined as a sudden and tender increase in the size of the disease-bearing sites, including the lymph nodes, spleen and/or the liver often accompanied by low-grade fever, diffuse rash, and in some cases increase in the peripheral blood lymphocyte counts. TFR will be assessed according to the following criteria:

- Grade 1: Mild pain not interfering with function
- Grade 2: Moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living (ADL)
- Grade 3: Severe pain; pain or analgesics interfering with function and interfering with ADL
- Grade 4: Disabling pain
- Grade 5: Death

<u>TFR Management Guidelines</u>

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that ≥ grade 2 TFR be treated with corticosteroids at the investigator's discretion. NSAIDs (ie, ibuprofen 400 to 600 mg orally every 4 to 6 hours as needed) and/or narcotic analgesics for pain management may also be administered as needed. In mild to moderate cases, it is suggested that epcoritamab is continued along with symptomatic treatment as indicated above.

8 DISCONTINUATION AND FOLLOW UP

8.1 Discontinuation of Trial Treatment

A subject's trial treatment must be discontinued for any of the following reasons:

- Disease progression according to LYRIC response criteria (see Section 9.2.3)
- Unacceptable AE requiring treatment discontinuation (see Section 7)
- Subject non-compliance
- Sponsor decision
- Pregnancy
- Subject request to discontinue trial treatment

Discontinuation of components of SOC treatment should follow local practice drug labels for these drugs.

8.2 Withdrawal from the Trial

A subject may withdraw/may be withdrawn from the trial for any of the following reasons:

- Death
- Lost to follow-up (see Section 8.7)
- The investigator or sponsor believes (eg, that for safety or tolerability reasons [eg, AE]) it is in the best interest of the subject to discontinue trial treatment
- Subject withdraws consent from trial
- Subject consents to be rolled over to a maintenance/extension protocol, if available

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected or generated before such a withdrawal of consent. A subject may choose to discontinue from any future trial assessments (eg, dosing, imaging, blood sampling) but agree to remain in the trial and to be followed for survival follow-up, without withdrawal of consent.

If a subject withdraws consent from the trial, he/she may request destruction of any samples (including those collected for biomarker testing) taken and not tested, and the investigator must document this in the site trial records. When a subject withdraws consent, the reason for withdrawal is to be documented in the source document. All randomized subjects who withdraw from trial participation should be followed for survival status (ie, whether the subject is alive or dead and date of death). Eg, medical records and publicly available information may be used to determine survival status. Subjects may withdraw their consent to the data collection of survival status.

Trial drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

8.3 End of Treatment Visit

All subjects should have an end of treatment visit as soon as possible after the last dose of trial treatment.

8.4 Safety Follow-up Visit

Subjects discontinuing treatment for any reason will have a safety follow-up visit 60 days (+14 days) after the last dose. If the subject initiates new anti-cancer therapy within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.

8.5 Post-treatment Follow-up

After the safety follow-up visit, subjects who discontinue trial treatment due to disease progression or initiation of new systemic anti-cancer treatment will move into survival follow-up (see Section 8.6).

Subjects who discontinue trial treatment for other reasons than disease progression or initiating new systemic anti-cancer therapy will move into post-treatment follow-up and will continue to have safety assessments (Section 9.3), imaging assessments (see Section 9.2 and Section 9.2.2), and quality of life assessments (see Section 9.8). First post-treatment follow-up visit should occur 4 weeks (±14 days) after the safety follow-up visit. Post-treatment follow-up visits should be performed every 4 weeks (±14 days) until progressive disease or start of new systemic anti-cancer therapy. After disease progression or start of new systemic anti-cancer therapy, subjects will move into survival follow-up (see Section 8.6).

8.6 Survival Follow-up

Survival status (ie, whether the subject is alive or dead and date of death), second primary malignancy, and new anti-cancer treatment will be collected every 60 days (±14 days) counted from the safety follow-up visit (for subjects not moving into post-treatment follow-up) and from the last post-treatment follow-up visit (for subjects in post-treatment follow-up after the safety follow-up visit). To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested by the sponsor. Subjects without a scheduled trial contact during the sponsor-defined time period will be contacted for their survival status.

If a subject at any time during trial wants to stop all trial visits, but agrees to continue in survival follow-up, next survival follow-up should be counted from date of last trial related visit. Survival follow-up continues until the subject dies or withdraws consent to survival status data collection. Data will be collected at a visit, via telephone or email contact, or via eg medical records and publicly available information (eg, national registries). Information about survival status may be given by the subject or a family member. If a randomized subject or a family member is not available, every effort should be done by the site to collect survival status information via eg medical records or publicly available information.

8.7 Lost to Follow-up

For subjects whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show “due diligence” by contacting the subject, family or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters. A subject should not be considered lost to follow-up until due diligence has been completed (at a minimum 3 documented attempts). If a randomized subject is lost to follow-up, every effort should be done by the site to collect survival status information (ie, whether the subject is alive or dead and date of death) via eg medical records or publicly available information.

8.8 Participation in Other Trials

During treatment phase, safety follow-up, and post-treatment follow-up: Subjects are allowed to participate in observational (no intervention) studies that do not require on-site attendance.

During survival follow-up: Subjects are allowed to participate in any trial.

8.9 Roll-over to Maintenance/Extension Protocol

Once the primary analysis has been conducted, trial subjects may roll over to a maintenance/extension protocol, if available, for continued treatment and/or follow-up as applicable.

9 TRIAL ASSESSMENTS

All trial assessments will be conducted as specified in the Visit Assessment Schedule (see Schedule of Activities for all treatment arms in Section 1). Procedures conducted as part of the subject's routine clinical management (eg, CT scan) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined.

9.1 Demography and Baseline Assessments

9.1.1 Demographics

Demographic details will be assessed at screening.

9.1.2 Diagnosis and Disease Status

The following should be documented as specified in Section 1:

- Date of lymphoma diagnosis
- Ann Arbor Staging at diagnosis and at screening, including constitutional symptoms (B symptoms) (see Appendix 5)
- Prior evidence of CD20 positivity

9.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of trial drug should be documented in the source documents as medical history. Medical conditions that occur after the ICF is signed and prior to first dose of trial drug should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of trial drug will be documented as an AE. See additional details in Section 10.

9.1.4 Prior and Concomitant Medication

Prior and concomitant medication given within 28 days prior to screening and throughout the trial should be documented. Once a subject moves into survival follow-up, only new anti-cancer treatment information will be collected. As relevant medical history, vaccination(s) >28 days prior to screening may also be collected.

Concomitant medications and therapies are described in Section 6.9.

9.1.5 Concomitant Procedures

Diagnostic or medical treatment procedures that have been performed or are ongoing during the trial should be documented (eg, bronchoscopy, appendectomy). The associated diagnosis related to the procedure should be documented as an AE (eg, appendicitis). The exception to this is when a diagnostic or medical treatment procedure is performed as part of routine care for a pre-existing condition that has not worsened from baseline and is documented as part of the subject's medical history.

9.1.6 Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies for NHL, including surgery, radiotherapy, chemo-radiotherapy, systemic treatment regimens, etc., from the time of the initial diagnosis until enrollment in this trial will be documented.

In addition, the best response, reason for discontinuation, dates of administration, and progression should be reported for anti-cancer therapies.

9.2 Efficacy Assessments

Efficacy assessments will be conducted at the time points specified in the Visit Assessment Schedules (see Section 1). Imaging must be performed every 6 weeks (+7 days) for the first 24 weeks, every 12 weeks (+7 days) through week 48, and then every 24 weeks (±2 weeks) thereafter. Imaging must continue until the subject experiences disease progression, begins new systemic anti-cancer therapy, withdraws from imaging assessments, withdraws from trial, or dies, whichever comes first. Imaging assessment timepoints are counted from the date of the first dose of trial treatment; the timepoints are counted by calendar days, not by dosing cycles.

9.2.1 Definition of Target and Non-Target Disease

Eligible subjects must have at least 1 measurable site of disease (see inclusion criteria, Section 5.1) for disease evaluations. Measurable sites of lymphoma are defined as lymph nodes, lymph node masses or extranodal sites. The measurement must be determined by imaging evaluation by the radiologist or equivalent. Up to 6 measurable sites will be followed as target lesions for each subject. A previously radiated lesion should only be considered target if the lesion is the only measurable lesion and metabolic progression has been documented since last dose of radiation therapy. Sites not measurable as defined above (ie, non-target lesions) will be considered assessable by objective evidence of disease (ie, radiographic imaging, physical examination, or other procedures as necessary). Examples of assessable disease may include bone marrow involvement, bone lesions, effusions, or thickening of bowel wall.

9.2.2 Evaluations

For the imaging assessments, the same radiographic modality used at screening for disease evaluation should be used throughout the trial for the response evaluations. Disease evaluation by alternative radiological imaging, physical examination, or other procedures is to be performed at the site level throughout the trial, as indicated (using the same method of assessment used to assess disease at screening).

9.2.2.1 Radiographic Assessments

An FDG-PET/CT scan (or CT/MRI and FDG-PET when PET-CT scan not available) must be performed within 30 days before Cycle 1 Day 1. For subjects with FDG-avid tumors at screening, all subsequent disease assessments will include FDG-PET using the 5-point scale (Barrington et al., 2014) (see Appendix 11). For subjects with non-avid or variably FDG-avid tumors, CT scan with IV contrast of neck/chest/abdomen/pelvis/additional known lesions will be performed. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET.

If contrast enhanced PET-CT is not available, a standalone diagnostic CT/MRI and a standard FDG-PET should be performed. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET is recommended to be performed prior to the CT with IV contrast in order not to compromise PET results. The PET-CT acquisition methodology

(eg, administration of intravenous contrast) should remain consistent between screening and subsequent assessments for any given subject.

Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast.

MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT, for subjects intolerant of CT contrast agents or based on local imaging practice. In cases where MRI is the imaging modality of choice, the MRI must be obtained at screening and at all subsequent response evaluations.

An MRI scan or CT scan of the brain is required at screening and performed during the trial only if clinically indicated.

9.2.2.2 Bone Marrow Assessment

Screening: A bone marrow biopsy is required at screening. A bone marrow biopsy obtained as routine SOC may be used instead if taken up to 42 days before first dose of trial drug.

After C1D1: A bone marrow biopsy (mandatory) and aspirate (optional) are to be collected as follows (see Table 9-1):

- For subjects with bone marrow involvement at screening who later achieve CR by imaging: a confirmatory bone marrow biopsy and aspirate (aspirate is optional) (performed at local laboratory) is required for documentation of a CR and should be done within 30 days of the initial documentation of CR (Cheson et al., 2014). Bone marrow evaluation must include morphological examination and either flow cytometry or IHC, if warranted, to confirm the presence or absence (complete remission) of lymphoma. If bone marrow involvement can be confirmed with morphology, IHC/flow cytometry may not be done if this is not part of a trial-site standard practice.

For subjects with no bone marrow involvement at screening, no bone marrow evaluation is required at the time of CR.

Table 9-1 Bone Marrow Assessments

Purpose	**Determination of bone marrow involvement**	**Confirmation of CR determined by FDG-PET**
Time point	Screening	Within 30 days of initial documentation of metabolic/radiologic CR
Sample type	Bone marrow biopsy	Mandatory bone marrow biopsy and aspirate (aspirate is optional) (unless bone marrow biopsy at screening was negative). • To confirm CR by morphological examination and, if needed, flow cytometry/IHC

CR=complete response; FDG-PET= fluorodeoxyglucose-positron emission tomography; IHC=immunohistochemistry.

9.2.3 Assessment of Disease Response and Progressive Disease

Response will be assessed according to both Lugano criteria (Appendix 12) and LYRIC (see Appendix 13).

Response assessments will be performed by the investigators at the site to make decisions for continuation of treatment.

The response assessments and disease progression will also be reviewed by an independent review committee (IRC) that will be blinded to the treatment assignment. The process for the IRC is described in a separate charter.

9.3 Clinical Safety Assessments

Safety assessments will be conducted at the time points specified in the Visit Assessment Schedules (see Section 1).

9.3.1 Physical Examination

The investigator or qualified designee will perform a full physical examination according to site SOC during the screening period and at Day 1 of any repriming cycles. Any relevant findings during screening should be reported as medical history.

Limited physical examinations should be performed on Day 1 of Cycle 1, and then as clinically indicated.

Physical examinations (complete and limited examinations) should at a minimum evaluate possible presence of palpable lymph nodes, tumor masses, enlargement of liver and spleen, and include inspection and description of the treatment injection site. Limited physical examinations may include other body systems as clinically indicated. Complete physical examinations will include evaluation of additional organ systems as per site SOC.

Report any medical conditions as an AE if they were assessed by the investigator to have been caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications. After the first dose of trial drug, report any new or worsening findings since the last assessment as AEs.

9.3.2 Neurologic Evaluation

Assessment for ICANS must be performed during the trial by the trial site staff. ICANS evaluation (based on ASTCT ICANS Consensus Grading (Lee et al., 2019)) should be performed as indicated in Section 1. During scheduled or unscheduled hospitalization, the ICANS assessment must be performed once daily. Finally, additional ICANS assessment should always be performed when clinically indicated.

ICANS is a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused immune effector cells, including T-cells. Symptoms can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema (Lee et al., 2019).

The grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of 4 other neurologic domains: level of consciousness, seizures, motor symptoms, and signs of raised intracranial pressure/cerebral edema, which may occur with or without encephalopathy. See Appendix 9 for additional details for grading and management of ICANS.

Overall ICANS grade is 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. For example: subject with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS.

A subject with an ICE score of 0 may be classified as having grade 3 ICANS if the subject is awake with global aphasia. But a subject with an ICE score of 0 may be classified as having grade 4 ICANS if the subject is unarousable.

Depressed level of consciousness should not be attributable to another cause (eg, sedating medication).

Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE, but they do not influence ICANS grading.

Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE.

9.3.3 Body Measurements

Body weight (without overcoat and shoes) will be measured and rounded to the nearest kilogram. Height (without shoes) will be measured.

9.3.4 Vital Signs

Vital signs, including temperature (oral or auricular measurements recommended), blood pressure, heart rate, oxygen saturation, and respiratory rate, should be measured with the subject in a supine or reclined position and documented. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed at the time points indicated in Section 1. On non-infusion days, vital signs may be assessed any time during the visit.

9.3.5 Electrocardiograms

ECGs will be documented digitally at the sites by using the standard 12 leads at the time points outlined in Section 1. One ECG should be performed at the timepoints outlined in Table 1-1, Table 1-2, and Table 1-4. On dosing days, the ECG should be acquired before dosing. For the ECG recordings, the subjects should be resting and in a supine or reclined position for at least 10 minutes. If any irregularity is observed or occurs during the ECGs (eg, vomiting, cough), the ECG should be repeated. ECGs should also be performed as clinically indicated at the investigator's discretion.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the printout. ECGs will be transmitted from the sites electronically to a central laboratory for measurement of the cardiac intervals and morphologic assessment by a central cardiologist. The central reading will be used for trial analysis purposes.

9.3.6 ECOG Performance Status

The ECOG PS will be assessed by the investigator at the time points indicated in Section 1. Performance status will be scored using the ECOG PS scale index (Appendix 4).

9.3.7 Constitutional Symptoms

Constitutional symptoms will be evaluated and documented at the time points indicated in Section 1. Constitutional symptoms include night sweats, weight loss >10% over 6 months, fatigue, and fever without infection.

9.4 Clinical Laboratory Assessments

Blood samples for biochemistry and hematology will be collected as indicated in the Visit Assessment Schedules (Section 1); the laboratory assessments are detailed in Table 9-2. Central and local laboratories will be used for analyses. Details on the collection, shipment of samples, and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Local laboratory values for hematology, biochemistry, and coagulation must be obtained within 3 days prior to the first trial drug administration and reviewed by the investigator prior to the first trial drug administration to ensure that the subject is still eligible. For the subsequent doses, these laboratory values must be obtained within 1 day, preferably on the day, prior to trial drug administration and reviewed by the investigator prior to trial drug administration to ensure the subject can be dosed in line with the dosing instructions as defined in the protocol (Section 6).

The investigator must document this review and record any clinically relevant changes, including dose modifications or delays, as AEs.

A third-party vendor may be used to enter local laboratory results into the clinical database. This will be done by providing the vendor with anonymized copies of the local laboratory results, if allowed by local regulations. In countries where this process is not permitted, a centrally provided anonymized requisition will be used to transfer the local laboratory values to the third-party vendor.

For unscheduled visits, blood sampling should be performed as clinically indicated. In case of symptoms considered likely to be part of CRS, additional samples for C-reactive protein, ferritin, aPTT, and INR (PT is optional) at local laboratory are recommended in addition to sending additional samples for cytokine measurement and PK to the central laboratory.

Table 9-2 Protocol-Required Safety Local Laboratory Assessments

Laboratory Assessments	Test Name			
Hematology	Hematocrit Hemoglobin Platelet count RBC count	% Reticulocytes	WBC Count with Differential[a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Biochemistry	Albumin	Blood urea nitrogen	Gamma glutamyl transferase	Phosphate
	Alanine aminotransferase	Calcium	Glucose	Potassium
	Alkaline phosphatase	Chloride	Sodium	Total and direct bilirubin
	Amylase	C-reactive protein	Lactate dehydrogenase (LDH)	Total protein
	Aspartate aminotransferase	Creatinine and eGFR calculation	Lipase	Uric acid
	Magnesium	Ferritin[c]	Triglycerides[c]	Fibrinogen[c]
Tumor lysis sample	Uric acid	Potassium	Inorganic phosphorus (phosphate)	Calcium
	Creatinine			
Coagulation factors	Prothrombin time	International normalized ratio	Activated partial thromboplastin time	
Urinalysis	Leukocyte esterase/leukocytes	Protein	Urine pregnancy	
Serology	HBsAg and HBcAb. If positive serology, PCR for HBV-DNA to be performed. HCV antibody. If positive serology, PCR for HCV RNA to be performed. Cytomegalovirus PCR and Epstein-Barr virus PCR. HIV testing at screening only if required per local health authorities or institutional standards.			
Pregnancy test	Serum beta-hCG[b]			
Additional tests	Beta2-microglobulin Immunoglobulins: IgA, IgG, and IgM Tuberculosis test (preferably interferon gamma release assay [IGRA]); For subjects where another tuberculosis test (other than IGRA) has been performed: IGRA testing is required for subjects with documented BCG vaccine and a positive tuberculosis test result[d]			

BCG=Bacillus Calmette–Guérin; CRS=cytokine release syndrome; eGFR=estimated glomerular filtration rate; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; Ig=immunoglobulin; PCR=polymerase chain reaction; RBC=red blood cell; WBC=white blood cell.

a. WBC differential in either absolutes or percents.
b. Serum beta-hCG will be collected at screening; serum or urine pregnancy tests will be conducted on Day 1 of every cycle and at other visits as indicated in Section 1.
c. At baseline and if indicated during CRS.
d. Interferon gamma release assay may be performed either locally or by the central laboratory.

9.5 Pharmacokinetics

9.5.1 Pharmacokinetic Assessments

Venous blood samples will be collected for measurement of plasma concentrations of epcoritamab as specified in the Visit Assessment Schedules (see Section 1). The 24-hour clock time of each sample will be documented.

Each plasma sample will be divided into aliquots. Samples collected for analyses of plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

Further details are included in the laboratory manual.

9.5.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of epcoritamab using validated methods.

9.6 Immunogenicity

9.6.1 Immunogenicity Assessments

Venous blood samples will be collected from all subjects for assessing the presence of ADAs against epcoritamab in serum at the time points specified in the Visit Assessment Schedules (see Section 1). These samples will be tested by the sponsor or sponsor's designee. Serum samples will be screened for antibodies binding to epcoritamab and the titer of confirmed positive samples will be documented. Neutralization characterization of ADAs will be performed. Samples collected for ADAs to epcoritamab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity. Further details are included in the laboratory manual.

9.6.2 Analytical Procedures

The detection and characterization of antibodies to epcoritamab will be performed using validated methods under the supervision of the sponsor.

9.7 Biomarker Investigations

Biomarker assessments will be performed as detailed in the Visit Assessment Schedules (see Section 1).

Biomarker investigations in this trial will include both candidate predictive biomarkers that may predict drug response to the treatment, and pharmacodynamic biomarkers in order to confirm biological activity and the proposed MOA for epcoritamab.

Biomarker assessments will focus on:

- Evaluating circulating chemokines and cytokines as a potential pharmacodynamic biomarker.
- Evaluating the composition of the peripheral T, B and NK cells as a potential pharmacodynamic and/or predictive biomarker that can identify those subjects who will respond to epcoritamab.

All biomarker assessments will be performed at laboratories designated by Genmab.

9.7.1 Biomarker Assessments in Blood Samples

Biomarker assessments will be performed using whole blood samples to investigate potential pharmacodynamic and predictive markers such as circulating cytokines or chemokines and enumeration of circulating T, B and NK cells and to explore the relationship to efficacy or MOA of epcoritamab.

Assessments will be performed at the time points outlined in Section 1 in order to enable correlation analyses with response to treatment or disease progression.

9.7.2 Sample Collections

Samples for biomarker analyses will be collected as specified in Section 1.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (eg, sample handling sheets or laboratory manual).

9.8 Patient-Reported Outcomes

All questionnaires will be completed at the time points indicated in Section 1. All questionnaires will be completed in the subject's native language using an electronic data capture (EDC) (eg, tablet). It is strongly recommended that subjects complete the questionnaires prior to any other assessments and prior to seeing the investigator. The subject should be given enough instruction, space, time, and privacy to complete the questionnaires. The trial coordinator at the site should check the questionnaires for completeness and encourage the subject to complete any missing responses. Subjects should be encouraged to report any new symptoms or changes in symptoms to the investigator. The investigator will have access to compliance and quality metrics of the submitted data.

9.8.1 FACT-Lym

The FACT-Lym (Version 4) is a 42-item questionnaire to assess the quality of life in patients with lymphoma (Appendix 14). It consists of a 27-item component focused on general quality of life and a 15-item lymphoma-specific module. The FACT-Lym has been validated for quality of life assessments in adult patients (≥18 years old) with lymphoma. The FACT-Lym elicits patient responses to general quality of life and lymphoma specific statements using a 5-point rating scale (not at all, a little, somewhat, quite a bit, very much). The items and their corresponding responses are grouped into 5 subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and Lymphoma Subscale (ie, Additional Concerns). The FACT-Lym uses a 7-day recall period, and can be self-administered. Subscale scores and total scores can be generated from the responses according to the scoring manual for this instrument, with some items reverse scored to ensure higher scores reflect better quality of life.

9.8.2 EQ-5D-3L

The EQ-5D-3L is a widely used, self-administered questionnaire designed to assess health status in adults (see Appendix 15). The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The EQ-5D-3L elicits subject responses using a 3-level rating scale with response options including "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale anchored on "100" representing the "best possible health

state" and "0" representing the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today."

The EQ-5D-3L contains six items designed to assess health status in terms of an index valuation (score) of a given or health state. The EQ-5D-3L will be used to generate health state values for the respondents. Overall EQ-5D health state values/scores range from 0 to 1, with lower scores representing lower quality of life and higher scores representing better quality of life.

9.8.3 TASQ

The TASQ is a 19-item questionnaire assessing the impact of the mode of treatment administration. The questionnaire assesses impacts across five domains using 15 items, and the remaining 4 items are analyzed individually and separately. The 5 domains include Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction (Appendix 16). The items that contribute to the domain scores using a five-point rating scale to elicit responses for each item. In order for the respective domain score to be generated, all items within that domain should have no missing value/responses. Transformed domain scores are generated according to the scoring instructions of the TASQ, with lower scores interpreted as worse and higher scores interpreted as better impacts of the mode of treatment administration. The TASQ-IV version will be used to characterize impacts of intravenous treatment administration and TASQ-SC will be used to characterize impacts of subcutaneous treatment administration.

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

10.1 Adverse Event Definitions

10.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

10.1.2 Definition of Serious Adverse Events

An SAE is defined as an adverse event that meets 1 of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- An important medical event that may not be immediately life-threatening, or result in death, or require hospitalization may be considered a serious adverse event (SAE) when, based upon appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of seriousness (death, life-threatening, hospitalization, or extended existing hospitalization, severe disability or incapacity, congenital anomaly or birth defect).
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

[1] The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[2] Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the underlying disease
- Solely due to progression of the underlying disease
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not an SAE.

10.1.3 Definition of Adverse Events of Special Interest

AESIs are defined as events, serious or nonserious, which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

AESIs are defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 10.3 and in the IB.

10.2 Adverse Event Reporting

All subjects: All AEs, whether serious or nonserious (see definitions in Section 10.1), will be documented from the first dose of trial drug until 60 days after the last dose of trial drug, subject withdrew consent, subject started new systemic anti-cancer treatment, or the subject died, whichever comes first. SAEs judged by the investigator as related to trial drug should be reported after the safety follow-up visit (>60 days after last dose). Refer to Section 10.4 for additional guidance.

Subjects who move into post-treatment follow-up: In addition to above, all AEs, whether serious or nonserious (see definitions in Section 10.1), will be reported from the safety follow-up visit (ie, 60 days after last dose) until disease progression (date of scan showing progression) or start of new systemic anti-cancer therapy (start date of new systemic anti-cancer therapy).

Medical conditions that occur after the ICF is signed and prior to the first dose of trial drug should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

The investigator will use the National Cancer Institute's CTCAE, version 5.0 (NCI-CTCAE, 2017) to describe the intensity of AEs, except for CRS (see Appendix 7), TLS, (see Appendix 8), and ICANS (see Appendix 9). Changes in intensity of an ongoing AE should be assessed at each visit or more frequently if deemed necessary and should be reported.

Note:

- Final assessment of AEs must be performed by a medically qualified person, ie, a medical doctor.
- All AEs that occur during the AE reporting period must be reported, whether or not the event is treatment related.
- All AEs should be reported, and assessment should be made at each visit (or more frequently, if necessary)

The primary mechanism for reporting an SAE to the sponsor is the EDC tool. Pregnancies must be reported using the respective paper forms via secure transmission to ensure the event is reported within 24 hours following first knowledge of the event. When the EDC tool is unavailable to report SAEs (eg, trial has ended and the database is locked), the adverse event (eg, second primary malignancy or any related SAE) should be reported using the respective paper report forms via secure transmission.

10.2.1 Pre-existing Condition

In this trial, a pre-existing condition (ie, a disorder that was present before the AE reporting period has started and noted on the medical history form) is not to be reported as an AE. If, however, a pre-existing condition worsens during the treatment period, the event must be reported as an AE.

10.2.2 Diagnosis

The diagnosis/cause of an AE should be reported rather than the symptoms of the AE. If no diagnosis is available, each sign and symptom should be reported as individual AEs.

10.2.3 Disease-Related Events/Outcomes and Other Events/Procedures Not Qualifying as Adverse Events or Serious Adverse Events

10.2.3.1 Disease Progression or Death

The following should not be reported as an AE or SAE:

- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs or SAEs.
    - That is, the terms "disease progression," "progression of disease," or "malignant disease progression" and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
        - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
        - Clinical symptoms that cannot be determined as reasonably due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study should be reported as an AE or SAE.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

10.2.3.2 Unrelated Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, a medical condition for which an unscheduled procedure was performed should be reported if it meets the definition of an AE (eg, an acute appendicitis should be reported as the AE and not the appendectomy).

10.2.4 Laboratory Test Abnormalities

Laboratory abnormalities that are considered clinically significant, eg, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment should be documented as an AE. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, acute renal insufficiency due to acute tubular necrosis). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

10.3 Adverse Events of Special Interest

The following are considered AESIs for this trial:

- CRS graded according to ASTCT consensus criteria (Lee et al., 2019), see Appendix 7
- CTLS graded according to Cairo-Bishop (Coiffier et al., 2008), see Appendix 8
- ICANS graded according to ASTCT ICANS Consensus Grading (Lee et al., 2019), see Appendix 9.

Symptoms of immune related AEs should be quickly detected and treated as early as possible to prevent irreversible effects for which careful monitoring and timely management should follow

conventional standards. Investigators and study personnel must instruct subjects to contact the site if they experience signs and symptoms of CRS or ICANS (eg, fever, chills, dizziness, lightheadedness, syncope, dyspnea, neurologic symptoms, or altered mental status) for guidance on whether the subject must visit the study site or an alternative healthcare facility with experience in treating CRS/ICANS for further CRS/ICANS assessment and/or management (see Section 9.3.2 for information on ICANS assessment). Treatments may include corticosteroids as per investigator's discretion, along with other immune suppressive agents as required. Specific immune related AEs may present as CRS described above.

10.4 Events Requiring Immediate Reporting

10.4.1 Serious Adverse Events

SAEs must be reported from the investigational site to the sponsor no later than 24 hours following a) the subject's visit at which such AE was reported, noted, or recognized; b) the principal investigator's or any investigator personnel's receipt of the test results; or c) other information at, or from which, such development was reported, noted, or recognized.

Grade 3 and grade 4 abnormal laboratory test results if deemed serious (see Section 10.1.2) must be reported as SAEs, unless associated with a concurrent SAE that serves as a unifying diagnosis.

10.4.2 Second Primary Malignancy

Second primary malignancy(ies) (not a new lesion, recurrence, or transformation to a more aggressive histology of the disease under trial), regardless of relatedness to trial treatment, must be reported as an SAE to the sponsor during the trial, including survival follow-up.

10.4.3 Overdose and Medication Errors

10.4.3.1 Epcoritamab

An overdose is defined as a subject receiving a dose of epcoritamab in excess of 10% of that specified in this protocol. All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported as protocol deviations to the sponsor within 24 hours of knowledge of the event.

Overdose and medication errors with epcoritamab must be reported, whether associated with an AE or not, within 24 hours after awareness.

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

Rescue medication to reverse the action of epcoritamab is not available. In case of overdose, medication errors, misuse and/or abuse of trial drug, subjects should be monitored closely for potential side effects of epcoritamab and receive supportive care according to local guidelines for the management of the potential side effects.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.

- Closely monitor the subject for any AE/SAE and laboratory abnormalities until epcoritamab can no longer be detected systemically.
- Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

10.4.3.2 Standard of Care Agents

Refer to the local prescribing information for details on overdose for the SOC agents.

10.4.4 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported using the pregnancy reporting paper form available in the investigator site file. Pregnant trial subjects must be withdrawn from treatment immediately, whereas male subjects may continue in the trial should pregnancy of female partners occur. In this case, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy.

Each pregnancy, occurring during the trial or for 12 months after receiving the last administration of trial treatment, must be reported to the sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to the epcoritamab must be promptly reported to sponsor or designee.

10.4.5 Timelines for Reporting

All SAEs, events of overdose and/or medication errors with epcoritamab, and pregnancy must be reported to the sponsor within 24 hours after sites' awareness.

10.5 Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The sponsor will ensure that all relevant information about SUSARs is documented and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional 8 days. The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods according to local regulations.

The investigator should be aware of local reporting regulations to the IEC/IRB. The sponsor will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations.

The sponsor will notify all investigators of the SUSAR in predefined periods according to local regulations.

10.6 Follow-Up on Adverse Events

All subjects: All AEs should be followed until they are resolved, until the safety follow-up visit or the start of new systemic anti-cancer treatment, whichever comes first. However, all SAEs (independent of causality) still ongoing after the safety follow-up visit must be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic.

Subjects who move into post-treatment follow-up: In addition to the above, all nonserious AEs whether reported before the safety follow-up or during the post-treatment follow-up, are followed until disease progression (date of scan showing progression) or start of new systemic anti-cancer therapy (start date of new anti-cancer therapy).

10.7 Warnings and Precautions

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional relevant safety information collected between IB updates for drugs administered in this trial will be communicated in the form of investigator notifications. This information will be included in the subject informed consent and should be discussed with the subject during the trial as needed.

10.8 Annual Safety Reporting by Sponsor

The sponsor will submit a single Annual Safety Report for all Genmab trial drugs in this clinical trial. The rationale for a single submission is that only 1 Genmab trial drug is used in the study.

11 STATISTICS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

Unless otherwise specified, data from the Chinese cohort will be analyzed and reported separately. A SAP pertaining specifically to the Chinese cohort may be written.

11.1 Statistical Hypotheses

The primary hypothesis of this study is that epcoritamab arm will prolong OS as compared with SOC arm in subjects with R/R DLBCL who failed a previous ASCT or are ineligible for ASCT at screening.

11.2 Sample Size Determination

Based on the published data, the median OS for the SOC arm is assumed to be approximately 10 months, and with approximately 330 OS events expected at the primary analysis, the trial has 90% power at a 1-sided alpha of 0.025 to claim significant improvement in OS when the true hazard ratio (HR) is 0.7.

With a 15-month accrual period and an additional 10-month follow-up, the total sample size needed for the study was estimated to be approximately 480 (240 per arm) subjects.

11.2.1 Sample Size Determination for the Chinese Cohort

The total sample size of Chinese subjects is 15% of the global trial population (N=480) as per regulatory requirements from China CDE. Thus the Chinese cohort will consist of approximately 72 subjects.

11.3 Populations for Analyses

11.3.1 Intent-To-Treat Population

The primary analysis population will be the ITT population, which includes all randomized subjects outside of China. The analyses will be based on the assigned treatment group per randomization.

11.3.2 Safety Population

Safety summaries will be based on the safety population, which includes all subjects who have received at least one non-zero dose of any study drug. The analyses will be based on the actually received treatment group.

11.3.3 Pharmacokinetics-Evaluable Population

The PK-evaluable population is defined as subjects who have received at least one dose of epcoritamab and at least one PK concentration value available after the start of first dose.

11.3.4 Immunogenicity-Evaluable Population

The immunogenicity-evaluable set is defined as subjects who have received at least one dose of epcoritamab and at least one immunogenicity result available after the start of first dose.

11.3.5 Biomarker-Evaluable Population

The biomarker-evaluable population is defined as subjects who have received at least one dose of study drug and at least one biomarker value available after the start of first dose.

11.4 General Analysis Specifications

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.5 Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by IRC based on Lugano criteria (Appendix 12) and LYRIC (Appendix 13), and by the investigator based on the Lugano criteria.

For the primary endpoint of OS, the primary analysis will consist of a stratified log-rank test for the comparison of the OS distribution between the 2 treatment arms. The Kaplan-Meier method will be used to estimate the distribution of overall OS for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Other time-to-event efficacy endpoints, including PFS and time to next anti-lymphoma treatment, will be analyzed in the same fashion.

Comparison between the 2 treatment groups of ORRs, CR rate, and other binary endpoints will be conducted using the stratified Cochran Mantel Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% confidence interval, and will be provided as the measure of treatment effect. Duration of response among responders will be provided descriptively using Kaplan-Meier methods, without formal statistical comparison.

Strong control of family-wise Type I error rate will be controlled at a 1-sided significance level of 0.025. If the OS null hypothesis is rejected, the secondary endpoints will be tested at 1-sided alpha of 0.025 in the following sequence: PFS per Lugano criteria based on IRC assessment, ORR per Lugano criteria based on IRC assessment, CR rate per Lugano criteria based on IRC assessment, TTNT, and MRD negativity rate. Details about this hierarchical procedure will be specified in the statistical analysis plan prior to any efficacy analysis.

11.5.1 Efficacy Analyses for the Chinese Cohort

Due to the small sample size of the Chinese cohort, no formal testing will be performed, and the focus will be on point and confidence interval estimation. Consequently, the hierarchical testing procedure will not be performed for this cohort.

11.5.2 Subgroup Analyses

11.5.2.1 Chinese subjects only

The same methods for the analyses of the primary and secondary endpoints, as well as safety endpoints described for the global trial will be used for the analysis of efficacy and safety endpoints in Chinese subjects, when applicable. For the primary efficacy endpoint of OS, the primary analysis will proceed as indicated above. Other time-to-event efficacy endpoints, including PFS and time to next anti-lymphoma treatment, will be analyzed similarly.

11.5.2.2 Comparison of Chinese subjects vs. non-Chinese subjects and Asian subjects vs. Non-Asian subjects

"Chinese subjects" refers to subjects from mainland China clinical trial sites.

Asian subjects include subjects from mainland China, Hong Kong, Japan, Taiwan, Singapore and Korea.

Efficacy analyses will be performed on the Intention-to-treat Set (ITT) for the primary efficacy endpoint of OS. To examine if the efficacy of epcoritamab treatment arm is comparable between Chinese and non-Chinese subjects, a Chinese subgroup analysis will be performed on OS. In addition, the hazard ratios of OS for treatment arm compared to SOC arm will be estimated separately for data from the Chinese and non-Chinese subjects by fitting a stratified Cox-proportional hazards regression model.

Other secondary time-to-event endpoints will be evaluated using the similar methodology specified for the primary efficacy endpoint of OS.

A similar approach will be utilized for data from the Asian and non-Asian subgroups. Statistical methods and principles used for the analysis of the global study will be applied to these sub-analyses, and will be described in detail in the SAP prior to unblinded analysis of any data. Analysis of trend consistency between Asian and Non-Asian will also be reported as supportive evidence.

Results of these comparisons will be summarized separately from the clinical study report.

11.6 Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an adverse event or serious adverse event should be completed according to Section 10. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for applicable laboratory analyte(s) at baseline and for observed values and changes from baseline at post-baseline scheduled time point(s). Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI CTCAE (version 5.0).

Electrocardiogram (ECG)

Electrocardiogram data will be summarized and listed.

Vital Signs

Descriptive statistics of baseline temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values will be summarized.

11.7 PK and Immunogenicity Analyses

Pharmacokinetic analyses will be performed on the PK-evaluable population, including all subjects treated with epcoritamab and have at least one post-baseline PK sample. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics will be used to summarize epcoritamab serum concentrations at each sampling time point and PK parameters of epcoritamab such as C_{min}.

The incidence of antibodies to epcoritamab will be summarized for the immunogenicity-evaluable population, including all subjects treated with epcoritamab and have at least one post-baseline immunogenicity sample.

11.8 Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to epcoritamab. Analyses may be performed and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods.

Selected biomarker measures will be listed, tabulated, and where appropriate, plotted.

Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints may identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with epcoritamab. Complete responders will be utilized to investigate the prognostic effect of achieving MRD negative status on OS and PFS.

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.8.1 Biomarker Analyses for the Chinese Cohort

Selected biomarker measures will be listed, tabulated, and where appropriate, plotted. MRD analysis will not be performed for the Chinese cohort.

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.9 Patient-Reported Outcomes Analyses

Compliance rates for completion of all questionnaires at each time point will be generated based on number of expected. For FACT-Lym, descriptive statistics of the actual value for item and subscale scores should be presented at each visit the PRO is administered. Summary statistics should include the number of non-missing values, mean, standard deviation, minimum, maximum,

median, and interquartile range. If the PRO has categorical item responses, the distribution of responses should be summarized using the percentages of subjects in each category. If applicable, multivariate analyses, time to improvement/deterioration analyses, proportion of subjects with improvement/deterioration using minimal clinically important difference will be specified further in SAP.

EQ-5D analyses will be specified in a supplementary SAP, and may be reported separately.

11.10 Interim Analysis

No interim analysis will be performed for the global study.

11.10.1 Interim Analysis for the Chinese Cohort

No formal interim analysis is planned for the Chinese cohort. However, the IDMC will review safety and efficacy data when all subjects have been enrolled and completed two scans (unless imaging is considered completed before second scan). At this review no formal stopping boundaries apply.

If the global study achieves primary analysis prior to the planned approximately 50 OS events for the Chinese cohort are observed, enrolment and/or follow-up of the Chinese cohort may continue until a minimum of 72 Chinese subjects have been enrolled and approximately 50 OS events have been observed. The primary efficacy and safety analyses for the Chinese cohort will be carried out after accrual of approximately 50 OS events in this cohort and once the global cohort has met the trigger for their primary analysis.

11.11 Independent Data Monitoring Committee

The global trial will institute an IDMC, consisting of clinicians and at least 1 statistician, which will function independently of all other individuals associated with the conduct of this clinical trial, including the investigators participating in the trial. The functions and responsibilities of the IDMC will be described in the IDMC charter, which will be approved by the IDMC.

The IDMC will review cumulative safety data after 40 subjects (approximately 20 in the epcoritamab arm) have been treated for at least 1 cycle, and approximately every 4 months thereafter during the trial. The IDMC will also be available on an ad hoc basis, ie, to advise and recommend actions in relation to urgent safety signals, mitigation plans, etc. or if requested by the sponsor Safety Committee.

11.11.1 Independent Data Monitoring Committee Details for the Chinese Cohort

The IDMC will also review data from the Chinese cohort in accordance with a charter.

During the trial, the IDMC will review efficacy and safety results when all subjects have been enrolled and have completed two scans (unless imaging is considered completed before second scan); in addition, they will review cumulative safety data for the Chinese cohort at timepoints aligned with IDMC review of the global cohort.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and described in the monitoring guidelines (or equivalent) and captured in a source data verification log at the site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the informed consent. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. Limited redacted source documents may be shared with the sponsor during screening for eligibility, where permitted by local regulations. This allows the sponsor's medical monitor to have sufficient information to provide guidance, answer questions, and support investigators regarding the eligibility of their patients. Signed and dated informed consent forms will be stored and archived according to local requirements. In addition, the following information, at minimum, will also be recorded in the hospital/medical source records for each subject:

- Subject's name and date of birth
- Screening number
- Trial identification
- Confirmation of eligibility of participation in the trial, including diagnosis
- Medical history
- Date of each visit
- Any assessment performed, eg, results of safety and efficacy parameters
- Concomitant medications
- Occurrence of any AEs/SAEs (including description and duration)
- Status of the subject at the end of trial
- Reason for discontinuation/withdrawal, if applicable

Any worksheets used to capture data to facilitate completion of the eCRF will become part of the subject's source documentation. In addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, PROs). Such data are considered source data, and are accessible by both the investigator and sponsor.

The author of an entry in the source should be identifiable.

Information included in the subject's hospital records may be subject to local regulations. If there is a discrepancy between local requirements and the protocol, local regulations should be followed.

12.2 Case Report Form Completion

CRF data will be transcribed into an EDC system by trial-site personnel from the source documents. Both EDC and other electronically captured trial data are transmitted in a secure manner to the sponsor within agreed upon timeframes.

Data relating to the trial must be documented and reported in English. Trial site personnel must complete the CRF as soon as possible after the data are available and preferably within 5 days. Source data and the CRFs should be available for review at the next scheduled monitoring visit.

All eCRF entries, responses to queries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel. The completed eCRF must be verified and approved by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form.

Corrections to the eCRF after data entry can be done as follows:

- Trial-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool)
- The monitor can generate a query for resolution by the trial-site personnel
- The sponsor or designee can generate a query for resolution by the trial-site personnel

12.3 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include 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 (or the sponsor's delegate), and direct transmission of clinical laboratory from a central laboratory, ECG data from the ECG vendor, and review of radiographic scans and pathology reports from the central imaging vendor (if applicable) into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided. The sponsor/contract research organization will review eCRFs for accuracy and completeness during on-site or remote monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database they will be verified for accuracy and consistency with the data sources.

12.4 Survival Data Sweeps

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the course of the study by the sponsor. For example. updated survival status may be requested prior to but not limited to an external IDMC review or final analysis. Upon sponsor notification, all subjects who do not/will not have a scheduled visit or study contact during the sponsor-defined time period will be contacted for their survival status (excluding subjects for whom a death event has been previously recorded in the eCRF).

12.5 Record Retention

In compliance with ICH GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH GCP guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the

responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a qualified and trained person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

13 ETHICS

13.1 Trial-Specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure.

This trial is being conducted to compare the safety and efficacy of epcoritamab with SOC (R-GemOx or BR) in subjects with relapsed/refractory DLBCL.

As with all clinical and PK trials, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which may cause additional discomfort, the use of IV indwelling catheters is permitted in this trial. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the PK of epcoritamab. Additionally, there are medical risks related to obtaining fresh biopsies. To mitigate such risks, fresh biopsies in this trial are performed only where it is considered feasible, without a high risk of complications for the subject, based on the discretion of the investigator.

Potential subjects will be fully informed of the risks and requirements of the trial and, during the trial, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily will be enrolled.

13.2 Regulatory Ethics Compliance

13.2.1 Regulatory and Ethical Considerations

The principles of the Declaration of Helsinki, the consolidated ICH-GCP, and applicable regulations and national law(s) (eg, 21 CFR and European regulation 536/2014 for clinical trials, 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]) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

ICH GCP E6(R2) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IEC/IRB by the investigator and reviewed and approved by the IEC/IRB before the trial is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects. In these emergency situations, the implemented deviation or change, the reasons

for it, and, if appropriate, the proposed protocol amendment(s), will be submitted to the IEC/IRB and, if required, health authorities for approval as soon as possible.

13.2.2 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

13.2.3 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), unless the amendment is issued to eliminate immediate hazards to trial subjects.

Where applicable, interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator to the IEC/IRB at intervals stipulated in its guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

13.2.4 Informed Consent

The ICFs that are used must be approved by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines, applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable laws or regulations. By signing the ICF, the subject is authorizing such access and agrees to allow their trial physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, including scans, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately documented by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

13.2.5 Privacy of Personal Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor/ sponsor's representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed Informed Consent Documents will be maintained by the investigator in strict confidence.

In relation to the collection and handling of data, including any personal data, potential risks to the subjects have been assessed and adequate technical and organizational measures are implemented to ensure a level of security appropriate to the risk. The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data is only stored on IT systems and networks that are protected against virus, malware, and unauthorized access.
- Data is backed-up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data is encrypted when at rest.
- Data has been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial and as specifically defined in the protocol.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, as detailed above. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent or description of other legal basis for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries, as specified in the ICF.

The subject has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will

be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including any other relevant agreement and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

In case of a potential data breach of the personal data, the investigator will inform the sponsor immediately and will contain the breach from spreading, where possible. Investigator and sponsor will work together to assess the risk to the individuals concerned, based on the circumstances of the case, including which data was involved, what security measures were in place (for instance, if the data was encrypted or pseudonymized), who might have accessed the data, etc.

Based on this assessment, the data breach might be reported to the relevant authorities and/or the individuals concerned. Mitigating actions will be taken to avoid this event from reoccurring.

13.2.6 Return of Research Data Related to Other Objectives to Subjects and Investigators

Biomarker research related to Other objectives (Section 3) is not conducted under standards appropriate for the return of data to subjects or investigators. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from this research. Therefore, research data related to Other objectives will not be returned to subjects or investigators, unless required by law or local regulations.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see contact information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data documented in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

14.2 Regulatory Documentation

14.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A trial may not be initiated until all local regulatory requirements are met.

14.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to assign a unique subject identification to protect the subject's identity and to permit easy identification of each subject during and after the trial. All reports and communications relating to the trial will identify subjects by the unique subject identifier and year of birth or age.

The investigator must complete a subject screening and enrollment log, which reports on all subjects who consent to be on trial, are screened, screen failed, including those who meet eligibility for inclusion in the trial. The subject identification log will be treated as confidential and will be filed by the investigator in the trial file. The screening and enrollment logs will be reviewed by the sponsor or designee for completeness.

14.4 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site

personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with local regulations, eg, in the event of a national emergency, and in agreement with the investigator, remote source data verification or source data review may be performed.

The investigator must permit the monitor access to all source data, including electronic medical records and/or documents for the purpose of verifying that the data documented in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet/talk with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, appropriate trial-site personnel will be available to provide an update on the progress of the trial at the site.

14.5 On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

14.6 Publication

All information, including but not limited to information regarding epcoritamab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data related to Other objectives (Section 3), generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of epcoritamab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be documented in a CSR generated by the sponsor and will contain eCRF data from all trial sites that participated in the trial and may include direct transmission of

clinical laboratory data into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2016; ICMJE, 2018), the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish trial site-specific data after the primary data are published. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication.

Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work (ICMJE, 2010).

14.7 Registration of Clinical Trials and Disclosure of Results

It is the responsibility of Genmab to register the trial in an appropriate public registry according to applicable regulations (eg, clinicaltrials.gov, Clinical Trials Information System [CTIS], and/or other national registries/health authority websites). A summary of the trial results is made publicly available in accordance with applicable regulatory requirements (eg, clinicaltrials.gov, CTIS).

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16 APPENDICES

Appendix 1 Calculation of Estimated Glomerular Filtration Rate

Cockcroft-Gault Formula

$$\text{eGFR (CrCl)} = \frac{(140 - \text{age}) \times \text{weight} \times F_S}{\text{serum creatinine} \times 72}$$

Units: mL/min; age (years); body weight (kg); F_S is a correction Factor for Sex: in males F_S=1, in females F_S=0.85; serum creatinine (mg/dL).

Appendix 2 New York Heart Association Criteria

The table below describes the most commonly used classification system for heart failure, the NYHA Functional Classification. It places subjects in 1 of 4 categories based on how much they are limited during physical activity.

Class	Subject Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Adapted from (Dolgin, 1994). Original source (New York Heart Association, 1964).

Appendix 3 Corticosteroid Dose Equivalents - Conversion Table

Glucocorticoid	Approximate equivalent dose (mg)
Short-acting	
Cortisone (PO)	500
Hydrocortisone (IV or PO)	400
Intermediate-acting	
Methylprednisolone (IV or PO)	80
Prednisolone (PO)	100
Prednisone (IV or PO)	100
Triamcinolone (IV)	80
Long-acting	
Betamethasone (IV)	15
Dexamethasone (IV or PO)	15

Appendix 4 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken et al., 1982)

Appendix 5 Ann Arbor Staging Classification for Hodgkin and Non-Hodgkin Lymphoma

Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)[1]
Stage II	Involvement of 2 or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extra-lymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may include the spleen (IIIS) or limited, contiguous extra-lymphatic organ or site (IIIE), or both (IIIES)
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

1. The designation "E" generally refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

All cases are subclassified to indicate the absence (A) or presence (B) of the systemic ("B") symptoms of significant unexplained fever (> 38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

Clinical stage refers to the extent of disease determined by diagnostic tests following a single diagnostic biopsy. If a second biopsy of any kind is obtained, even if negative, the term pathologic stage is used.

Adapted from (Carbone et al., 1971) and (Lister et al., 1989).

Appendix 6 Revised International Prognostic Index for Newly Diagnosed Subjects With Diffuse Large B-Cell Lymphoma

The R-IPI applies to subjects with newly diagnosed DLBCL who are receiving R-CHOP as first-line therapy.

Revised International Prognostic Index Scoring

IPI Risk Factor	
Ann Arbor Stage III or IV Age >60 years Lactate dehydrogenase level elevated ECOG performance score ≥2 More than 1 extranodal site	
R-IPI Risk Group	**Number of IPI Risk Factors**
Very good	0
Good	1 or 2
Poor	3 to 5

ECOG=Eastern Cooperative Oncology Group; R-IPI = Revised International Prognostic Index
Source: (Sehn, 2007)

Appendix 7 Grading and Management of Cytokine Release Syndrome

Harmonized definitions and grading criteria for CRS, per the American Society for Transplantation and Cellular Therapy (ASTCT), formerly American Society for Blood and Marrow Transplantation, (ASBMT), are presented below.

Grading of Cytokine Release Syndrome

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever[1]	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C	Death due to CRS in which another cause is not the principle factor leading to this outcome
With hypotension[2]	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)	
And/or hypoxia[2]	None	Requiring low-flow (≤6 L/minute) nasal cannula or blow-by	Requiring high-flow (>6 L/minute) nasal cannula, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure ventilation[3] (eg, CPAP, BiPAP, intubation and mechanical ventilation)	

BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; IV=intravenous.

Note: organ toxicities or constitutional symptoms associated with CRS may be graded according to CTCAE but they do not influence CRS grading.

1. Fever is defined as temperature ≥38.0°C not attributable to any other cause, with or without constitutional symptoms (eg, myalgia, arthralgia, malaise). In subjects who have CRS receiving antipyretics, anticytokine therapy, and/or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. Both systolic blood pressure and mean arterial pressure are acceptable for blood pressure measurement. No specific limits are required, but hypotension should be determined on a case-by-case basis, accounting for age and the subject's individual baseline, ie, a blood pressure that is below the normal expected for an individual in a given environment.
3. Intubation of a subject without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not by definition grade 4 CRS.

Source: (Lee et al., 2019)

CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT)[a] Guidelines

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
Grade 1	Hold epcoritamab until resolution of CRS. If CRS is combined with MAS/HLH, permanently discontinue epcoritamab. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Supportive care per institutional standard of care (antipyretics and IV hydration). Closely monitor neurologic status.	Consider anticytokine therapy[e] in certain cases, eg, advanced age, high tumor burden, circulating tumor cells, fever refractory to antipyretics. Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra).	Dexamethasone 10-20 mg per day (or equivalent) may be initiated. Note: In case of concurrent ICANS, initiation of corticosteroids are highly recommended (see ICANS guidelines in Appendix 9).
Grade 2	Hold epcoritamab until resolution of CRS. If CRS is combined with MAS/HLH, permanently discontinue epcoritamab. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Continuous cardiac telemetry and pulse oximetry as	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra).	Consider dexamethasone 10-20 mg per day (or equivalent). Note: In case of concurrent ICANS, initiation of corticosteroids is highly recommended (see ICANS guidelines in Appendix 9).

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	indicated. IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids. Supplemental oxygen as indicated.		
Grade 3	Hold epcoritamab until resolution of CRS. If CRS is combined with MAS/HLH, permanently discontinue epcoritamab. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Vasopressor support and/or supplemental oxygen as indicated.[c] Consider cardiac echocardiogram. IV fluids as indicated.	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra).	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.
Grade 4	Permanently discontinue epcoritamab. In-person evaluation by medical professional, ideally at site or center with experience managing CRS.	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy.	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Mechanical ventilation and/or renal replacement therapy may be required. Vasopressor support as indicated.[c] IV fluids as indicated. Consider and assess for development of MAS/HLH[d], including monitoring of fibrinogen and triglyceride levels.	Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra).	
MAS/HLH	If MAS/HLH is combined with CRS, permanently discontinue epcoritamab. Intensive supportive care is essential because of frequent life-threatening, severe manifestations at presentation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation.	First-line treatment: Includes IL-6R-blockade with tocilizumab, unless tocilizumab was already administered for the management of CRS. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed). Second-line treatment: Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg SC. In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100-200 mg SC twice daily (every 12 hours), or higher doses (up to 8 mg/kg/day) in severe cases, should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment. In case of rapidly progressing clinical course with ongoing CRS, anakinra should be administered as first-line treatment.	

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; IV=intravenous(ly); MAS/HLH=macrophage activation syndrome/hemophagocytic lymphohistiocytosis; SC=subcutaneous(ly).

a. Source: (Lee et al., 2019)
b. Refer to tocilizumab, siltuximab, or anakinra local prescribing information for product details.
c. If indicated, high-dose vasopressors in table below.
d. Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids (Lehmberg et al., 2015).
e. Suggested anticytokine dosing:
   - Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period.
   - Siltuximab 11 mg/kg IV over 1 hour, one time only.
   - Anakinra 100 mg SC once/day.
     - In more severe CRS cases, especially if combined with MAS/HLH and/or neurotoxicity, anakinra 100-200 mg twice daily (every 12 hours) SC should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment.

High-Dose Vasopressors (all Doses are Required for ≥3 Hours)[a]

Pressor	Dose
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on vasopressin	Vasopressin 1 norepinephrine equivalent of ≥10 µg/min[b]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min[b]

a. Source: (Lee et al., 2014)
b. Vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) / 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) / 10]

Appendix 8 Classification and Management of Laboratory and Clinical Tumor Lysis Syndrome

In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities (ie, hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter or 6 mg/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <4.5 mg/dL (1.12 mmol/liter)[1]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[2]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value >1.5 times the upper limit of the age appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

Note: In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

1. The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 – albumin in grams per deciliter).
2. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome. Data about acute kidney injury are from (Levin et al., 2007).

Source: (Howard et al., 2011)

Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine[1]	1.5 × ULN	> 1.5–3.0 × ULN	> 3.0-6.0 × ULN	> 6.0 × ULN	Death
Cardiac arrhythmia	Intervention not indicated	Nonurgent medical intervention needed	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	
Seizure	None	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	

ADL=activities of daily living; CHF=congestive heart failure; ULN=upper limit of normal.
1. If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.
Source: (Coiffier et al., 2008)

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise re-check in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis syndrome. • At the discretion of the investigator, consider re-checking TLS laboratory values prior to hospitalization. If stable or decreased, and still within normal limits (WNL), hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be re-checked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis syndrome.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Re-check potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.

Abnormality	Management Recommendations
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	• Administer rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis syndrome.
Creatinine	
Increase ≥25% from baseline	• Start or increase rate of IV fluids. • Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 – 2 hours STAT.

Appendix 9 ASTCT ICANS Consensus Grading and Management for Adults

Management Guidelines for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Based on ASTCT Guidelines

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
Grade 1 • ICE score[a] 7-9 and/or depressed level of consciousness[b] but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema • Confusion: mild disorientation • Encephalopathy: mild limiting of ADLs • Dysphasia: not impairing ability to communicate	• Hold epcoritamab until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS • Aspiration precautions • Recommend brain imaging and EEG per institutional guidelines	No concurrent CRS: Anticytokine therapy not indicated Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Appendix 7.) • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone, 10 mg IV every 12 hours
Grade 2 • ICE score[a] 3-6 and/or depressed level of consciousness[b] but awakens to voice • No seizures, motor weakness, or raised ICP/cerebral edema • Somnolence-moderate, limiting instrumental ADLs • Confusion: moderate disorientation	• Hold epcoritamab until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Appendix 7.) • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours)	Dexamethasone at 10-20 mg IV every 12 hours

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
• Encephalopathy: limiting instrumental ADLs • Dysphasia: moderate impairing ability to communicate spontaneously	• Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication	depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
Grade 3 • ICE score[a] 0-2 and/or depressed level of consciousness[b] but awakens to tactile stimulus • And clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention • No motor weakness • Focal/local edema on neuroimaging • Somnolence-obtundation or stupor • Confusion: severe disorientation • Encephalopathy: limiting self-care ADLs • Dysphasia: severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Permanently discontinue epcoritamab. • Management in monitored care or intensive care unit. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication • Levetiracetam/non-sedating antiepileptics if subject has seizures	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Appendix 7.) • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day.
Grade 4 • ICE score[a] 0 and patient is unarousable or requires	• Permanently discontinue epcoritamab. • Management in monitored care or intensive care unit.	No concurrent CRS: Anticytokine therapy not indicated.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
vigorous or repetitive tactile stimuli to arouse or stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness[c] such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging[d]; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation	• Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication • Levetiracetam/non-sedating antiepileptics if subject has seizures • Mechanical ventilation may be required • Consider imaging of spine for focal motor weakness • Lower intracranial pressure (ICP) by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema • Aggressive management of ICP with institutional standard of care	Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Appendix 7.) • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	mg/day
Grade 5 (Fatal) Death due to ICANS in which another cause is not the principal factor leading to this outcome.			

ADLs=activities of daily living; ASBMT=American Society for Bone Marrow Transplant; CRS=cytokine release syndrome; EEG=electroencephalogram; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; IV=intravenous; MRI=magnetic resonance imaging; SC=subcutaneous.
Note: ICANS grade is determined by the most severe domain event not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.
a. A subject with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
Sources: (Lee et al., 2019; Neelapu, 2019)

Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; eg, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. Grade 5 is considered to be fatal.
N/A indicates not applicable.
a. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0.
Source: (Lee et al., 2019)

Immune Effector Cell-Associated Encephalopathy Assessment Tool

Cognitive Domain	Task	Points	ICE scoring:
Orientation	Orientation to year Orientation to month Orientation to city Orientation to hospital	1 1 1 1	**10:** No impairment **7-9** Grade 1 ICANS **3-6** Grade 2 ICANS **0-2:** Grade 3 ICANS **0** due to subject unarousable and unable to perform ICE assessment: Grade 4 ICANS
Naming	Ability to name 3 common objects (eg, point to clock, pen, button)	3	
Following commands	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1	
Writing	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1	
Attention	Ability to count backwards from 100 by 10	1	
Maximum ICE score		**10**	

Appendix 10 Definition of Reproductive Potential and Contraception

In this trial, subjects are considered to have reproductive potential unless they are postmenopausal or permanently sterile.

- A postmenopausal state is defined as no menses in subjects >45 years of age for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 12 months after receiving the last administration of trial treatment.

Female subjects of reproductive potential must agree to use adequate contraception during and for 12 months after the last administration of trial treatment. Adequate contraception is defined as highly effective methods of contraception (see table below). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.

Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[4]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[4]:
  - Oral
  - Injectable
  - Implantable[1]
- Intrauterine device[1]
- Intrauterine hormone-releasing system[1, 4]
- Bilateral tubal occlusion[1]
- Vasectomized partner[1, 2]
- Sexual abstinence[3]

[1] Contraception methods that, in the context of this guidance, are considered to have low user dependency.

[2] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

[4] Other methods of contraception should be considered if the gastrointestinal disorder is likely to be prolonged.

Table adapted from "Recommendations related to contraception and pregnancy testing in clinical trials." Advisory non-binding guidance represented at the CTFG meeting in Rome 2014 (CTFG, 2014).

Appendix 11 PET Positivity Evaluation Using the Five-Point Scale

Evaluation of FDG-PET positivity should be performed according to the 5-point scale (5-PS) adopted from the Deauville criteria described in (Barrington et al., 2014).

Five-Point Scale (5-PS)
At each time point where FDG-PET scans are submitted, visualized disease will be qualitatively assessed and evaluated according to the 5-PS to determine uptake (with mediastinum and liver cutoffs).

Score	Definition
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma
NE	Not evaluable

Notes:
- "X" will represent any area of uptake identified by the radiologist or equivalent as not likely to be related to lymphoma. At screening, these areas could be due to prior radiation therapy, surgery, or evidence of a benign radiographic abnormality. These will have no impact on the response.
- At the End of Treatment assessment time point and at Follow-up (if applicable), X will represent any new areas of FDG-uptake unlikely due to lymphoma. These will have no impact on the response.
- Diffusely increased bone marrow, even if greater than liver uptake, is likely not due to lymphoma and rather, due to cytokine effect.

Appendix 12 Lugano Response Criteria for Malignant Lymphoma

Target and Non-target Lesions

Target lesions should consist of up to six of the largest dominant nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters and should preferably be from different body regions representative of the subject's overall disease burden, including mediastinal and retroperitoneal disease, where applicable. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative target lesions. At baseline, measurable extranodal lesions should be greater than 10 mm in LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease (PD). The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Lugano Response Criteria for Malignant Lymphoma

Response	Site	PET-CT–Based Response	CT-Based Response
Complete Response		**Complete metabolic response**	**Complete radiologic response** *(all of the following)*
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[1] with or without a residual mass on 5PS[2] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response		**Partial metabolic response**	**Partial remission** *(all of the following)*
	Lymph nodes and extralymphatic sites	Score 4 or 5[2] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Response	Site	PET-CT–Based Response	CT-Based Response
No response or Stable disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5[2] with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
	Individual target nodes/nodal masses, extranodal lesions	Score 4 or 5[2] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: – LDi >1.5 cm and – Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir – 0.5 cm for lesions ≤2 cm – 1.0 cm for lesions ≤2 cm In the setting of splenomegaly (>13 cm), the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Response	Site	PET-CT–Based Response	CT-Based Response

5PS=5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

1. A score of 3 in many subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

   - Measured dominant (target) lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters.
     - Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
     - Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation.
   - Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured.
     - These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.
   - In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

2. PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Source: (Cheson et al., 2014)

Appendix 13 Lymphoma Response to Immunomodulatory Therapy Criteria

Clinical studies have shown that cancer immunotherapies may result in early apparent radiographic progression (including the appearance of new lesions), followed by a delayed response. As this initial increase in tumor size might be caused by immune-cell infiltration in the setting of a T-cell response, this progression may not be indicative of true disease progression and is therefore called "pseudoprogression" (Wolchok et al., 2009).

The association of epcoritamab (GEN3013; DuoBody®-CD3xCD20) with pseudoprogression is currently unknown, but its mechanism of action implies that pseudoprogression is to be expected.

The current Lugano response assessment criteria (Cheson et al., 2014) does not take pseudoprogression into account, and there is a significant risk of premature discontinuation of a potentially efficacious immunomodulatory drug following the observation of an atypical response. Atypical responses are characterized either by the early progression of existing lesions, later followed by response, or by the development of new lesions, with or without tumor shrinkage elsewhere.

LYRIC is a modification of the Lugano response assessment criteria, which has been adapted to immune-based therapies, and it implements a new, mitigating response category: the "indeterminate response" (IR) designation (Cheson et al., 2016). This IR designation was introduced to potentially identify "atypical response" cases until confirmed as flare/pseudoprogression or true PD by either biopsy or subsequent imaging. LYRIC and the Lugano criteria will be assessed in this study.

Indeterminate Response (IR) Category

A subject who shows PD according Lugano Classification (Cheson et al., 2016) will be considered to have IR in 1 or more of the 3 following circumstances.

IR (1): Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥50% of up to 6 target lesions in the first 12 weeks of therapy, without clinical deterioration.

IR (2): Appearance of new lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (SPD <50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.

IR (3): Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

Screening assessment: At screening, the FDG-PET/CT and diagnostic CT or MRI scans should be read according to Lugano Classification, as detailed in Appendix 12.

On-treatment assessment: Response at on-treatment time points should be read according to Lugano Classification for patients showing CR, PR, and SD. For patients showing PD according to Lugano Classification, further evaluation should be performed to see if the subject can be considered to have IR (according to LYRIC).

	CR	PR	SD	PD
LYRIC	Same as Lugano Classification	Same as Lugano Classification	Same as Lugano Classification	As with Lugano with the following exceptions: **IR Categories:** **IR (1):** ≥50% increase in SPD in first 12 weeks of therapy **IR (2):** <50% increase in SPD with New lesion(s), or ≥50% increase of 1 lesion or set of lesions at any time during treatment **IR (3):** Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

It is possible that, at a single time point, a subject could fulfill criteria for both IR(1) or IR(2) and IR(3): for example there could be a new FDG-avid lesion in the absence of overall progression (IR[2]), and, at the same time, increase in FDG uptake of a separate lesion (IR[3]). In such cases, the designation of IR(1) or IR (2) should take priority (eg IR[2] in the above example).

Follow-up of Indeterminate Response (IR) Category

In subjects categorized as having any of the IR types, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the subject should be considered to have true PD with the following considerations:

Follow-up IR(1): In case of IR(1), comparison should be made between the first IR(1) and the current SPD

- The IR(1) will become PD if;

SPD increase by ≥10% from first IR1 AND

an increase of ≥5 mm (in either dimension) of ≥1 lesion for lesions ≤2 cm and ≥10 mm for lesions >2 cm, to be consistent with Lugano

Follow-up IR(2): In case of IR(2), the new or growing lesion(s) should be added to the target lesion(s), up to a total of no more than 6 total lesions

- The IR(2) will become PD if;

≥50% increase in SPD (newly defined set of target lesions) from nadir value

Follow-up IR(3): The IR(3) will become PD if lesion with increased FDG uptake also shows size increase.

When “IR” changes to “PD” at a subsequent time point, the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR.

Appendix 14 FACT-Lym

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)
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FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEIJ1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEIJ6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEIJ7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEIJ4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

Appendix 15 EQ-5D-3L



Health Questionnaire

English version for the UK

(Validated for Ireland)

Sample

UK (English) © 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain / Discomfort

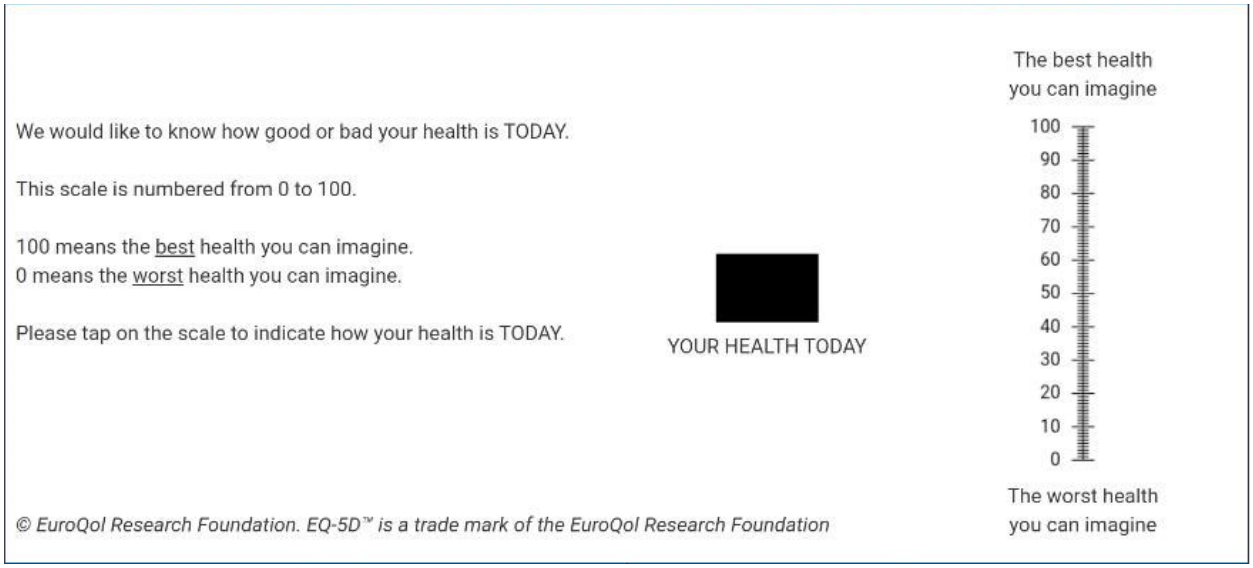
I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety / Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

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Sample


We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Please tap on the scale to indicate how your health is TODAY.
YOUR HEALTH TODAY
The best health you can imagine
100
90
80
70
60
50
40
30
20
10
0
The worst health you can imagine
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Appendix 16 TASQ

Treatment Administration Satisfaction Questionnaire
(TASQ-IV and TASQ-SC)

TASQ-IV

Instructions: Please complete the following questions based on your most recent treatment prior to this study. Your most recent treatment was given through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion. Please answer the questions **based on your most recent IV infusion treatment prior to this study**.

1. Thinking about the IV infusion, how satisfied or dissatisfied are you with the IV infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the IV infusion, how do you rate the pain, swelling, or redness you experienced at the site of the IV infusion?

None	Mild	Moderate	Severe	Very Severe

3. Thinking about the IV infusion, how do you rate the pain you experience with the IV infusion process?

None	Mild	Moderate	Severe	Very Severe

4. Thinking about the IV infusion, are the side effects of the IV infusion as you expected?

Much better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

5. Before you receive the IV infusion do you feel anxious about having the infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. When you receive the IV infusion do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much

7. When you receive the IV infusion do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

8. Thinking about IV infusion, how confident are you that the IV infusion is treating your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

9. When you receive the IV treatment do you feel restricted by the IV infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

10. Thinking about the IV infusion, how convenient is it for you to get your IV infusion?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

11. Thinking about the IV infusion, how do you feel about the amount of time it takes to get your IV infusion?

Too short	Just right	Too long	

12. Thinking about the IV infusion, do you feel that the length of time to get your IV infusion was as you expected?

Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

13. Thinking about the IV infusion, how bothered are you by the amount of time it takes to get the infusion?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

14. How much does the IV infusion:

a) Interfere with your usual or daily activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much

b) Limit your daily activities?

Never	Rarely	Sometimes	Most of the time	Always

15. Because of the length of time to apply the IV infusion do you feel that you have lost or gained time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

16. When you receive the IV infusion treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

17. Does the IV infusion impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

18. Thinking about the IV infusion, if given the option, which would you prefer (both options treat your disease in the same way)? Please check one.

- ☐ Prefer intravenous (IV) infusion given through a port or a thin plastic tube and a needle into your vein (IV drip). This treatment option usually takes 1.5 to 3 hours.
- ☐ Prefer subcutaneous (SC) injection, applied with a device on the thigh or abdomen (or belly).
- ☐ No preference for treatment option.

19. Thinking about the IV infusion, would you recommend the way you received the treatment (IV infusion) to another patient?

Definitely yes	Probably yes	I don’t know	Probably not	Definitely not

TASQ-SC

Instructions: Please complete the following questions based on your **epcoritamab** treatment. Your **epcoritamab** was given through an injection placed onto your, thigh or abdomen (or belly) area, called a subcutaneous or SC injection. Please answer the questions **based on your most recent epcoritamab SC injection**.

1. Thinking about the SC injection, how satisfied or dissatisfied are you with the SC - injection?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the SC injection, how do you rate the pain, swelling, or redness you experienced at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

3. Thinking about the SC injection, how do you rate the pain you experience with the SC injection process?

None	Mild	Moderate	Severe	Very Severe

4. Thinking about the SC injection, are the side effects of the SC injection as you expected?

Much better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

5. Before you receive the SC injection do you feel anxious about having the injection?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. When you receive the SC injection do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much

7. When you receive the SC injection do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

8. Thinking about SC injection, how confident are you that the SC injection is treating your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

9. When you receive the SC treatment do you feel restricted by the SC injection?

Not at all	A little bit	Somewhat	Quite a bit	Very much

10. Thinking about the SC injection, how convenient is it for you to get your SC injection?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

11. Thinking about the SC injection, how do you feel about the amount of time it takes to get your SC injection?

Too short	Just right	Too long	

12. Thinking about the SC injection, do you feel that the length of time to get your SC injection was as you expected?

Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

13. Thinking about the SC injection, how bothered are you by the amount of time it takes to get the injection?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

14. How much does the SC injection:

a) Interfere with your usual or daily activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much

b) Limit your daily activities?

Never	Rarely	Sometimes	Most of the time	Always

15. Because of the length of time to apply the SC injection do you feel that you have lost or gained time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

16. When you receive the SC injection treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

17. Does the SC injection impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

18. Thinking about the SC treatment, if given the option, which would you prefer (both options treat your disease in the same way)? Please check one.

- ☐ Prefer intravenous (IV) infusion given through a port or a thin plastic tube and a needle into your vein (IV drip). This treatment option usually takes 1.5 to 3 hours.
- ☐ Prefer subcutaneous (SC) injection, applied with an injection on the thigh or abdomen (or belly).
- ☐ No preference for treatment option.

19. Thinking about the SC treatment, would you recommend the way you received the treatment (SC injection) to another patient?

Definitely yes Probably yes I don’t know Probably not Definitely not

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure that they are fully informed regarding the trial drug, the conduct of the trial, and the obligations of confidentiality.

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the EU.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(dd-Mmm-yyyy)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(dd-Mmm-yyyy)

Note: If the address or telephone number of the investigator changes during the course of the trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.