CLINICAL TRIAL PROTOCOL

Protocol Title	Phase 1/2 Study of PRO1160 in Patients with Metastatic Renal Cell Carcinoma (RCC), Metastatic or Relapsed Nasopharyngeal Carcinoma (NPC), or Advanced (Stage III or IV) Non-Hodgkin Lymphoma (NHL)		
Protocol Number	PRO1160-001 (GCT1160-01)***		
Compound	PRO1160 (GEN1160)***		
Brief Title	Phase 1/2 Trial of PRO1160 in Relapsed or Refractory NHL (PRO1160-001)		
Trial Phase	1/2		
Sponsor Name	Genmab*		
Regulatory Agency Identifier Numbers	**NCT No.**	NCT05721222	
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Protocol Approver**	**Name**	PPD , MD, PhD	
	Title	PPD	
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** This protocol was approved via electronic signature on the approval page appended to the document.
*** Following the acquisition of ProfoundBio US Co. by Genmab US, Inc. on 21 May 2024, the compound PRO1160 is now also referred to as GEN1160. Similarly, protocol PRO1160-001 is now known as GCT1160-01. Both compound and protocol codes are interchangeable.

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SPONSOR INFORMATION PAGE

Sponsor information for countries in the European Union/European Economic Area, the United Kingdom, Georgia, Moldova, and Serbia	Genmab A/S Carl Jacobsens Vej 30 2500 Valby Denmark
Sponsor information for China	Genmab (Suzhou) Co., Ltd. Unit 101, 102, Building 1, Zone A, Phase III Bio-Pharmaceutical Industrial Park No. 1, Xinze Road Suzhou, China Pilot Free Trade Zone
Sponsor information for all other countries	Genmab US, Inc. 777 Scudders Mill Rd Plainsboro, New Jersey 08536 United States of America

The sponsor contact information page will be provided separately, listing the study responsible medical director, as well as the CRO(s), laboratory(ies) (names and addresses), and other technical/medical services used. Additional contact information may be found in the study-specific manuals (eg, IMP Manual, Laboratory Manual).

INVESTIGATOR AGREEMENT

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

I agree to comply with the ICH Tripartite Guideline on GCP, the principles in the Declaration of Helsinki, and applicable national or regional regulations/guidelines.

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

Principal (Site) Investigator:	
Name (typed or printed):	
Institution and Address:	
Telephone Number:	

Signature: _____ Date: _____
(DD Mmm YYYY)

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the European Union, where applicable.

Coordinating Investigator (where required):	
Name (typed or printed):	
Institution and Address:	

Signature: _____ Date: _____
(DD Mmm YYYY)

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

Completed and signed forms will be filed separately from the protocol.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
CCI	[redacted]
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE(s)	adverse event(s)
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AMP	auxiliary medicinal product
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-last}}$	area under the curve up to the last quantifiable time-point
β-hCG	beta human chorionic gonadotropin
B-NHL	B-cell non-Hodgkin lymphoma
BOR	best overall response
BSA	body surface area
bsAb(s)	bispecific monoclonal antibody(-ies)
BTKi	Bruton's tyrosine kinase inhibitor
C1q	complement component 1q
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell
ccRCC	clear cell renal cell carcinoma
C_{max}	maximum concentration
CBC	complete blood count
CDX	cell line-derived xenograft
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CMP	comprehensive metabolic panel
CNS	central nervous system

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor(s)
CR	complete response
CRF	case report form
CRO	contract research organization
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CTLS	clinical tumor lysis syndrome
CV	coefficient of variation
CVP	cyclophosphamide, vincristine, and prednisone
CYP3A	cytochrome P450 3A
CYP1A2	cytochrome P450 1A2
DAS	DLT-evaluable analysis set
DCR	disease control rate
DILI	drug-induced liver injury
DL(s)	dose level(s)
DLBCL	diffuse large B-cell lymphoma
DLT(s)	dose-limiting toxicity(-ies)
DNA	deoxyribonucleic acid
DOR	duration of objective response
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment

Abbreviation	Definition
EU	European Union
EZH2	enhancer of zeste homolog 2
FAS	full analysis set
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Indicator
FSH	follicle-stimulating hormone
CCI	[redacted]
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GELF	Groupe d'Etude des Lymphomes Folliculaires
GI	gastrointestinal
GLP	Good Laboratory Practice
GVHD	graft versus host disease
HBV	Hepatitis B virus
HDT/ASCT	high-dose therapy and autologous stem cell therapy
Hgb	hemoglobin
HIV	human immunodeficiency virus
HIPPA	Health Insurance Portability and Accountability Act
HL	Hodgkin lymphoma
HNSCC	head and neck squamous cell carcinoma
CCI	[redacted]
HSCT	hematopoietic stem cell transplant
hyper-CVAD	cyclophosphamide, vincristine sulphate, doxorubicin, hydrochloride, and dexamethasone
IAS	immunogenicity analysis set
IB	investigator's brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitors
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IIV	interindividual variability
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR(s)	infusion-related reaction(s)
IT	information technology
IV	intravenous
J-GCP	Japanese Ministerial Ordinance on Good Clinical Practice for Drugs
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LDi	longest diameter
LLOQ	lower limit of quantification
LTLS	laboratory tumor lysis syndrome
LVEF	left ventricular ejection fraction
mAb(s)	monoclonal antibody(-ies)
MAD	maximum administered dose
MCL	mantle cell lymphoma
MM	multiple myeloma
MOA	mechanism of action
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition

Abbreviation	Definition
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NPC	nasopharyngeal carcinoma
NOS	not otherwise specified
NTD	non-tolerated dose
ORR	objective response rate
OS	overall survival
PAS	pharmacokinetic analysis set
PCR	polymerase chain reaction
PD	progressive disease
PD(L)-1	programmed cell death (ligand) 1
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per oral (by mouth)
POD24	progression of disease within 24 months of diagnosis
PPD(s)	perpendicular diameter(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
Q3W	every 3 weeks
QA	quality assurance
QTcF	QT corrected for heart rate using Fridericia's formula
R-	rituximab
RANK	receptor activator of nuclear factor kappa-B ligand
RCC	renal cell carcinoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab, dexamethasone, high-dose cytarabine (Ara-C), and cisplatin
R-GDP	rituximab, gemcitabine, cisplatin, and dexamethasone

Abbreviation	Definition
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
RES	response evaluable analysis set
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
RT	radiation therapy
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SARS-CoV-2	coronavirus disease
SAS	safety analysis set
SD	stable disease
SDi	smallest diameter
SMC	Safety Monitoring Committee
SOC	standard of care
SOP(s)	standard operating procedure(s)
SUSAR	suspected unexpected serious adverse reaction
TAb	total antibody
TCL	T-cell lymphoma
TEAE(s)	treatment-emergent adverse event(s)
TKI(s)	tyrosine kinase inhibitor(s)
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TTR	time-to-response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VR-CAP	bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Protocol Title:	Phase 1/2 Study of PRO1160 in Patients with Metastatic Renal Cell Carcinoma (RCC), Metastatic or Relapsed Nasopharyngeal Carcinoma (NPC), or Advanced (Stage III or IV) Non-Hodgkin Lymphoma (NHL)
Brief Title:	Phase 1/2 Study of PRO1160 in Relapsed or Refractory NHL (PRO1160-001)
Trial Phase:	1/2
Indication:	NHL, RCC, NPC

Rationale:

The aim of this Phase 1/2 trial is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of GEN1160 in participants with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), metastatic or relapsed renal cell carcinoma (RCC), and nasopharyngeal carcinoma (NPC). In the Dose Escalation, dose-liming toxicities (DLTs) will be monitored to determine the expansion dose, and if reached, the maximum tolerated dose (MTD) for both R/R NHL and RCC/NPC, respectively. It is expected that the safety and efficacy profile of GEN1160 may differ in NHL versus RCC/NPC. Therefore, dose escalations will be conducted in 2 disease cohorts. The totality of the data including safety, immunogenicity, PK, pharmacodynamics, and preliminary efficacy will be evaluated to guide further development for Expansion.

Following the Dose Escalation, in the Expansion Part A, the clinical activity of GEN1160 at the expansion dose identified among R/R NHL participants will be evaluated in R/R diffuse large B-cell lymphoma (DLBCL) participants, as well as safety, tolerability, PK, pharmacodynamics, and biomarkers. After an interim analysis of the efficacy and safety data for Expansion Part A, the Expansion Part B will be initiated and the clinical activity of GEN1160 will be further evaluated in participants with R/R DLBCL using CCI [redacted].

Objectives and Endpoints (Dose Escalation):

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of GEN1160 • Identify the maximum tolerated dose (MTD), if reached, and the recommended Phase 2 dose (RP2D) of GEN1160	• Type, incidence, severity, and seriousness of adverse events (AEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of dose-limiting toxicities (DLTs)

Secondary	

• Assess the antitumor activity of GEN1160
• Assess the pharmacokinetics (PK) and immunogenicity of GEN1160
	• Objective response rate (ORR):
	  ○ Renal cell carcinoma (RCC) and nasopharyngeal carcinoma (NPC): per the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
	  ○ Non-Hodgkin lymphoma (NHL): per the Lugano Classification 2014
	• Disease control rate (DCR)
	• Progression-free survival (PFS)
	• Duration of objective response (DOR)
	• PK parameters (such as maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the curve up to the last quantifiable time-point [$AUC_{0\text{-}last}$], etc) for GEN1160-related analytes
	• Incidence of antidrug antibodies (ADA)

Objectives and Endpoints (Expansion [Part A and Part B] - DLBCL):	
Objectives	**Endpoints**
Primary	
• Assess the preliminary antitumor activity of GEN1160	• ORR based on the Lugano criteria as assessed by investigators
Secondary	
• Evaluate antitumor activity and efficacy of GEN1160	• Complete response (CR) rate • DOR • Time-to-response (TTR) • PFS • OS
• Evaluate safety and immunogenicity of GEN1160	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, electrocardiograms (ECGs) • Immunogenicity: Anti-GEN1160 antibodies
• Characterize the PK and immunogenicity of GEN1160	• PK parameters (such as maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the curve up to the last quantifiable time-point [$AUC_{0\text{-}last}$], etc) for GEN1160-related analytes • Incidence of ADAs

Trial Design and Duration:

This is a Phase 1/2, open-label, multicenter, trial to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity and efficacy of GEN1160 (PRO1160) in participants with R/R NHL or metastatic or relapsed RCC and NPC.

The trial will be conducted in 3 parts: Dose Escalation (Phase 1), Expansion Part A (Phase 2), and Expansion Part B (Phase 2).

Each part will consist of the following:

1. Screening period (up to 28 days prior to Cycle 1 Day 1 for Dose Escalation and up to 21 days prior to Cycle 1 Day 1 for Expansion Part A and Part B),
2. Treatment period (Cycle 1 Day 1 until GEN1160 treatment discontinuation),
3. Follow-up period (ie, 30-day safety follow-up from the last dose of GEN1160 or before the initiation of a new anticancer treatment, whichever comes first; post-treatment follow-up for participants who discontinue GEN1160 prior to disease progression; and survival follow-up by telephone contact or retrospective chart review until death, lost to follow-up, or the End of Trial, whichever comes first).

In Dose Escalation, there are 2 disease cohorts: R/R NHL and RCC/NPC. GEN1160 will be administered as an intravenous (IV) infusion in 21-day cycles on Day 1 of each treatment cycle until one of the GEN1160 treatment discontinuation criteria has been met. Assessments will be performed as detailed in the Schedule of Activities. In Dose Escalation, GEN1160 will be evaluated in R/R NHL and RCC/NPC using the "3 + 3" design. At each dose level (DL), DLTs will be assessed in the first treatment cycle plus 7 days, ie, a DLT evaluation period of 28 days from Cycle 1 Day 1. The MTD of each disease cohort, if reached, along with the maximum administered dose (MAD) and expansion dose of each disease cohort will be determined based on the totality of the data of each disease cohort.

In Expansion Part A, the antitumor activity of GEN1160 will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers in R/R DLBCL. GEN1160 will be administered at the expansion dose identified from the Dose Escalation as an IV infusion in 21-day cycles on Day 1 of each treatment cycle until one of the GEN1160 treatment discontinuation criteria has been met. Assessments will be performed as detailed in the Schedule of Activities. To confirm the antitumor activity of GEN1160, participants with DLBCL who received GEN1160 at the expansion dose during the Dose Escalation phase of the trial may be counted toward the 10-participant lead-in analysis prior to starting Expansion Part B.

In Expansion Part B, the clinical activity of GEN1160 will be evaluated in R/R DLBCL at 2 dosing regimens in 21-day cycles as follows:

- DLBCL-DL1: GEN1160 administered at the expansion dose every 3 weeks (Q3W) on Day 1 of each treatment cycle; or
- DLBCL-DL2: CCI [redacted]

Number of Participants:

Given the exploratory nature of the trial, no formal sample size calculation will be done for the Dose Escalation part, but approximately 50 participants are expected to be enrolled. Similarly, no formal sample size for Expansion Parts A and B, but up to 60 participants are expected to be enrolled across both parts.

Summary of Key Eligibility Criteria (Dose Escalation):

Key Inclusion Criteria:

- All participants must have pathologically confirmed diagnosis of one of the following tumor types:
  - Metastatic RCC, including clear cell renal cell carcinoma (ccRCC) or papillary RCC
  - Metastatic or relapsed Epstein Barr virus (EBV)-associated NPC not amenable to further local therapies (EBV association may have been determined by testing on tumor tissue or peripheral blood)
  - Advanced (Stage III or IV) NHL, including DLBCL, follicular lymphoma (FL) requiring systemic therapy, and mantle cell lymphoma (MCL)
- Participants must have relapsed or refractory disease following prior systemic therapies known to confer clinical benefit. At minimum, participants should have received the following therapies (unless deemed ineligible, refused by the participant, or not available in the region):
  - Participants with RCC must have received a minimum of one prior treatment regimen, and have received a tyrosine kinase inhibitor (TKI) and a programmed cell death (ligand) ([PD[L)])-1 inhibitor
  - Participants with EBV-associated NPC must have received a minimum of one prior treatment regimen, which must include a platinum-based chemotherapy regimen
  - Participants with DLBCL must have received a minimum of 2 prior treatment regimens, including a multi-agent chemoimmunotherapy regimen given with curative intent (eg, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]), and participants must have received intensive salvage chemotherapy with hematopoietic stem cell transplant (HSCT) if considered eligible by the investigator
  - Participants with FL must have received a minimum of 2 prior treatment regimens, which must include a multi-agent chemoimmunotherapy regimen including an anti-CD20 agent
  - Participants with MCL must have received a minimum of 2 prior treatment regimens, which must include a multi-agent chemoimmunotherapy regimen including an anti-CD20 agent
- Measurable disease at baseline:
  - Participants with RCC and NPC must have measurable disease as defined per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer et al., 2009)
  - Participants with NHL must have measurable disease as defined by the Lugano Classification (Cheson et al., 2014)
  - Participants must be willing to provide a pre-treatment tumor specimen (archival or new tissue biopsy samples). If a new tissue biopsy is required, procedures more invasive than a core biopsy or significant risk procedures for which the procedure-associated absolute risk of mortality or major morbidity in the participant's clinical setting and specific institution is 2% or higher, should not be utilized.

Key Exclusion Criteria:

- Prior treatment with anti-CD70 directed therapy
- Prior therapy with an antibody-drug conjugate (ADC) with a topoisomerase 1 inhibitor payload
- Prior allogeneic HSCT. Participants with prior autologous HSCT must have completed the procedure at least 100 days prior to the first dose of study drug.
- Known active central nervous system metastases, including carcinomatous meningitis. Participants with brain metastases may participate provided the metastases have been treated and are stable for at least 4 weeks prior to the first dose of study drug, they have no new or enlarging brain metastases and have discontinued corticosteroids prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Participants with a history of brain metastases, suspected new brain metastases, or a diagnosis of RCC should have a magnetic resonance imaging (MRI) of the brain at screening.

Summary of Key Eligibility Criteria (Expansion):

Key Inclusion Criteria:

- Has pathological diagnosis of DLBCL, not otherwise specified (NOS) as defined by the World Health Organization (WHO) 2016 classification including both de novo or histologically transformed.
- Has relapsed or refractory disease with no available standard therapy or is not a candidate for available standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1160 may be beneficial. Participant must have received at least 2 systemic treatment regimens including CD20-containing chemoimmunotherapy.
- Has measurable disease according to the 2014 Lugano criteria (Cheson et al., 2014):
  - A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan demonstrating positive lesion compatible with computed tomography (CT)- or MRI-defined anatomical tumor sites; AND
  - A CT scan (or MRI) with involvement of ≥ 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).
- Has ECOG performance status of 0, 1, or 2
- Has a fresh biopsy (if clinically feasible and not considered as a high-risk procedure) or an archival tumor biopsy and submit to the central laboratory for CD70 assay
- Has acceptable laboratory test results as follows:

Parameter	Result
a. Creatinine clearance (CrCl) or serum creatinine	CrCl ≥ 50 mL/min estimated by Cockcroft-Gault *OR* Serum creatinine ≤ 1.5×upper limit of normal (ULN)
b. Serum ALT	≤ 2.5×ULN
c. Serum AST	≤ 2.5×ULN
d. Total bilirubin	≤ 1.5×ULN (participant with Gilbert's syndrome or hepatic involvement with lymphoma may be included if total bilirubin is ≤ 3×ULN and direct bilirubin is ≤ 1.5×ULN)
e. Hemoglobin	≥ 8 g/dL or ≥ 5 mmol/L
f. Absolute neutrophil count	≥ 1.0×10^9/L (≥ 1000/μL)
g. Platelet count	≥ 75×10^9/L (≥ 75,000/μL) *Note: In presence of bone marrow involvement, platelets ≥ 50×10^9/L (≥ 50,000/μL)*
h. Coagulation status: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤ 1.5×ULN, unless receiving anticoagulation

Key Exclusion Criteria:

- Primary central nervous system (CNS) tumor or known CNS involvement.
- Has been exposed to any of the following prior therapies within the specified timeframes:
  - Received prior investigational CD70-targeting therapy, eg, CD70-directed chimeric antigen receptor T-cell (CAR-T) therapy, anti-CD70 monoclonal antibody (mAb), CD3 x CD70 bispecific monoclonal antibody (bsAb), or CD70 antibody-drug conjugate.
  - Autologous stem cell transplant within 60 days prior to the first dose of GEN1160.
  - Allogeneic stem cell transplant within 90 days prior to the first dose of GEN1160.

- Chemotherapy within 2 weeks or major surgery within 4 weeks of the first dose of GEN1160.
- Curative radiotherapy within 4 weeks or palliative radiotherapy within 2 weeks prior to the first dose of GEN1160.
- Treatment with an investigational drug within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of GEN1160 or currently receiving any other investigational agents.
- Prior treatment with live, attenuated vaccines within 30 days prior to the first dose of GEN1160. 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 nonauthorized coronavirus disease (SARS-CoV-2) vaccinations are not allowed.
- Receiving immunosuppressive drugs or systemic corticosteroids such as prednisone at doses > 25 mg daily or its equivalent within 14 days prior to the first dose of GEN1160.

- History of symptomatic autoimmune disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [eg, Wegener's granulomatosis]).
- Has clinically significant cardiac disease, including:
  - Myocardial infarction within 6 months prior to the first dose of GEN1160, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III or IV), cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0 Grade 2 or higher), or clinically significant ECG abnormalities.
  - Screening 12-lead ECG showing a baseline QT interval as corrected by QTcF > 480 msec.
  - Echocardiogram (ECHO) or multigated acquisition (MUGA) scan with left ventricular ejection fraction (LVEF) < 45%.
- Has clinically significant toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade 1 or lower. Note, participants with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the trial.
- Active graft versus host disease (GVHD) requiring immune suppression regardless of grade.

Trial Treatment:

Investigational Medicinal Product(s):

GEN1160 (administered IV) will be tested at DLs ranging from CCI (Dose Escalation) and at selected expansion dose in 21-days cycles.

Statistics:

The trial is exploratory, and no formal statistical hypothesis is defined.

No formal sample size calculation will be done for the Dose Escalation part, but approximately 50 participants are expected to be enrolled.

No formal sample size calculation will be done for Expansion Part A. A sample of 10 participants per cohort per DL is deemed enough to provide a preliminary assessment of efficacy and is in line with recommendations in the Food and Drug Administration's (FDA) Guidance on expansion cohorts.

No formal sample size calculation will be done for Expansion Part B, but assuming a 40% ORR the exact 95% confidence interval (CI) is (21%, 61%) with 25 participants in an Expansion part. When assuming a 30% ORR the exact 95% CI is (12%, 49%).

Dose Escalation:

The primary endpoints for the Dose Escalation part of the trial are the incidence and severity of AEs and the incidence of DLTs. The incidence of DLTs will be presented for the DLT-Evaluable Analysis Set using descriptive statistics. The incidence of AEs will be based on the Safety Analysis Set (SAS)

All secondary efficacy analyses (ORR, DCR, PFS, DOR) will be based on the Full Analysis Set (FAS). Analyses of PK and immunogenicity will be based on the Pharmacokinetic Analysis Set (PAS) and the Immunogenicity Analysis Set (IAS) respectively.

Expansion Parts A and B:

The primary endpoint for the Expansion part of the trial is ORR based on the Lugano criteria as assessed by the investigators. The ORR is defined as the proportion of participants with a best overall response of CR or PR. All other categories, including not evaluable, are considered non-response.

Best overall response will be summarized in conjunction with the ORR. The estimated ORR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented using the FAS and the Response Evaluable Set (RES).

All secondary efficacy analyses (CRR, DOR, TTR, PFS, and OS) will be based on the FAS and RES. The PAS will be used for PK analyses, the IAS will be used for immunogenicity analyses, and the SAS will be used for the incidence of AEs.

1.2 Schema

Figure 1: Trial Schema



1.3 Schedule of Activities

Table 1:	Schedule of Activities – Dose Escalation (R/R NHL, RCC, and NPC)
Table 2:	Schedule of Pharmacokinetics, ADA, and Biomarker Assessments Dose Escalation (R/R NHL, RCC, and NPC)
Table 3:	Schedule of Activities – Expansion Part A (R/R DLBCL)
Table 4:	Schedule of Pharmacokinetics, ADA, and Biomarker Assessments for Expansion Part A (R/R DLBCL)

Table 1: Schedule of Activities – Dose Escalation (R/R NHL, RCC, and NPC)

Category	Day	Screening/Baseline		Enrollment	Every 21-day cycle			EOT	Follow-up
		D 28-1	D –14 to -1	Within 7D of 1st dose	D1	D8	D15	30 days after last dose[a]	Every 12 wks[b]
	Visit window				± 2D[c]	± 2D	± 2D	+7D	± 1 wk
Screening/Baseline and Safety Assessments	Informed consent	X		Submit eligibility confirmation to sponsor prior to treatment					
	Inclusion/Exclusion, medical history	X			X[d]				
	Submission of tumor-related sample (archived or new tissue biopsy) to central lab[e]	X							
	Brain MRI[f]	X							
	Physical examination including weight[g]		X		X[h]			X	
	Height		X[i]						
	Vital signs	X			X[j]			X	
	Electrocardiogram	X[k]			X[k]			X[k]	
	ECOG performance status		X		X[h]			X	
	CBC with differential[l]		X		X[h,m]	X[n]	X[n]	X	
	PT/PTT/INR		X					X	
	Comprehensive metabolic panel[o]		X		X[h,m]	X[n]	X[n]	X	
	Fasting glucose	X							
	Hgb A1c	X							
	Fasting lipid panel[p]	X							
	Amylase and lipase		X						
	Hepatitis B and C screening[q]	X							
	HIV	X							

Category	Day	Screening/Baseline		Enrollment	Every 21-day cycle			EOT	Follow-up
		D 28-1	D –14 to -1	Within 7D of 1st dose	D1	D8	D15	30 days after last dose[a]	Every 12 wks[b]
	Visit window				± 2D[c]	± 2D	± 2D	+7D	± 1 wk
	Pregnancy test for participants of reproductive potential		X[r]		X[s]			X[s]	
	Urinalysis and UPC ratio		X[t]		X[h,m,t]			X[t]	
	Concomitant medications	Related to study procedures[u]			Collect from D1 predose through 30 days post last dose				
	Adverse event collection								X[v]
Treatment	**GEN1160 study drug administration**				X[c]				
PK/Immunogenicity/ CCI	Blood sample collection				See Table 2 for additional sample collection visits and details.				
Response Assessment	PET or CT and/or MRI of chest, abdomen, pelvis (and neck if documented or suspected involvement in this region)	X					X[w]	X[x]	X[y]
	RCC participants – Bone scan or FDG-PET	X					X[w]	X[x]	X[y]
	NHL participants – FDG-PET- CT	X					X[w]	X[x]	X[y]
	NHL participants – B symptom assessment	X					X[w]	X[x]	X[y]
	NHL participants – BMA and biopsy (optional)[z]		X[z]				X[aa]	X[x,aa]	
Survival Status, Collection of First Subsequent Therapy									X[bb]

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; CBC=complete blood count; CMP=comprehensive metabolic panel; CR=complete response; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FDG=fluorodeoxyglucose; HCV=hepatitis C virus; HDL=high-density lipoprotein; Hgb=hemoglobin; HIV=human immunodeficiency virus; LDL=low-density lipoprotein; MRI=magnetic resonance imaging; NHL=non-Hodgkin lymphoma; PCR=polymerase chain reaction; PET=positron emission tomography; PK=pharmacokinetics; PR=partial response; PT/PTT/INR=prothrombin time/partial thromboplastin time/international normalized ratio; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; R/R=relapsed/refractory; UPC=urine protein/creatinine ratio; wk(s)=week(s).

[a] EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30 days following the participant's last study treatment to ensure that no changes in AE profile have occurred.

[b] Every 12 weeks from the most recent prior response evaluation until documentation of disease progression or initiation of a new therapy, and every 12 weeks from the prior follow-up visit thereafter.

[c] The ± 2-day window does not apply to Cycle 1 infusion.

[d] Day 1 review of Inclusion/Exclusion criteria, medical history required during Cycle 1 only.

[e] The most recent available archived tumor specimen collected within 24 months is requested for all enrolled participants. If an archived biopsy sample is not available a new tissue biopsy is required.

[f] Only for participants with a history of brain metastases, those with suspected new brain metastases, or a diagnosis of RCC.

[g] Physical examinations should include assessments of the following: abdomen, extremities, head, heart, lungs, neck, and neurological system and weight.

[h] Assessments should be performed prior to dosing on Day 1 of each cycle. Not required in Cycle 1 if baseline was assessed within 3 days prior to first dose of study drug. Predose CBC and CMP window are within 72 hours of study drug administration on Day 1 of each cycle.

[i] Height measured in the last 12 months may be used.

[j] Vital signs should be recorded predose, post-dose (within 10 minutes after completion of GEN1160 administration), approximately 30 minutes post-dose, and approximately 2 hours post-dose (during Cycles 1-3). Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature.

[k] Routine safety ECGs required at screening, Cycles 1 and 3, and EOT as described in Section 8.3.4.

[l] The CBC with differential is to include, but is not limited to, the following tests: red blood cell count, white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), absolute neutrophil count, platelet count, Hgb, and hematocrit. CBC should be collected at least weekly during dose delays.

[m] The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

[n] Day 8 and Day 15 CBC with differential and CMP are required during Cycles 1 through 4.

[o] The CMP is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, carbon dioxide, creatinine, chloride, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, and total bilirubin. CMP should be collected at least weekly during dose delays.

[p] Fasting lipid panel is to include the following tests: total cholesterol, LDL, HDL, and triglycerides.

[q] Includes hepatitis B surface antigen (HBsAg) and hepatitis C virus ribonucleic acid (RNA) test by PCR.

[r] A serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline.

[s] After the first cycle, pregnancy tests may be performed up to 7 days prior to Day 1 of each cycle and at EOT. Postbaseline urine pregnancy tests are acceptable, and any positives should be confirmed by serum testing.

[t] Reflexive microscopy required for abnormal urine analysis.

[u] From the time of informed consent.

[v] If ongoing after the EOT visit, certain nonserious AEs of interest should continue to be assessed per the follow-up schedule until resolution, return to baseline, or study closure.

[w] Tumor assessment according to RECIST Version 1.1 for RCC/NPC and Lugano Classification 2014 for NHL. Tumor assessments will be performed every 6 weeks (±4 days) for the first 12 months after the first dose of GEN1160 and then every 12 weeks (±8 days) thereafter. FDG-PET may be performed every 12 weeks after the week 12 assessment for RCC/NPC. FDG PET-CT scans are required for NHL at screening and all timepoint assessments. Objective responses (CR or PR) will be confirmed with repeat scans 4 to 6 weeks after the first documentation of response.

[x] EOT response assessment not required if done within 4 weeks prior to EOT visit.

[y] Follow-up response assessments not required after documented disease progression or initiation of first subsequent therapy.

[z] Collection of bone marrow aspirate and biopsy is optional.

[aa] Only required if positive at baseline and to confirm CR; should be obtained within 2 weeks after documentation of response.

[bb] Until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Table 2: Schedule of Pharmacokinetics, ADA, and Biomarker Assessments Dose Escalation (R/R NHL, RCC, and NPC)

Cycle	Cycle Day	Time	Window	Relative Time	Plasma for PK	Serum for ADA	CCI
Screening	-28 to 1	N/A	N/A	N/A			
Cycles 1 and 3	Day 1	Predose	Within 4 h	START of infusion	X	X	
		End of infusion	Within 15 min	END of infusion	X		
		2 h	± 30 min	END of infusion	X		
	Day 2	24 h	± 8 h	END of infusion	X		
	Day 4	72 h	± 24 h	END of infusion	X		
	Day 8	168 h	± 48 h	END of infusion	X		
	Day 15	336 h	± 48 h	END of infusion	X	X	
Cycles 2, 4, and every 4th cycle thereafter (eg, Cycle 8, 12, etc)	Day 1	Predose	Within 4 h	START of infusion	X	X	
		End of infusion	Within 15 min	END of infusion	X		
End of Treatment					X	X	

Abbreviations: ADA=antidrug antibody; EOT=end of treatment; CCI h=hour(s); min=minute(s); N/A=not available; PK=pharmacokinetic(s).

[a] Samples for assessments of pharmacodynamic endpoints will be collected predose for each cycle and at EOT.

[b] CCI

[c] For participants discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

Table 3: Schedule of Activities – Expansion Part A (R/R DLBCL)

Trial Period	Screening Period[a] (D -21 to -1)	Treatment Period[b]							Post-Treatment			UNS[c]	Notes
Cycle/Visit		C1			C2-C8			C9+	EOT[d]	SFU[e]	SvFU[f]		
Cycle Day		D1	D8	D15	D1	D8	D15	D1					
Visit Window (days)		-	±1d	±1d	±3d	±3d	±3d	±3d	-	+14d	±14d		
General and Safety Assessments													
Informed consent	X												Consent must occur prior to trial related activity
Demographics	X												
Medical history	X												Any medical condition prior to first dose of trial drug(s)
Eligibility criteria	X												
Diagnosis and disease status and subtype	X												
ECOG PS	X	X			X			X	X			X	
Prior anticancer therapy and surgery	X												
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X		X	Any medications or vaccine and blood transfusions received within 28 days prior to the first dose of GEN1160 must be documented. Additionally, any SARS-CoV-2 vaccines and seasonal flu vaccinations received within 3 months prior to the first dose of GEN1160 must be documented.
Concomitant procedures	X	X	X	X	X	X	X	X	X	X		X	
Physical examination (including lymph node assessment)	X	X			X			X	X			X	
MRI/CT scan (brain)	X*											X	X*: If CNS involvement is suspected, screening MRI/CT scan (brain) is required. If CNS involvement is not suspected, no need to conduct MRI/CT scan (brain).
Constitutional symptoms (B symptoms)	X	X			X			X	X			X	

Trial Period	Screening Period[a] (D -21 to -1)	Treatment Period[b]							Post-Treatment			UNS[c]	Notes
Cycle/Visit		C1			C2-C8			C9+	EOT[d]	SFU[e]	SvFU[f]		
Cycle Day		D1	D8	D15	D1	D8	D15	D1					
Visit Window (days)		-	±1d	±1d	±3d	±3d	±3d	±3d	-	+14d	±14d		
Adverse events	X*	X	X	X	X	X	X	X	X	X	X#	X	X*: AEs related to protocol-mandated procedures X#: No monitoring required, but if investigator becomes aware of a treatment-related SAE, it must be reported.
Height	X												
Body Weight	X	X			X			X	X			X	
Vital signs	X	X	X	X	X	X	X	X	X			X	Conduct before and 1-hour post (±30 min) GEN1160 administration
ECGs (12-lead ECG)	X	X	X	X	X			X	X			X	Triplicate ECGs are to be collected at screening, before each administration of GEN1160 at the specified timepoints
Echocardiogram (and/or MUGA)	X								X			X	
Subsequent anticancer therapy										X	X	X	
Survival status											X		
Local Laboratory Assessments													
Serology testing	X											X	Includes CMV, HBV, HCV, and HIV.
Pregnancy test (serum/urine)	X*	X			X			X	X			X	Only required for female participants of reproductive potential (Section 10.3). Testing required on a dosing day should be performed within 24 hours of dosing and results must be available before dosing. X*: Serum pregnancy test required. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm.
Hematology	X	X	X	X	X	X	X	X	X			X	CBC should be collected at least twice weekly to monitor cytopenia and count recovery when TEAE of cytopenia is the cause for dose delay.
Biochemistry	X	X	X	X	X	X	X	X	X			X	CMP should be collected at least weekly to monitor transaminase elevations and recovery when TEAE of ALT/AST elevation is the cause for dose delay.

Trial Period	Screening Period[a] (D -21 to -1)	Treatment Period[b]							Post-Treatment			UNS[c]	Notes
Cycle/Visit		C1			C2-C8			C9+	EOT[d]	SFU[e]	SvFU[f]		
Cycle Day		D1	D8	D15	D1	D8	D15	D1					
Visit Window (days)		-	±1d	±1d	±3d	±3d	±3d	±3d	-	+14d	±14d		
TLS panel		X										X	24-, 48-, and 72-hours post-dose on Cycle 1 Day 1 (±6 hours at each time point); for subsequent doses, apply same time point monitoring to high-risk participants or as clinically indicated.
Immunoglobulins (IgA, IgE, IgG, IgM)	X	X			X			X	X			X	
β2-microglobulin	X											X	
Coagulation	X	X	X	X	X	X	X	X	X			X	
Urinalysis	X	X			X			X	X			X	
Central Laboratory Assessments													
CCI		Refer to Table 4											
GEN1160 PK													
GEN1160 ADA													
CCI													
Disease Assessments													
Bone marrow aspirate and/or bone marrow biopsy	X*											X	X*: Required at screening for participants with known bone marrow involvement or whose disease is suspected to have bone marrow involvement and to confirm CR or suspected CR; otherwise as clinically indicated.
FDG PET-CT scan	X	Week 6 ± 7 days, Week 12 ± 7 days, Week 18 ± 7 days, Week 24 ± 7 days, Week 30 ± 7 days, Week 36 ± 7 days, Week 42 ± 7 days, Week 48 ± 7 days, and then every 6 months (± 14 days) until participant has disease progression, starts new anticancer therapy, withdraws from trial, or dies, whichever comes first.										X	Combined PET-CT requested. Imaging assessment time points are counted from the date of the first dose of GEN1160; the time points are counted by calendar days, not by treatment cycles.
Response assessment		Week 6 ± 7 days, Week 12 ± 7 days, Week 18 ± 7 days, Week 24 ± 7 days, Week 30 ± 7 days, Week 36 ± 7 days, Week 42 ± 7 days, Week 48 ± 7 days, and then every 6 months (± 14 days) until participant has disease progression, starts new anticancer therapy, withdraws from trial, or dies, whichever comes first.										X	Response assessment time points are counted from the date of the first dose of GEN1160; the time points are counted by calendar days, not by treatment cycles.

Trial Period	Screening Period[a] (D -21 to -1)	Treatment Period[b]							Post-Treatment			UNS[c]	Notes
Cycle/Visit		C1			C2-C8			C9+	EOT[d]	SFU[e]	SvFU[f]		
Cycle Day		D1	D8	D15	D1	D8	D15	D1					
Visit Window (days)		-	±1d	±1d	±3d	±3d	±3d	±3d	-	+14d	±14d		
Trial Treatment Administration													
Premedication		X											
GEN1160		X			X			X					

Abbreviations: ADA=anti-drug antibody; AE=adverse event; C=cycle; CNS=central nervous system; CT=computed tomography; D/d=day(s); ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EOT=end of treatment; FDG=fluorodeoxyglucose; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; Ig=immunoglobulin; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; PET=positron emission tomography; PK=pharmacokinetic(s); SAE=serious adverse event; SARS-CoV-2=coronavirus disease; SFU=safety follow-up; SvFU=survival follow-up; SOC=standard of care; TLS=tumor lysis syndrome; UNS=unscheduled.

[a] The screening period must be completed within 21 days of signing informed consent. Assessments performed as SOC (imaging, bone marrow sample, ECHO/MUGA) prior to the participant signing of informed consent may be submitted as screening assessment, if assessment is performed within 42 days of Cycle 1 Day 1.

[b] During the treatment period, all assessments are to be performed prior to trial drug administration, unless otherwise indicated. For Cycle 1 Day 1, physical examination may be performed within 1 day prior to GEN1160 dosing. Local laboratory values for biochemistry, hematology, and coagulation must be obtained at screening and repeated 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 participant is still eligible.

[c] Unscheduled visits may be performed at any time at investigator's discretion. Assessments should be performed as clinically indicated.

[d] The EOT assessments should be performed as soon as possible after the last dose of GEN1160 and no more than 7 days from the decision to end the GEN1160 treatment. It should be performed before the start of subsequent therapy.

[e] The SFU visit should be performed 30 days (+14 days) after last dose of GEN1160 or prior to the initiation of new anticancer therapy, whichever comes first (see Section 7.1.2 for further details). The EOT and SFU may be performed concurrently if the timing occurs within the designated window for each visit.

[f] Survival status will be assessed every 12 weeks (±14 days), beginning from the day the participant receives the last dose of GEN1160 and continuing until the participant dies, withdraws consents for survival status follow-up, or the trial ends, whichever occurs first (see Section 7.1.4 for further details).

Table 4: Schedule of Pharmacokinetics, ADA, and Biomarker Assessments for Expansion Part A (R/R DLBCL)

Cycle	Cycle Day	Time	Window	Relative Time	Plasma for PK	Serum for ADA	CCI
Screening	-21 to 1	N/A	N/A	N/A			
Cycles 1 and 3	Day 1	Predose	Within 4 h	START of infusion	X	X	
		End of infusion	Within 15 min	END of infusion	X		
		2 h	± 30 min	END of infusion	X		
	Day 2	24 h	± 8 h	END of infusion	X[c]		
	Day 4	72 h	± 24 h	END of infusion	X[c]		
	Day 8	168 h	± 48 h	END of infusion	X[c]		
	Day 15	336 h	± 48 h	END of infusion	X[c]	X	
Cycles 2, 4, and every 4th cycle thereafter (eg, Cycle 8, 12, etc)	Day 1	Predose	Within 4 h	START of infusion	X	X	
		End of infusion	Within 15 min	END of infusion	X		
End of Treatment					X	X	

Abbreviations: ADA=antidrug antibody; ECG=electrocardiogram(s); EOT=end of treatment; CCI h=hour(s); min=minute(s); N/A=not available; PK=pharmacokinetic(s).

[a] Samples for assessments of pharmacodynamic endpoints will be collected predose for each cycle and at EOT.

[b] CCI

[c] Only collect for the first 5 participants.

[d] For participants discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

2 INTRODUCTION

2.1 Background

2.1.1 Disease Background

2.1.1.1 Non-Hodgkin Lymphoma

Diffuse Large B-cell Lymphoma

Standard first-line therapy for advanced diffuse large B-cell lymphoma (DLBCL) is chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which induced an estimated 2-year progression-free survival (PFS) of 70.2% in a recent study and durable remissions in a substantial fraction of patients (Tilly et al., 2022).

Second-line chemoimmunotherapy followed by high-dose therapy and autologous stem cell therapy (HDT/ASCT) is recommended for patients who qualify based on medical fitness and tumor chemosensitivity. Typical second-line therapy agents include rituximab, ifosfamide, carboplatin, and etoposide (R-ICE), rituximab, dexamethasone, high dose cytarabine (Ara-C), and cisplatin (R-DHAP), and rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP), which have similar outcomes in randomized studies (Crump et al., 2014; Gisselbrecht et al., 2012), with response rates of 44% to 64%. Patients who attain a partial response (PR) or complete response (CR) can proceed to HDT/ASCT, which induces long-term PFS in approximately half of the treated patients.

Patients who have no response to frontline R-CHOP or who relapse within 12 months of treatment have a particularly poor prognosis and may be candidates for chimeric antigen receptor (CAR)-T cell therapy. In a Phase 3 trial, patients were randomized to receive either axicabtagene ciloleucel (YESCARTA USPI, 2022) or standard second-line chemotherapy and HDT/ASCT. The 18-month event-free survival (EFS) rate was 41.5% versus 17.0% for axicabtagene ciloleucel and the standard therapy arm, respectively (YESCARTA USPI, 2022).

CAR-T cell therapy may also be an option for patients with no response to second-line therapy. In patients with relapsed or refractory DLBCL, axicabtagene ciloleucel and tisagenlecleucel produced response rates of 72% and 50%, respectively in single-arm studies. CAR-T cell therapies carry serious risks including cytokine release syndrome, neurologic toxicities, infections, prolonged cytopenias, and secondary malignancies, and are available only through restricted Risk Evaluation and Mitigation Strategy (REMS) programs (KYMRIAH USPI, 2022; YESCARTA USPI, 2022).

Treatment options for patients who are not candidates for HDT/ASCT (either due to physical fitness or lack of treatment response) are limited.

Polatuzumab vedotin is a CD79-targeted antibody-drug conjugate (ADC) for the treatment of patients with DLBCL who have received at least 2 prior therapies, based on a Phase 2 randomized study. Polatuzumab vedotin induced a response rate of 45%, with 64% of responses maintained at 6 months. Treatment-related toxicities included peripheral neuropathy, infusion-related reactions (IRRs), myelosuppression, and serious and opportunistic infections (POLIVY USPI, 2020).

Additional treatment options approved for patients who have received at least 2 prior therapies include: tafasatimab plus lenalidomide, loncastuximab tesirine, selinexor, and bispecific antibodies (epcoritamab, glofitamab). Response rate (and median duration of response) were 39% (21.7 months) for tafasatimab plus lenalidomide, 48.3% (10.3 months) for loncastuximab tesirine, 39% (less than 6 months) for selinexor, 61% (15.6 months) for epcoritamab, and 56% (18.4 months) for glofitamab (COLUMVI USPI, 2023; EPKINLY USPI, 2023; MONJUVI USPI, 2021; XPOVIO USPI, 2022; ZYNLONTA USPI, 2021).

Mantle Cell Lymphoma

Advanced mantle cell lymphoma (MCL) has a clinical course that varies from indolent to aggressive but is generally considered incurable with current therapies. Less aggressive first-line treatments for indolent disease include chemoimmunotherapy with R-bendamustine, R-CHOP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP), and R-lenalidomide. More aggressive first-line treatments include intense chemotherapy such as cyclophosphamide, vincristine sulphate, doxorubicin, hydrochloride, and dexamethasone (hyper-CVAD), alternating R-CHOP and R-DHAP, and the Nordic regimen, followed by HDT/ASCT and rituximab maintenance in patients who have obtained at least a PR. For patients with relapsed or refractory MCL after first-line approaches, treatment options are limited.

Therapy with Bruton's tyrosine kinase inhibitor (BTKi), including acalabrutinib, ibrutinib, and zanubrutinib, has been studied in single-arm trials, producing response rates of 66% to 84%, with median response durations of approximately 18 months or more. Of note, BTKi treatment is not time-limited, and continued response is dependent on continued therapy. Risks of therapy with BTKi's include cytopenias, infections, hemorrhage, cardiac arrhythmias, and secondary malignancies. Acalabrutinib, ibrutinib, and zanubrutinib have received accelerated approval from the United States (US) Food and Drug Administration (FDA) (BRUKINSA USPI, 2021; CALQUENCE USPI, 2022; IMBRUVICA USPI, 2022).

CAR-T cell therapy may be an option for eligible patients with relapsed or refractory MCL. Brexucabtagene ciloleucil received accelerated approval from the US FDA based on a single-arm trial in patients with MCL who received prior chemoimmunotherapy with an anti-CD20 agent and a BTKi. Among efficacy-evaluable patients, the objective response rate was 87% with a median duration of response not reached. Therapy with brexucabtagene ciloleucil carries serious risks including cytokine release syndrome, neurologic toxicities, infections, prolonged cytopenias, and secondary malignancies, and is available only through a REMS program (TECARTUS USPI, 2021).

Due to the limited randomized data for treatment of relapsed or refractory MCL after first-line therapy and HDT/ASCT in transplant-eligible patients, investigational therapies may be an appropriate option in this setting.

Follicular Lymphoma

Follicular lymphoma (FL) is the second most frequently diagnosed subtype of non-Hodgkin lymphoma (NHL) and advanced stage cases are incurable with current therapies. The clinical course may follow an indolent or aggressive course, and several prognostic criteria have been developed. The Follicular Lymphoma International Prognostic Indicator (FLIPI) uses patient age, Ann Arbor stage, hemoglobin level, number of nodal areas, and serum lactate dehydrogenase levels to define patient risk groups. Predicted 5-year overall survival (OS) rates are approximately 44% for the high-risk group and 88% for the low-risk group (Solal-Céligny et al., 2004). For patients with relapsed or refractory disease, progression of disease within 24 months of diagnosis (POD24) is an important prognostic factor that identifies a subgroup of patients with significantly decreased OS (Casulo et al., 2015).

In general, therapy for FL is indicated when the disease meets Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, which includes factors such as size and number of tumors, presence of B-symptoms, splenic enlargement, compression of vital organs, effusions, leukemia or cytopenias (Brice, 2022).

Chemoimmunotherapy with an anti-CD20 monoclonal antibody (obinutuzumab or rituximab) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), cyclophosphamide, vincristine, and prednisone (CVP), bendamustine, or lenalidomide is the standard first-line therapy for patients with advanced stage FL requiring treatment, producing a response rate of 88% to 91% and a 3-year PFS rate of 73% to 80% (GAZYVA USPI, 2022).

Indications for retreatment for relapsed or refractory (R/R) disease follow similar considerations, and a period of observation is an option for patients who do not meet the GELF criteria. Options for treatment include alternate non-cross resistant chemoimmunotherapy with an anti-CD20 agent, such as bendamustine plus obinutuzumab, or rituximab plus lenalidomide which produces a response rate of 79% to 80% and median PFS of 29 to 39 months (GAZYVA USPI, 2022; REVLIMID USPI, 2022). Patients who have R/R disease after frontline therapy meeting the POD24 criteria represent a subgroup with an increased risk of mortality with standard therapies, and who therefore may be appropriate for novel or investigational therapies (Casulo et al., 2015).

Options for third- or subsequent lines of therapy have generally been investigated in single-arm Phase 2 studies, and include copanlisib, tazemetostat, and CAR-T cell therapy.

Tazemetostat is an EZH2 inhibitor that received accelerated approval from the US FDA based on results of a single-arm trial in which a response rate of 69% was observed in patients with an enhancer of zeste homolog 2 (EZH2) mutation and a response rate of 34% was observed in patients without a EZH2 mutation. The median duration of response for the 2 groups were 10.9 and 13 months, respectively. Risks associated with therapy included low rates of ≥ Grade 3 neutropenia, and an increased risk of secondary malignancies (TAZVERIK USPI, 2022).

Some patients with R/R FL may fit criteria to receive autologous CAR-T cell therapy, including axicabtagene ciloleucel or tisagenlecleucel, which have received accelerated approval from the US FDA. These therapies produce response rates of 86% to 91%, with 71% to 76% of patients maintaining responses at 12 months. However, CAR-T cell therapy is associated with serious toxicities including cytokine release syndrome, neurologic toxicities, serious infections, prolonged cytopenias, and secondary malignancies (KYMRIAH USPI, 2022; YESCARTA USPI, 2022).

Based on the incurable nature of FL and the lack of randomized data for patients who have received 2 or more prior regimens, investigational approaches may be appropriate for these patients. Additionally, patients who have received one prior line of treatment with chemoimmunotherapy include an anti-CD20 agent and who meet POD24 criteria have an increased risk of death with standard treatment and may consider investigational approaches.

2.1.1.2 Renal Cell Carcinoma and Nasopharyngeal Carcinoma

Renal Cell Carcinoma (RCC)

Systemic treatment options for metastatic or locally advanced renal cell carcinoma (RCC) include treatment with vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICI). Recently, several combinations of VEGF-TKI plus ICI combination regimens have received regulatory approval for first-line treatment of RCC, including axitinib plus pembrolizumab, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab. These therapies provide a response rate of 56% to 70%, median PFS of 15 to 24 months, and median OS of approximately 3 years or more (CABOMETYX USPI, 2019; INLYTA USPI, 2020; LENVIMA USPI, 2022). Another option for first-line treatment of RCC is an ICI doublet of nivolumab plus ipilimumab, which produces a response rate of 42% and a median PFS of approximately 12 months in patients with poor or intermediate risk RCC (OPDIVO USPI).

Options for patients with refractory RCC following first-line therapy include VEGF-TKIs or ICI, especially if not used as the initial therapy.

In a retrospective review of patients who received ICI monotherapy or doublet therapy as first-line treatment, subsequent therapy with cabozantinib induced a response rate of 43% (Procopio et al., 2021). However, for patients who have been previously treated with VEGF-TKIs (without an ICI), subsequent therapy with another VEGF-TKI such as tivozanib, cabozantinib, or lenvatinib plus everolimus, induced response rates of 17% to 19% in prospective randomized studies, with a median PFS of 5.6 to 14.6 months, but no statistically significant improvement in OS compared to everolimus alone (CABOMETYX USPI, 2019; FOTIVDA USPI, 2021; LENVIMA USPI, 2022).

Nivolumab induced responses in 25% of patients who had been previously treated with VEGF-TKI (without an ICI) (Motzer et al., 2015). However, for patients who had been previously treated with an ICI, re-challenge with nivolumab with or without ipilimumab produced a response rate of only 17% (Choueiri et al., 2022).

With the rapidly evolving first-line treatment landscape, little prospective data exist for therapy following treatment with a VEGF-TKI plus ICI combination regimen. In a retrospective review, patients who had previously received a VEGF-TKI plus ICI combination had a response rate of 22% following treatment with subsequent lenvatinib (Wiele et al., 2021). Ongoing studies are currently evaluating the optimal therapeutic approach following TKI-ICI treatment.

As most second-line agents received regulatory approval prior to the establishment of first-line VEGF-TKI plus ICI combinations, there are currently no preferred second- or subsequent-line therapies for patients who have received both of these agents. As such, investigational therapies may be an appropriate option for patients who have received both a VEGF-TKI and ICI, either in combination or as 2 separate regimens.

Nasopharyngeal Carcinoma (NPC)

First-line therapy for patients with advanced stage nasopharyngeal carcinoma (NPC) includes platinum-based induction chemotherapy followed by concurrent radiotherapy (RT)/chemotherapy, or adjuvant chemotherapy following concurrent systemic therapy/RT (Zhang et al., 2019).

Platinum-based chemotherapy is also recommended for patients with metastatic or recurrent disease and for whom surgery or RT are not considered treatment options. In a recent Phase 3 trial in this population, the median PFS was 7.0 months for patients receiving gemcitabine plus cisplatin and 5.6 months for patients receiving fluorouracil plus cisplatin (Zhang et al., 2016).

Few treatment options exist for patients with recurrent NPC after platinum-based chemotherapy. In small single-arm studies, the ICIs nivolumab and pembrolizumab induced response rates of 21% to 26%, with 38% of responses maintained at 6 months. However, these agents are not yet approved by US regulators for treatment of patients with NPC (Hsu et al., 2017; Ma et al., 2018). Further studies are underway.

Based on the lack of options for patients with metastatic or relapsed NPC not amenable to further local therapy, and who have previously received platinum-based chemotherapy, investigational therapies may be an appropriate therapeutic option.

2.1.2 Introduction to GEN1160 (PRO1160)

2.1.2.1 CD70

CD70 is a transmembrane protein member of the tumor necrosis factor (TNF) superfamily, which is frequently expressed on multiple solid tumor types and hematological malignancies (Jacobs et al., 2015a). Expression of CD70 is highly regulated: under physiological conditions, CD70 is transiently upregulated only on activated T cells, B cells, and mature dendritic cells (Nolte et al., 2009).

In contrast to the limited expression on normal tissue, CD70 overexpression has been reported in diverse tumor types such as RCC, NPC, and NHL (Agathanggelou et al., 1995; De Meulenaere et al., 2017; Law et al., 2006; Yang et al., 2007); see Table 5. This overexpression facilitates

survival of regulatory T cells and apoptosis of immune effector cells, thereby promoting tumor survival and growth (Claus et al., 2012; Diegmann et al., 2006; Wischhusen et al., 2002; Yang et al., 2007). Targeting CD70 may therefore stimulate antitumor immune responses and induce direct cytotoxicity towards tumor cells (Jacobs et al., 2015b).

Table 5: CD70 Expression on Diverse Tumor Types

Cancer Type	CD70-positive (%)	Area of CD70 Expression[a]			
		1-25%	>25-50%	>50-75%	>75-100%
RCC[a,b,c,d]	70-87%	0%	7%	29%	64%
Clear cell[c,d]	82-93%				
Papillary[c,d]	50-67%				
Chromophobe[c,d]	0%				
Nasopharyngeal carcinoma[e]	80%				
Pancreatic[c]	25%				
Ovarian[c]	15%				
NHL[a,b,d]	60-77%	10%	22%	17%	51%
DLBCL[d]	84%				
FL[d]	77%				
MCL[d]	67%				
Hodgkin lymphoma[a]	97%	0%	0%	0%	100%
Multiple myeloma[a]	39%	31%	15%	31%	23%

Abbreviations: DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; IHC=immunohistochemistry; MCL=mantle cell lymphoma; NHL=non-Hodgkin lymphoma; RCC=renal cell carcinoma.

[a] CD70 expression measured by IHC, ≥ 1% of cells; (McEarchern et al., 2008)

[b] CD70 expression measured by IHC, ≥ 1% of cells; (Tannir et al., 2014)

[c] CD70 expression by IHC, cut off not specified; (Ryan et al., 2010)

[d] Percentage with 3+ intensity membranous staining by IHC; (Wood et al., 2015)

[e] CD70 expression by IHC, cut off not specified; (Agathanggelou et al., 1995)

2.1.2.2 GEN1160 (PRO1160)

GEN1160 (PRO1160) is a novel ADC that is directed to CD70, and comprises (1) a human monoclonal antibody (mAb) specific for CD70, with reduced complement component 1q (C1q) and Fc gamma receptor (FcγR) binding due to the CCI Fc mutations; (2) a protease-cleavable hydrophilic linker; and (3) exatecan, a topoisomerase 1 inhibitor. Upon binding to CD70 on the surface of malignant cells, GEN1160 is internalized and exatecan released through enzymatic cleavage of the linker. Exatecan prevents re-ligation of deoxyribonucleic acid (DNA) during replication and generates DNA single- and double-strand breaks, which leads to cell death.

GEN1160 has demonstrated robust antitumor activity in vitro in CD70-expressing cell lines derived from NHL, RCC, and NPC. In multiple cell-derived xenograft mouse models, GEN1160 also demonstrated potent and sustained tumor growth inhibition. The in vivo pharmacokinetics (PK) in rats showed that GEN1160 is stable in circulation and displays PK characteristics CCI. In the Good Laboratory Practice (GLP) toxicity study in cynomolgus monkeys, the primary GEN1160-related toxicity was in the thymus and bone marrow; the toxicity profile was consistent with exatecan toxicities and reversible. CCI These nonclinical data suggest a potentially large therapeutic window and warrant development of GEN1160 for the treatment of patients with CD70-expressing hematologic and solid tumor cancers.

2.1.3 Summary of Nonclinical Studies

Nonclinical studies support the clinical development of GEN1160. CCI Taken together, these data provide support that GEN1160 is a promising candidate for further development in the clinic for various cancers.

For additional details regarding nonclinical studies, refer to the GEN1160 Investigator's Brochure (IB).

2.1.3.1 Nonclinical Pharmacology

The mechanism of action and clinical potential of GEN1160 were evaluated in a series of in vitro and in vivo studies.

2.1.3.1.1 In Vitro Pharmacodynamics

GEN1160 demonstrated strong binding to both human and cynomolgus monkey CD70 with similar affinity and no binding to rat or mouse CD70. Cynomolgus monkeys are therefore the appropriate species for toxicological evaluation of GEN1160. GEN1160 showed CCI on human CD70-expressing cell lines. GEN1160 displayed rapid internalization on CD70-expressing tumor cell lines but not on cells with negligible CD70 expression. GEN1160 also elicited robust cytotoxic effects in human CD70-expressing tumor cells. GEN1160 CCI

2.1.3.1.2 In Vivo Pharmacodynamics

GEN1160 produced robust and durable tumor growth inhibition in cell line-derived xenograft models for RCC (786-O and Caki-1), NHL (CCI), and NPC (CCI) in single- or multiple-dose regimens, CCI. Tumor growth inhibition by GEN1160 was shown to be CCI. The nonbinding ADC control exerted minimal inhibitory effect on tumor growth, suggesting that the antitumor effect by GEN1160 is target mediated. CCI

CCI [redacted]

2.1.3.1.3 Nonclinical Toxicology

The toxicity of GEN1160 following intravenous (IV) administration has been evaluated in cynomolgus monkeys (single and repeat doses every 3 weeks). A recovery period was incorporated to evaluate the reversibility, persistence, or delayed occurrence of any effects. Intravenous administration of GEN1160 resulted in monitorable and reversible myelosuppression as well as monitorable effects on rapidly proliferating cells at tolerated dose levels.

The cynomolgus monkey is considered the relevant species for toxicological evaluation based on the similar binding affinity of GEN1160 for human and cynomolgus monkey CD70 and absence of species cross-reactivity with rat or mouse CD70. GEN1160 was administered IV at CCI [redacted] on 3 occasions, 3 weeks apart. The CCI [redacted] in cynomolgus monkeys.

Relevant findings include:

- Myelosuppression: Transient, dose-related cytopenias were observed. Similar findings were observed in related tissues that contain highly proliferating cell types, including the thymus and bone marrow.
- Skin: Focal/multifocal black discoloration was noted on the skin of the hindlimbs of animals in the CCI [redacted] dose groups. No corresponding evidence of histopathology-related findings were observed, and the discoloration was reversed or displayed a trend of reversal within the recovery period. The relationship between these findings and GEN1160 was not clear.

2.1.4 Summary of Clinical Trials

This is the first time GEN1160 is being tested in humans. As of the data cutoff date (31 March 2025), 41 patients (RCC/NPC: 33; NHL: 8) have received GEN1160 at CCI [redacted].

- RCC/NPC Cohort (N=33): Thirty-three RCC/NPC patients were treated with GEN1160 at 6 dose levels (DLs): CCI [redacted]. Dose-limiting toxicities (DLTs) including thrombocytopenia, anemia, epistaxis, febrile neutropenia, and hemoptysis were reported at DLs of CCI [redacted].

Among the 33 RCC/NPC patients treated with GEN1160, the most common treatment-emergent adverse events (TEAEs) in ≥ 5 patients treated across all dose levels include nausea (23 patients [69.7%]), vomiting (20 patients [60.6%]), anemia (16 patients [48.5%]), fatigue (14 patients [42.4%]), decreased appetite and neutropenia (11 patients [33.3%] each), diarrhea (10 patients [30.3%]), constipation, hyponatremia, thrombocytopenia (9 patients [27.3%] each), white blood cell count decreased (8 patients [24.2%]), dizziness (6 patients [18.2%]), and alanine

aminotransferase increased, aspartate aminotransferase increased, dehydration, hypokalemia, and weight decreased (5 patients [15.2%] each).

Two out of 33 patients achieved a response: 1 RCC at CCI and 1 NPC at CCI. Based on the totality of data and benefit-risk assessment, it was decided to permanently discontinue further development of GEN1160 in RCC/NPC.

- NHL Cohort (N=8): 8 NHL patients were treated with GEN1160 at 3 DLs: CCI. No DLT was observed.

Among the 8 NHL patients treated with GEN1160, the most common TEAEs in ≥ 2 patients treated across all dose levels include neutropenia (7 patients [87.5%]), followed by anemia, thrombocytopenia, and white blood cell count decreased (6 patients [75.0%] each), diarrhea and lymphocyte count decreased (4 patients [50.0%] each), nausea (3 patients [37.5%]), and aspartate aminotransferase increased, hyperglycemia, hyponatremia, and vomiting (2 patients [25%] each).

Preliminary antitumor activity has been observed in R/R B-cell NHL patients with GEN1160 monotherapy including 1 CR in MCL CCI, 1 PR in MCL CCI, and 2 PR in DLBCL (1 each at CCI). The development for NHL will continue with a focus on R/R DLBCL.

2.2 Trial Rationale

Nonclinically, CD70-targeting GEN1160 has demonstrated potent tumor-cell killing across a variety of cell lines including CD70-expressing B-NHL, RCC, and NPC in vitro. In cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models, various degrees of tumor regression was observed in NHL, RCC, head and neck squamous cell carcinoma (HNSCC), and NPC. CCI The above nonclinical observations support developing GEN1160 in the clinical setting.

The aim of this Phase 1/2 trial is to characterize the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of GEN1160 in participants with R/R NHL, metastatic or relapsed RCC and NPC. In the Dose Escalation, DLTs will be monitored to determine the expansion dose, and if reached, the maximum tolerated dose (MTD) for both R/R NHL and RCC/NPC, respectively. CCI, dose escalations will be conducted in 2 disease cohorts. The totality of the data including safety, immunogenicity, PK, pharmacodynamics, and preliminary efficacy will be evaluated to guide further development for Expansion.

Following the Dose Escalation, in the Expansion Part A, the clinical activity of GEN1160 at the expansion dose identified among R/R NHL participants will be evaluated in participants with R/R DLBCL, as well as safety, tolerability, PK, pharmacodynamics, and biomarkers. After an interim analysis of the efficacy and safety data for Expansion Part A, the Expansion Part B will be initiated and the clinical activity of GEN1160 will be further evaluated in participants with R/R DLBCL using CCI. It is expected that the populations to be enrolled

in this trial are heavily pretreated. CCI [redacted] may potentially be explored in Expansion Part B. Detailed trial rationale and design will be added via a future protocol amendment based on supporting nonclinical data and preliminary clinical data for GEN1160 and will be submitted to Health Authorities and institutional review board (IRB) for approval prior to initiation.

2.3 Benefit-Risk Assessment

GCT1160-01 is a first-in-human (FIH) trial and limited clinical data are available. The trial population is limited to R/R NHL, metastatic or relapsed RCC or NPC who have exhausted standard therapies or are ineligible for standard therapies. The risk to participants in this trial should be minimized by compliance with the eligibility criteria, trial procedures, close monitoring, and proper/prompt management of TEAEs.

2.3.1 Potential Benefit

CD70 is a validated therapeutic target for hematologic malignancies (eg, NHL, Hodgkin lymphoma [HL], multiple myeloma [MM], T-cell lymphoma [TCL], acute myeloid leukemia [AML]) and solid tumor types (eg, RCC, NPC).

Exatecan, the payload used for GEN1160 has an established safety profile with cytopenia and gastrointestinal toxicities being the most common side effects. No peripheral neuropathy or ocular toxicity is expected with exatecan which makes GEN1160 CCI [redacted] ADC in terms of safety and tolerability.

Patients with relapsed or refractory B-NHL, who have exhausted the standard of care (SOC), such as CAR-T, bispecific antibodies, have limited treatment options and have high unmet medical need. Preliminary data indicates GEN1160 had single agent activity in R/R B-NHL patients.

2.3.2 Potential Risks

There is limited clinical data to date with GEN1160. The assessment of potential side effects of GEN1160 is based on nonclinical studies, preliminary safety data from the ongoing GCT1160-01 trial (Section 2.1.3 and Section 2.1.4), and the literature.

Based on data from the ongoing clinical trial, GEN1160 has an acceptable safety profile. The most common hematologic TEAEs were neutropenia, thrombocytopenia, anemia, leukopenia and usually reversible. The most common non-hematologic adverse events (AEs) were nausea, vomiting, and diarrhea. Both cytopenia and gastrointestinal toxicities were known toxicities from the payload exatecan.

Infusion-related reactions have been reported in treatment with monoclonal antibodies, mostly in the first treatment cycle, and IRRs may be expected with GEN1160 treatment. Refer to Section 6.1.1 for premedication prophylaxis and management of IRRs.

Tumor lysis syndrome (TLS) is a known risk when treating hematologic malignancies. Participants will be closely monitored for laboratory changes suspicious for TLS (see Section 10.8).

2.3.3 Conclusion

Collectively, nonclinical data of GEN1160 and clinical data from 8 NHL patients treated with GEN1160 warrant clinical development of GEN1160 in R/R NHL. GEN1160 has the potential to address the high unmet medical need in these patient populations. With safety precautions and a close monitoring plan in place, the described risks are outweighed by the potential benefit participants might receive from GEN1160.

For comprehensive information on nonclinical studies, potential safety aspects, and the known and anticipated benefits and risks, please refer to the GEN1160 Investigator's Brochure (IB).

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints for the Dose Escalation, Expansion Part A, and Expansion Part B of the trial are described in Table 6, Table 7, and Table 8, respectively.

Table 6: Objectives and Endpoints – Dose Escalation

Primary Objectives	**Primary Endpoints**
• Evaluate the safety and tolerability of GEN1160 • Identify the maximum tolerated dose (MTD), if reached, and the recommended Phase 2 dose (RP2D) of GEN1160	• Type, incidence, severity, and seriousness of adverse events (AEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of dose-limiting toxicities (DLTs)
Secondary Objectives	**Secondary Endpoints**
• Assess the antitumor activity of GEN1160 • Assess the pharmacokinetics (PK) and immunogenicity of GEN1160	• Objective response rate (ORR): o Renal cell carcinoma (RCC) and nasopharyngeal carcinoma (NPC): per the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 o Non-Hodgkin lymphoma (NHL): per the Lugano Classification 2014 • Disease control rate (DCR) • Progression-free survival (PFS) • Duration of objective response (DOR) • PK parameters (such as maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the curve up to the last quantifiable time-point [$AUC_{0\text{-}last}$], etc) for GEN1160-related analytes • Incidence of antidrug antibodies (ADA)
Exploratory Objectives	**Exploratory Endpoints**
• Assess baseline and pharmacodynamic biomarkers in peripheral blood and tumor specimens in relation to antitumor activity, safety, and resistance to GEN1160	• Overall survival (OS) • Exploratory biomarkers of GEN1160-mediated and disease-related pharmacodynamic effects and tumoral CD70 expression.

Table 7: Objectives and Endpoints – Expansion Part A (R/R DLBCL)

Objectives	Endpoints
Primary	
• Assess the preliminary antitumor activity of GEN1160	• Objective response rate (ORR) based on the Lugano criteria as assessed by investigators
Secondary	
• Evaluate antitumor activity and efficacy of GEN1160	• Complete response (CR) rate • Duration of objective response (DOR) • Time-to-response (TTR) • Progression-free survival (PFS) • Overall survival (OS)
• Evaluate safety and immunogenicity of GEN1160	• Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory values, vital signs, electrocardiograms (ECGs) • Immunogenicity: Anti-GEN1160 antibodies
• Characterize the pharmacokinetics (PK) and immunogenicity of GEN1160	• PK parameters (such as maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the curve up to the last quantifiable time-point [$AUC_{0\text{-}last}$], etc) for GEN1160-related analytes • Incidence of antidrug antibodies (ADA)
Exploratory	
• Assess baseline and pharmacodynamic biomarkers in peripheral blood and tumor specimens in relation to antitumor activity, safety, and resistance to GEN1160.	• Exploratory biomarkers of GEN1160-mediated and disease-related pharmacodynamic effects and tumoral CD70 expression.

Abbreviations: DLBCL=diffuse large B-cell lymphoma; R/R=relapsed/refractory.

Table 8: Objectives and Endpoints – Expansion Part B (R/R DLBCL)

Objectives	Endpoints
Primary	
• Assess the preliminary antitumor activity of GEN1160	• Objective response rate (ORR) based on the Lugano criteria as assessed by investigators
Secondary	
• Evaluate antitumor activity and efficacy of GEN1160	• Complete response (CR) rate • Duration of objective response (DOR) • Time-to-response (TTR) • Progression-free survival (PFS) • Overall survival (OS)
• Evaluate safety and immunogenicity of GEN1160	• Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory values, vital signs, electrocardiograms (ECGs) • Immunogenicity: Anti-GEN1160 antibodies
• Characterize the pharmacokinetics (PK) and immunogenicity of GEN1160	• PK parameters (such as maximum concentration [C_{max}], time to maximum concentration [T_{max}], area under the curve up to the last quantifiable time-point [$AUC_{0\text{-}last}$], etc) for GEN1160-related analytes • Incidence of antidrug antibodies (ADA)
Exploratory	
• Assess baseline and pharmacodynamic biomarkers in peripheral blood and tumor specimens in relation to antitumor activity, safety, and resistance to GEN1160	• Exploratory biomarkers of GEN1160-mediated and disease-related pharmacodynamic effects and tumoral CD70 expression.

Abbreviations: DLBCL=diffuse large B-cell lymphoma; R/R=relapsed/refractory.

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a Phase 1/2, open-label, multicenter, trial to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity and efficacy of GEN1160 (PRO1160) in participants with R/R NHL or metastatic or relapsed RCC and NPC.

The trial will be conducted in 3 parts: Dose Escalation (Phase 1; Section 4.1.1), Expansion Part A (Phase 2; Section 4.1.2), and Expansion Part B (Phase 2; Section 4.1.3).

Each part will consist of the following:

1. Screening period (up to 28 days prior to Cycle 1 Day 1 for Dose Escalation and up to 21 days prior to Cycle 1 Day 1 for Expansion Part A and Part B),
2. Treatment period (Cycle 1 Day 1 until GEN1160 treatment discontinuation),
3. Follow-up period (ie, 30-day safety follow-up from the last dose of GEN1160 or before the initiation of a new anticancer treatment, whichever comes first; post-treatment follow-up for participants who discontinue GEN1160 prior to disease progression; and survival follow-up by telephone contact or retrospective chart review until death, lost to follow-up, or the end of trial, whichever comes first).

In Dose Escalation, there are 2 disease cohorts: R/R NHL and RCC/NPC. GEN1160 will be administered as an IV infusion in 21-day cycles on Day 1 of each treatment cycle (Section 6.1) until one of the GEN1160 treatment discontinuation criteria has been met (Section 7.1). Assessments will be performed as detailed in the Schedule of Activities (Section 1.3). In Dose Escalation, GEN1160 will be evaluated in R/R NHL and RCC/NPC using the “3 + 3” design. At each DL, DLTs will be assessed in the first treatment cycle plus 7 days, ie, a DLT evaluation period of 28 days from Cycle 1 Day 1. The MTD of each disease cohort, if reached, along with the maximum administered dose (MAD) and expansion dose of each disease cohort will be determined based on the totality of the data of each disease cohort.

In Expansion Part A, the antitumor activity of GEN1160 will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers in R/R DLBCL. GEN1160 will be administered at the expansion dose identified from the Dose Escalation as an IV infusion in 21-day cycles on Day 1 of each treatment cycle (Section 6.1) until one of the GEN1160 treatment discontinuation criteria has been met (Section 7.1). Assessments will be performed as detailed in the Schedule of Activities (Section 1.3). To confirm the antitumor activity of GEN1160, participants with DLBCL who received GEN1160 at the expansion dose during the Dose Escalation phase of the trial may be counted toward the 10-participant lead-in analysis prior to starting Expansion Part B.

In Expansion Part B, the clinical activity of GEN1160 will be evaluated in R/R DLBCL at 2 dosing regimens (randomized at 1:1 ratio) in 21-day cycles as follows:

- DLBCL-DL1 (N=25): GEN1160 administered Q3W on Day 1 of each treatment cycle at the expansion dose identified from the R/R NHL Cohort of Dose Escalation; or,
- DLBCL-DL2 (N=25): CCI [redacted]

Approximately 50 participants are expected to be enrolled in the Dose Escalation part of the trial. For Expansion, approximately 10 participants are expected to be enrolled in Part A and approximately 50 participants are expected to be enrolled in Part B of the trial.

During Dose Escalation, a Safety Monitoring Committee (SMC) will review the preliminary data from participants treated at a specific DL according to the SMC Charter and evaluate potential DLTs. The SMC will make recommendations on escalating to the next DL. SMC will propose the expansion dose/MTD/MAD to the Safety Committee, who will have to endorse the proposed expansion dose for further development in the Expansion.

During Expansion, the Safety Committee will assess the totality of safety information of the trial and identify additional safety signals. Refer to the Committees Structure in Section 10.1.8 for details.

Treatment for a participant should continue until the participant fulfills one of the treatment discontinuation criteria (refer to Section 7.1).

A diagram of the trial design is provided in Figure 1.

4.1.1 Dose Escalation

In Dose Escalation, GEN1160 will be tested in 2 disease cohorts:

- R/R NHL Cohort (see Section 5.1 and Section 5.2 for inclusion and exclusion criteria, respectively): Adult participants 18 years and older will be enrolled. Eligible NHL tumor types include advanced (Stage III or IV) NHL, including DLBCL, MCL, and FL requiring systemic therapy.
- Metastatic and relapsed RCC and NPC Cohort (see Section 5.1 and Section 5.2 for inclusion and exclusion criteria, respectively): Adult participants 18 years and older will be enrolled. Eligible RCC tumor types include pathologically confirmed metastatic RCC, including clear cell RCC (ccRCC) or papillary RCC. Eligible NPC tumor types include pathologically confirmed metastatic or relapsed Epstein Barr virus (EBV)-associated NPC not amenable to further local therapies. ***Note:*** *Participants will no longer be enrolled in the metastatic and relapsed RCC/NPC cohort per Protocol Amendment 2.*

GEN1160 will be tested at DLs ranging from CCI via IV infusions in 21-day cycles. Intraparticipant dose escalation will not be allowed. At each DL, DLTs will be assessed in treatment Cycle 1 plus an additional 7 days (ie, DLT period is 28 days).

Planned DLs are outlined in Table 9.

Table 9: GEN1160 Dose Levels in Dose Escalation

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CCI

4.1.1.1 Dose Escalation Strategy

Dose escalation decisions will be based on safety data obtained during each participant's first 28 days of treatment (which must include 7 days of follow-up after the second dose). The SMC will evaluate all available safety data after each dose level completes the DLT period and make a recommendation on whether dose escalation should proceed. Complete DLT information must be available for each dose cohort before the next dose cohort can be enrolled. Participants who are considered not evaluable for a DLT may be replaced. De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC.

The "3 + 3" design will be applied to guide dose escalations for each disease cohort separately (see Section 4.1.1.2). However, the first 2 DLs, ie, CCI, are intended to be single-participant DLs. The trigger point to expand a 1-participant DL into a 3-participant DL (eg, adding 2 more participants to a single-participant DL) is the observation of a qualifying event (see list below) during the DLT period or that the third DL is reached.

- Qualifying events:
  - A DLT
  - Any ≥ Grade 2 non-hematologic toxicity (except for AEs unequivocally due to the underlying disease or an extraneous cause)
  - ≥ Grade 3 anemia
  - ≥ Grade 3 neutropenia (with an absolute decrease of at least 250/µL for participants with Grade 2 neutropenia at baseline)

- ≥ Grade 2 neutropenia
- Other ≥ Grade 3 hematologic AEs that worsen by at least one grade from baseline

In the single-participant cohort portion, dose escalation will occur when there is no qualifying event (DLT or any ≥ Grade 2 representing at least one grade worsening from baseline) that is not clearly related to the underlying malignancy or extraneous causes.

If a qualifying event triggers the change to 3 + 3 design, the first dose level expanded will be the dose at which the qualifying event occurred.

CCI

4.1.1.2 Dose Escalation Principles

When dose escalation converts to the standard 3 + 3 design, 3 participants will be enrolled into each dose level and evaluated for the occurrence of DLTs (see Table 10). If no DLTs occur in the first 3 evaluable participants at a dose level, the dose will be escalated, and 3 participants will be enrolled at the next level. However, if a DLT occurs in 1 of the 3 participants at a dose level, an additional 3 participants will be enrolled at the same dose level. If no DLTs occur in the additional 3 participants, that dose level will have completed the DLT evaluation period, and dose escalation will proceed to the next dose level. If ≥ 2 DLTs occur among 6 participants at a dose level, that dose will be assessed as a non-tolerated dose (NTD), and the dose level below the NTD will be defined as the MTD. The SMC may also recommend evaluation of intermediate dose levels, not exceeding the NTD.

Table 10: 3 + 3 Dose Escalation Rules

DLT observed in:	Then:
0 of 3 participants	Proceed with enrollment in next dose level
1 of 3 participants	Enroll 3 additional participants in current dose level
1 of 6 participants	Proceed with enrollment in next dose level
≥ 2 of 6 participants	Do not escalate; enroll 3 additional participants in previous dose level or new intermediate dose level
≥ 2 of 3 participants	Do not escalate; enroll 3 additional participants in previous dose level or new intermediate dose level

Over-enrollment by 1 additional participant at each dose level is permitted during the Dose Escalation part. Such additional participants will not be considered in dose escalation decisions except in the case of a qualifying event during the DLT period for the first enrolled participant of the single-participant cohorts or a DLT during the DLT period of the third enrolled participant of the 3 + 3 cohorts.

4.1.1.3 Parallel Cohorts

To better understand the safety, tolerability, PK, pharmacodynamic, or antitumor activity, approximately 7 additional participants may be allocated to DLs that are considered safe (ie, DLs that have been cleared by the SMC) for such allocation (DLs at or below the currently investigated one). Up to a total of approximately 10 participants can be allocated per dose level.

4.1.1.4 Maximum Tolerated Dose/Expansion Dose

The MAD, expansion dose, and MTD (if reached) for the 2 disease cohorts will be determined based on the observed toxicity within each cohort.

The estimated MTD will be the highest dose, at which at least 6 participants were enrolled with a DLT rate of ≤ 25%. GEN1160 will initially be administered on Day 1 of a 21-day cycle at the planned doses. Longer dosing intervals may be evaluated during the Dose Escalation part after consultation with the SMC. The SMC may also recommend investigation of lower and/or intermediate dose levels.

The expansion dose will be selected based on an integrated analysis of safety, tolerability, PK, pharmacodynamics, and antitumor activity data from the Dose Escalation part. Any toxicities that meet DLT criteria that occur outside of the DLT window or prolonged toxicities that are not captured by the DLT definition will be considered in the evaluation of dose levels and doses considered for further evaluation.

4.1.2 Expansion Part A

In Expansion Part A, there is one disease cohort. Ten (10) participants with R/R DLBCL will be treated with GEN1160 at the expansion dose.

Data from the initial 10 response-evaluable participants (defined in Section 9.2), including those participants with R/R DLBCL who received GEN1160 expansion dose from the Dose Escalation and/or from the Expansion Part A, will be reviewed by the Safety Committee when they have completed at least 2 cycles of treatment. If [redacted] or more (out of the initial 10) participants respond to GEN1160 (Section 9.3.6.2), the Expansion Part B will be initiated; see Section 9.3.3. Assessment of disease response will be conducted by the investigator in accordance with the Lugano criteria (see Section 10.11).

4.1.3 Expansion Part B

If the preliminary efficacy and safety are judged to be favorable in the initial 10 participants with R/R DLBCL who received the expansion dose (in the Dose Escalation or Expansion Part A), an additional 50 participants with R/R DLBCL will be enrolled into Expansion Part B and randomized 1:1 to:

- DLBCL-DL1 (N=25): GEN1160 administered Q3W on Day 1 of each treatment cycle at the expansion dose identified from the R/R NHL Cohort of Dose Escalation; or,

- DLBCL-DL2 (N=25): CCI [redacted]

Based on the data from participants with DLBCL treated with the GEN1160 monotherapy, Expansion Part B will be updated via a protocol amendment to include: 1) CCI [redacted].

Dose reductions or delays for individual participants may be implemented as outlined in Section 6.7 based on the individual participant toxicity profile, after consultation and agreement from the study Medical Monitor.

Safety will be continuously monitored throughout the study by the sponsor. An ongoing, quarterly review of participant safety and serious adverse events (SAEs) will be conducted by the Safety Committee during Part B.

4.2 Trial Design Rationale

This trial is being conducted in 3 parts. The Dose Escalation is being conducted to identify the expansion dose and the MAD/MTD (if reached), and to evaluate safety, and obtain preliminary efficacy of GEN1160 in participants with R/R NHL and RCC/NPC. Escalation and de-escalation in the Dose Escalation phase will be guided by the "3 + 3" design.

The Expansion Part A is being conducted to evaluate clinical activity of GEN1160 together with safety, tolerability, PK, pharmacodynamics, and biomarkers at the selected expansion dose in R/R DLBCL. An interim analysis (Section 9.3.6.2) will be conducted for Expansion Part A to determine the scope of development in Expansion Part B.

The Expansion Part B is being conducted to evaluate 2 dosing regimens of GEN1160 in participants with R/R DLBCL, with the goal of optimizing dose selection. CCI [redacted]

4.3 GEN1160 Dose and Schedule Rationale

The cynomolgus monkey is considered the relevant toxicological species based on the similar binding affinity for human and cynomolgus monkey CD70. CCI [redacted]

The proposed starting dose for this first-in-human study was set using a CCI [redacted] with CCI [redacted] identified in cynomolgus monkeys. Using standard allometric scaling across species and converting to a body-surface area adjusted dose, the starting dose is CCI [redacted].

4.4 Primary Completion Date, Estimated Trial Duration, and End of Trial Definitions

4.4.1 Primary Completion Date

The primary completion date is defined as the date when the last participant is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the trial concluded as planned in the protocol or was terminated early.

Primary completion is anticipated to occur at the same time as the end of trial.

4.4.2 Estimated Trial Duration for an Individual Participant

The estimated trial duration for an individual participant is approximately 2 years, consisting of a 28-day (Dose Escalation) or 21-day (Expansion Part A and Part B) screening period, an estimated 1-year treatment period (the duration of treatment may vary for each participant), a 30-day safety follow-up period, and a survival follow-up period. A participant is considered to have completed the trial if the participant has completed all periods of the trial including the last visit shown in the Schedule of Activities (Section 1.3).

4.4.3 End of Trial and Estimated Trial Duration

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

The maximum trial duration is 3 years after the last enrolled participant's first treatment in the trial.

Participants will continue to receive study treatment until the first instance of disease progression, unacceptable toxicity, investigator decision, consent withdrawal, study termination by the sponsor, initiation of non-GEN1160 anticancer therapy, participant noncompliance, pregnancy, or death. Participants who present equivocal findings of disease progression may be allowed to continue study treatment with approval of the Medical Monitor and if, in the opinion of the investigator, the participant is clinically stable.

In addition, the sponsor reserves the right to terminate the study earlier than the planned completion. For participants with a potential treatment benefit, participants may be eligible for continued treatment with GEN1160 by an extension protocol or as provided for by the local country's regulatory mechanism. Unless otherwise required under national, mandatory law, Genmab reserves the unilateral right, at its sole discretion, to determine whether to supply GEN1160 and by what mechanism, after termination of the trial and before the product(s) is/are available commercially.

5 TRIAL POPULATION

The appropriate written informed consent must be obtained before any trial-specific activities/procedures are performed. After signing the informed consent form (ICF), participants will be assigned a unique participant identifier before undergoing any screening procedures. Participants who meet all of the eligibility criteria may be enrolled (see Section 5.3).

The inclusion and exclusion criteria for enrolling participants in this trial are described below. If there is a question about these criteria, the investigator must consult with the sponsor and resolve any issues before enrolling a participant in the trial. Waivers are not allowed.

NOTE: Investigators, in coordination with the sponsor's medical director (or delegate), should ensure enrollment criteria are met and the eligibility review is completed. If a participant's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of trial treatment is given, the investigator must ensure the participant fulfills all eligibility criteria prior to the first dose.

To be eligible for retreatment, participants must meet all inclusion and none of the exclusion criteria outlined in the sections below with the exception of exclusion criterion 4 (Section 5.1.1).

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria - Dose Escalation

1. All participants must have pathologically confirmed diagnosis of one of the following tumor types:
   - Metastatic RCC, including ccRCC or papillary RCC
   - Metastatic or relapsed EBV-associated NPC not amenable to further local therapies (EBV association may have been determined by testing on tumor tissue or peripheral blood)
   - Advanced (Stage III or IV) NHL, including DLBCL, FL requiring systemic therapy, and MCL
2. Participants must have relapsed or refractory disease following prior systemic therapies known to confer clinical benefit. At minimum, participants should have received the following therapies (unless deemed ineligible, refused by the participant, or not available in the region):
   - Participants with RCC must have received a minimum of one prior treatment regimen, and have received a tyrosine kinase inhibitor (TKI) and a programmed cell death (ligand) (PD[L])-1 inhibitor
   - Participants with EBV-associated NPC must have received a minimum of one prior treatment regimen, which must include a platinum-based chemotherapy regimen
   - Participants with DLBCL must have received a minimum of 2 prior treatment regimens, including a multi-agent chemoimmunotherapy regimen given with curative intent (eg, R-CHOP), and participants must have received intensive salvage chemotherapy with hematopoietic stem cell transplant (HSCT) if considered eligible by the investigator

- Participants with FL must have received a minimum of 2 prior treatment regimens, which must include a multi-agent chemoimmunotherapy regimen including an anti-CD20 agent
- Participants with MCL must have received a minimum of 2 prior treatment regimens, which must include a multi-agent chemoimmunotherapy regimen including an anti-CD20 agent

3. Measurable disease at baseline:
   - Participants with RCC and NPC must have measurable disease as defined per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al., 2009)
   - Participants with NHL must have measurable disease as defined by the Lugano Classification (Cheson et al., 2014)
4. Participants must be willing to provide a pre-treatment tumor specimen (archival or new tissue biopsy samples). If a new tissue biopsy is required, procedures more invasive than a core biopsy or significant risk procedures for which the procedure-associated absolute risk of mortality or major morbidity in the participant's clinical setting and specific institution is 2% or higher, should not be utilized.
5. Age 18 years or older at time of informed consent
6. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
7. The following screening laboratory data are required. Participants cannot receive supportive care (transfusions or growth factors) for low platelets, neutrophils, or hemoglobin within 2 weeks prior to the screening laboratory assessment.
   - Absolute neutrophil count (ANC) ≥ 1500/μL, or ≥ 1000/μL for participants with benign ethnic neutropenia
   - Absolute lymphocyte count (ALC) ≥ 200/μL
   - Hemoglobin ≥ 9 g/dL
   - Platelet count ≥ 100,000/μL
   - Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for participants with Gilbert's disease
   - Estimated creatinine clearance according to the Cockcroft and Gault equation (Section 10.7):
     - Participants with NHL or NPC must have estimated creatinine clearance of ≥ 60 mL/min
     - Participants with RCC must have estimated creatinine clearance of ≥ 50 mL/min
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if there is evidence of hepatic involvement by malignant disease)
8. All toxicities related to prior radiotherapy, chemotherapy, or surgical procedure must have recovered to baseline or Grade ≤ 1 based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 except alopecia, Grade 2

peripheral neuropathy, stable chronic changes due to radiation or surgery, and Grade 2 laboratory abnormalities that meet eligibility requirements

9. The participant must provide written informed consent

5.1.2 Inclusion Criteria - Expansion Part A and Expansion Part B

Each potential participant must fulfill all of the following inclusion criteria to be enrolled in the Expansion part(s).

1. Must be at least 18 years of age
2. Must sign an ICF prior to any screening procedures indicating that the purpose of the trial and the procedures required for the trial are understood and indicating that the participant is willing to participate in the trial
3. Has pathological diagnosis of DLBCL, not otherwise specified (NOS) as defined by the World Health Organization (WHO) 2016 classification including both de novo or histologically transformed
4. Has relapsed or refractory disease with no available standard therapy or is not a candidate for available standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1160 may be beneficial. Participant must have received at least 2 systemic treatment regimens including CD20-containing chemoimmunotherapy.
5. Has measurable disease according to the 2014 Lugano criteria (Cheson et al., 2014):
    a. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan demonstrating positive lesion compatible with computed tomography (CT)- or magnetic resonance imaging (MRI)-defined anatomical tumor sites

    AND

    b. A CT scan (or MRI) with involvement of ≥ 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)
6. Has ECOG performance status of 0, 1, or 2
7. Has a fresh biopsy (if clinically feasible and not considered as a high-risk procedure) or an archival tumor biopsy and submit to the central laboratory for CD70 assay
8. Has acceptable laboratory test results as follows:

Parameter	Result
a. Creatinine clearance (CrCl) or serum creatinine	CrCl ≥ 50 mL/min estimated by Cockcroft-Gault *OR* Serum creatinine ≤ 1.5 × ULN
b. Serum ALT	≤ 2.5 × ULN
c. Serum AST	≤ 2.5 × ULN

Parameter	Result
d. Total bilirubin	≤ 1.5 × ULN (participant with Gilbert's syndrome or hepatic involvement with lymphoma may be included if total bilirubin is ≤ 3 × ULN and direct bilirubin is ≤ 1.5 × ULN)
e. Hemoglobin	≥ 8 g/dL or ≥ 5 mmol/L
f. Absolute neutrophil count	≥ 1.0 × 10^9/L (≥ 1000/μL)
g. Platelet count	≥ 75 × 10^9/L (≥ 75,000/μL) *Note: In presence of bone marrow involvement, platelets ≥ 50 × 10^9/L (≥ 50,000/μL)*
h. Coagulation status: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤ 1.5 × ULN, unless receiving anticoagulation

9. Has a life expectancy of at least 3 months
10. A female participant with reproductive potential must agree to use adequate contraception during GEN1160 treatment and for 6 months after receiving the last dose of GEN1160. Reproductive potential and adequate contraception (ie, highly effective methods of contraception) are defined in Section 10.3.

    NOTE: If reproductive potential changes after start of the trial (eg, female with reproductive potential becomes sexually active, premenarchal female participant experiences menarche), a female participant must begin adequate contraception (ie, highly effective methods of contraception), as described in Section 10.3.
11. A female participant with reproductive potential must have a negative serum beta human chorionic gonadotropin (β-hCG) test at screening.
12. A female participant must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during GEN1160 treatment and for 6 months after receiving the last dose of GEN1160.
13. A male participant must agree not to donate sperm during GEN1160 treatment and for 6 months after receiving the last dose of GEN1160.
14. A male participant who is sexually active with a female with reproductive potential, and has not had a vasectomy, must agree to use a barrier method of birth control himself, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner must use an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for the duration of GEN1160 treatment and for 6 months after receiving the last dose of GEN1160.
15. Male participants (including males who have had vasectomies) whose partner is pregnant should use condoms for the duration of GEN1160 treatment and for 6 months after receiving the last dose of GEN1160.

16. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria - Dose Escalation

1. Prior treatment with anti-CD70 directed therapy
2. Prior therapy with an antibody-drug conjugate with a topoisomerase 1 inhibitor payload
3. Prior allogeneic HSCT. Participants with prior autologous HSCT must have completed the procedure at least 100 days prior to the first dose of study drug.
4. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥ 90%), such as but not limited to, adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, breast ductal carcinoma in situ, or Stage I uterine cancer.
5. Known active central nervous system metastases, including carcinomatous meningitis. Participants with brain metastases may participate provided the metastases have been treated and are stable for at least 4 weeks prior to the first dose of study drug, they have no new or enlarging brain metastases and have discontinued corticosteroids prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Participants with a history of brain metastases, suspected new brain metastases, or a diagnosis of RCC should have an MRI of the brain at screening.
6. Any uncontrolled ≥ Grade 3 viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
7. Positive for hepatitis B by surface antigen expression. Additional testing (eg, hepatitis B virus (HBV) core antibody testing) should also be performed for participants with increased risk factors.
8. Active hepatitis C infection (positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
9. Positive for human immunodeficiency virus (HIV)
10. History of hepatic cirrhosis, autoimmune hepatitis, or drug-associated hepatitis
11. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, serious cardiac arrhythmia, or congestive heart failure with symptoms consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug
12. History of uncontrolled seizure disorders or clinically significant neurodegenerative disorders

13. History of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
14. Clinically significant autoimmune disease, either currently present or present within the previous 2 years, including a current requirement for systemic immunosuppressive therapy equivalent to > 10 mg/prednisone daily (local immunosuppressive therapy such as inhaled or topical corticosteroids, is allowed)
15. Prior antitumor treatments must have a washout period of 2 weeks for chemotherapy or therapy with small molecules and 4 weeks for antibody-based therapeutics prior to first dose of study drug. If the underlying disease has progressed on treatment, a washout period of 2 weeks prior to the first dose of study drug is acceptable.
16. Use of strong cytochrome P450 3A (CYP3A) inhibitors within 2 weeks prior to the first dose of study drug
17. Radiotherapy or major surgery that is not completed 2 weeks prior to the first dose of study drug
18. Participants of reproductive potential, unless under the following conditions:
    a. Must have a negative serum pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of β-hCG) result within 2 weeks prior to the first dose of study drug. Participants with false positive results and documented verification that the participant is not pregnant are eligible for participation.
    b. Must agree not to try to become pregnant starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
    d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
19. Participants who can father children, unless under the following conditions:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final dose of study drug administration.
    b. If sexually active with a person of reproductive potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use 1 of 2 contraception options at time of informed consent and continuing

throughout the study and for at least 6 months after the final dose of study drug administration.

20. Known hypersensitivity to any excipient contained in the drug formulation of GEN1160
21. Estimated life expectancy < 12 weeks, in the opinion of the investigator
22. Other serious underlying medical condition that, in the opinion of the investigator, would impair the participant's ability to receive or tolerate the planned treatment and follow-up
23. Participants with a baseline QT corrected for heart rate using Fridericia's formula (QTcF) of > 480 ms

5.2.2 Exclusion Criteria - Expansion Part A and Expansion Part B

Any potential participant who meets any of the following criteria will be excluded from being treated in the Expansion part(s) of the trial.

1. Primary central nervous system (CNS) tumor or known CNS involvement
2. Has been exposed to any of the following prior therapies within the specified timeframes:
    a. Received prior investigational CD70-targeting therapy, eg, CD70-directed CAR-T cell therapy, anti-CD70 mAb, CD3 × CD70 bispecific monoclonal antibody (bsAb), or CD70 ADC.
    b. Autologous stem cell transplant within 60 days prior to the first dose of GEN1160
    c. Allogeneic stem cell transplant within 90 days prior to the first dose of GEN1160
    d. Chemotherapy or radiotherapy within 2 weeks or major surgery within 4 weeks of the first dose of GEN1160
    e. Treatment with an investigational drug within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of GEN1160 or currently receiving any other investigational agents
    f. Prior treatment with live, attenuated vaccines within 30 days prior to the first dose of GEN1160. 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 nonauthorized coronavirus disease (SARS-CoV-2) vaccinations are not allowed.
    g. Receiving immunosuppressive drugs or systemic corticosteroids such as prednisone at doses >25 mg daily or its equivalent within 14 days prior to the first dose of GEN1160.
3. History of symptomatic autoimmune disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [eg, Wegener's granulomatosis])

4. Has clinically significant cardiac disease, including:
    a. Myocardial infarction within 6 months prior to the first dose of GEN1160, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III or IV), cardiac arrhythmia (CTCAE Version 5.0 Grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities
    b. Screening 12-lead ECG showing a baseline QT interval as corrected by QTcF > 480 ms
    c. ECHO or MUGA with LVEF <45%
5. Has clinically significant toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade 1 or lower

    Note: Participants with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the trial.
6. Active graft versus host disease (GVHD) requiring immune suppression regardless of grade
7. Active infection requiring antibiotic/antifungal/antiviral treatment
8. Has a known history of seropositivity for HIV
9. Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to immunoglobulin (Ig) therapy)
10. Known medical history or ongoing hepatitis C infection that has not been cured
11. Active second malignancy or history of another malignancy within the past 3 years, except for:
    a. Cervical carcinoma of Stage 1B or less
    b. Noninvasive basal cell or squamous cell skin carcinoma
    c. Noninvasive, superficial bladder cancer
    d. Prostate cancer with a current prostate-specific antigen (PSA) level <0.1 ng/mL
    e. Any past malignancy considered cured for ≥ 2 years (ie, eligible participants must have CR of ≥ 2 years duration)
12. Has known allergies, hypersensitivity, or intolerance to mAbs, human proteins, or other product excipients
13. Is a female who is pregnant, breastfeeding, or planning to become pregnant during GEN1160 treatment and within 6 months after the last dose of GEN1160
14. Is a male who plans to father a child during GEN1160 treatment and within 6 months after the last dose of GEN1160
15. Has any other serious, life-threatening or unstable pre-existing medical conditions, or uncontrolled intercurrent illness, including but not limited to active infection including coronavirus disease 2019 (COVID-19) infection

16. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
17. Has CNS dysfunction: seizure disorder, dementia, cerebellar disease, posterior reversible encephalopathy syndrome (PRES), autoimmune disease with CNS involvement, or stroke or intracranial hemorrhage within 6 months of the first dose of GEN1160

5.3 Participant Enrollment

An eligible participant is enrolled after agreement to participate in a clinical trial following completion of the informed consent and screening processes. Potential participants who have consented and are screened for the purpose of determining eligibility for the trial are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any trial activity after eligibility has been confirmed.

Each participant who enters into the screening period for the trial (defined as when the participant signs the informed consent) receives a unique participant identification number before any trial-related activities/procedures are performed. The participant identification number will be assigned manually. This number will be used to identify the participant throughout the clinical trial and must be used on all trial documentation related to that participant.

The participant identification number must remain constant throughout the entire clinical trial; it must not be changed after initial assignment, including if a participant is rescreened.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet the protocol-defined eligibility criteria (refer to Section 5.1 and Section 5.2) as assessed during screening. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to follow International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from health authorities. Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, participant withdrew consent, or other reasons), and any AEs related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.

Individuals who screen fail may be rescreened once. Participants who are rescreened are required to sign a new ICF. All eligibility criteria must be reassessed at the rescreening visit. Previous screening assessments (eg, scans, certain labs) may be used for rescreening purposes if still considered to be within the protocol-required window for new planned date of Cycle 1 Day 1.

6 TRIAL TREATMENT

6.1 Investigational Medicinal Product

Trial treatment should be administered as described in Table 11 until 1 or more of the discontinuation criteria in Section 7 are met.

Detailed dose modification guidance is provided in Section 6.7.2. Information regarding concomitant therapy is provided in Section 6.6.3.

Table 11: Investigational Medicinal Product

Trial Drug Name	GEN1160[a]
Dosage Formulation	CCI for IV injection
Dose (including schedule and cycle length)	GEN1160 will be tested at DLs ranging from CCI (Dose Escalation) and at selected expansion dose (Expansion) in 21-days cycles
Route of Administration	IV
Dosing Instructions	Dosing is based on the participant's BSA calculated by the Mosteller's equation, based on assessments on Day 1 of each cycle. Participants who have a BSA > 2.2 m^2 will receive a dose based on BSA of 2.2 m^2. GEN1160 should be infused over a minimum of 30 minutes and maximum of 2 hours. The maximum rate of infusion should not exceed 250 mL/hr. In Dose Escalation, participants will be required to undergo a 2-hour observation period on Day 1 of the first 2 cycles following completion of the infusion. The infusion should be administered at a properly equipped site and staffed to manage anaphylaxis, should it occur. In Expansion, no observation period is required post-infusion. GEN1160 must not be administered as an IV push or bolus. GEN1160 requires dilution prior to administration. A 0.22 micron in-line polyethersulfone filter must be used during IV administration. GEN1160 should not be administered with other medications. The infusion site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Participants should be advised to report redness or discomfort promptly at the time of administration or after infusion. Institutional guidelines should be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in (Pérez Fidalgo et al., 2012; Polovich et al., 2014). Participants who experience a DLT should not receive further treatment with GEN1160 unless toxicity is adequately managed, the investigator considers resumption of GEN1160 to be appropriate, and there is approval from the study Medical Monitor. If a participant has a clinically significant, unresolved TEAE in Cycle 1 or beyond, the next dose may be delayed for up to 14 days. Delays due to other reasons or lasting > 7 days must be discussed with the Medical Monitor. During dose delay, CBC should be collected frequently (at least twice weekly) to monitor cytopenia and count recovery. CMP should be collected at least weekly to monitor transaminase elevations and recovery.

	Recommended dose modifications for study treatment-associated toxicity are summarized in Section 6.7.2. Refer to the IMP Manual for detailed instructions including drug dilution and injection volume.
Packaging	GEN1160 will be provided CCI [redacted]
Labeling	Trial drug labels will contain information to meet the applicable regulatory requirements. For further details see the IMP Manual
Storage and Handling	Vials and solutions containing GEN1160 should be refrigerated at 2°C to 8°C in a controlled location accessible only to the pharmacist, the investigator, or a duly designated person. GEN1160 vials and solutions should be stored protected from direct sunlight until the time of use. CCI [redacted]

Abbreviations: BSA=body surface area; CBC=complete blood count; CMP=comprehensive metabolic panel; DL(s)=dose level(s); DLT=dose-limiting toxicity; hr=hour; IMP=investigational medicinal product; IV=intravenous; TEAE=treatment-emergent adverse event.

[a] Refer to the IMP Manual for further details.

6.1.1 Premedication and Management of IRRs

6.1.1.1 Premedication for IRRs

The purpose of the premedication is to reduce the risk of an IRR. Premedication with antipyretics and antihistamines are required in Cycle 1:

1. Antipyretics: Acetaminophen 650 to 1000 mg by mouth (PO), or equivalent.
2. Antihistamine: Diphenhydramine 25 to 50 mg IV or PO, or equivalent.

Premedication should be administered 30 minutes to 2 hours prior to the GEN1160 infusion.

If there is no IRR or there is only Grade 1 or 2 IRR during Cycle 1, the use of premedication is optional for subsequent cycles.

In Dose Escalation, participants will be required to undergo a 2-hour observation period on Day 1 of the first 2 cycles following completion of the infusion. In Expansion, there is no requirement for post-infusion observation and participants should be monitored, per institutional practice.

6.1.1.2 Management of IRRs

Participants should be carefully observed during GEN1160 infusions. Trained trial staff should be prepared to intervene in case of any IRRs occurring, with resources necessary for resuscitation. Interrupt GEN1160 infusion for IRRs and institute medical management/supportive treatment as needed:

For Grade 1 IRRs, closely monitor the signs/symptoms of the IRR. Intervene the infusion if the IRR worsens.

For Grade 2 IRRs, stop the infusion immediately and treat the participant; once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. If the participant does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate.

For Grade 3 IRRs, stop the infusion immediately and treat the participant; once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. If the participant does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate. If, after resumption of the infusion, symptoms return (irrespective of grade), permanently discontinue administration of GEN1160 and manage the IRR symptoms accordingly.

For Grade 4 (life-threatening) IRR, permanently discontinue administration of GEN1160 and institute appropriate emergency care.

6.2 Product Complaints

A product 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 complaint may have an impact on the safety and efficacy of the product.

Product complaints must be reported to the sponsor's Quality Assurance (QA) department by trial-site personnel, within 24 hours of awareness of the event. The IMP Manual contains contact information (email and telephone) for Genmab QA and instructions for reporting complaints.

In addition to reporting the complaint, if the product defect is combined with an AE or SAE, the trial-site personnel must report the AE or SAE to the sponsor according to the AE and SAE reporting process and timelines (refer to Section 10.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Preparation, Handling, and Storage

Guidance for the preparation, handling, and storage of trial drug(s) is described in the investigational medicinal product (IMP) Manual.

6.3.2 Drug Accountability and Destruction

The investigator or designee must maintain an accurate record of received, returned, and/or destroyed IMP and administration of trial treatment to trial participants in a drug accountability log/record. Drug accountability will be verified by the site monitor on a continuous basis and at the completion of the trial.

When drug accountability has been verified by the site monitor, all expired/unused trial IMP (eg, vials, capsules, prefilled syringes) can be destroyed or returned to the sponsor in accordance with the guidance in the IMP Manual.

Final drug accountability will be assessed at the end of the trial (or at site closure, if applicable) in accordance with local regulations and guidelines.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Randomization will not be used in the Dose Escalation part of this trial.

During the Dose Escalation part, once a specific DL is open for enrollment, participants will be manually assigned to that DL. Site personnel must contact the contract research organization (CRO) and the sponsor when a potential participant has been identified. If there is an open slot for enrollment, the site will be given approval to start the consenting and screening process. If there is no open slot, investigators should decide on the appropriate treatment for the participant should the participant require immediate anticancer treatment; otherwise, the participant may be placed on the waiting list, and the site will be alerted once an opening has become available.

During Expansion Part A, participants will be manually allocated to the DLBCL cohort (see Section 5.3).

During Expansion Part B, participants will be randomized 1:1 using permuted block randomization to one of the selected DLs.

6.5 Treatment Compliance

The trial treatment will be administered in the controlled environment of a clinical research center, and the direct observation of trial treatment administration by trial staff will ensure compliance with trial requirements. The date and time of each trial treatment administration will be documented.

Treatment start and stop dates, including dates for trial treatment delays and/or dose reductions will also be documented.

6.6 Prior and Concomitant Therapies

The sponsor’s medical officer (or delegate) should be contacted if there are any questions regarding prior or concomitant medication or therapies.

6.6.1 Prior Anticancer Therapies

Prior anticancer therapies received from the time of initial diagnosis and until signing of informed consent for the treatment of study disease (including chemotherapy, radiotherapy,

antibody-drug conjugates, immune checkpoint inhibitors (CPIs), antibodies, transplantation, surgery, any investigational anticancer drugs, etc) must be documented.

The best response, reason for discontinuation, dates of administration, and date of progression should be reported for prior anticancer therapies.

Refer to Section 6.6.3.2 for details regarding prohibited prior anticancer therapies or washout periods for prior anticancer therapies.

6.6.2 Prior Therapies

Any medication, (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine, or blood transfusions received within 28 days before screening must be documented. Any SARS-COV-2 vaccines and seasonal flu vaccinations received within 3 months prior to the first dose of GEN1160 must be documented.

Refer to Section 6.6.3.2 for details regarding prohibited prior therapies or washout periods for prior therapies.

6.6.3 Concomitant Therapies

Participants must notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) they take after the start of GEN1160 administration. All medications (other than GEN1160) and significant nondrug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered during the trial (ie, beginning with administration of the first dose of GEN1160 until 30 days after the last dose of GEN1160) must be documented.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.6.3.2).

Concomitant therapies should also be documented beyond 30 days after the last dose of GEN1160 only in conjunction with worsening AEs or new SAEs related to GEN1160.

6.6.3.1 Permitted Concomitant Therapies

The following concomitant medication and therapies are permitted during the trial:

- SARS-CoV-2 vaccine is generally permitted, including messenger ribonucleic acid (mRNA)-based, protein-based, or nonreplicating viral vector-based vaccines. Consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired. SARS-CoV-2 vaccine should not be administered during the screening period and DLT observation period. For other immunizations, physicians should review the participant’s vaccination status and participants should, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating treatment.

- Hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor (G-CSF) (filgrastim, pegfilgrastim), granulocyte/macrophage colony-stimulating factor (sargramostim), or thrombopoietin (oprelvekin, eltrombopag) are permitted if clinically indicated. **Note: At the onset of Grade 3 or 4 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.
- Participants who are considered to have an increased risk for CTLS (see Section 10.8), eg, due to the type of lymphoma, the tumor burden (bulky disease and/or elevated lactate dehydrogenase [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 (Coiffier et al., 2008). If signs of CTLS 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 CTLS is recommended, for the minimum sampling time points for TLS, please refer to Table 3. For additional details please refer to Table 19 and Table 20.
- Anti-infection prophylaxis for bacterial, viral, fungal, or pneumocystis infections is allowed and should be given per institutional practice.
- IV immunoglobulins are allowed to manage hypogammaglobulinemia at the investigator's discretion per institutional practice.
- Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example, proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).
- Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

6.6.3.2 Prohibited Concomitant Therapy

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

The following concomitant therapies are prohibited from Cycle 1 Day 1 until 30 days after last dose of GEN1160 unless otherwise specified:

- Any anticancer therapy intended for the treatment of lymphomas, eg, cytotoxic chemotherapy, immunotherapy, radiotherapy or experimental therapy.

  Note: Local palliative radiotherapy on non-target lesions is allowed.
- Strong inhibitors of CYP3A and cytochrome P450 1A2 (CYP1A2) are prohibited (see Section 10.13) to minimize potential for increased exatecan exposure.
- Corticosteroid that exceeds a total daily dose of 25 mg of prednisolone or equivalent administered for more than 14 days unless for the management of AEs.

- Live, attenuated vaccines received within 30 days prior to the first dose of GEN1160, at any time during GEN1160 treatment, and for 3 months following the last dose of GEN1160.

  Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.

- In the Dose Escalation part, administration of SARS-CoV-2 vaccine during the screening period and DLT period is not permitted.
- Participation in any other investigational or interventional studies is not permitted.

Participants who require the use of any of these agents will be discontinued from GEN1160 treatment. The sponsor must be notified. Participants who are discontinued from GEN1160 treatment will be followed for safety outcomes for 30 days following the last dose of GEN1160 or until the participant receives a new anticancer therapy, whichever occurs first.

The above lists of medications are not necessarily all-inclusive. The investigator should contact the sponsor's Medical Monitor if questions arise regarding medications not listed above.

Supportive therapies for bone metastases, including bisphosphonates and receptor activator of nuclear factor kappa-B (RANK)-ligand inhibitors are allowed; however, initiation of these therapies during the first cycle of study treatment should be avoided to prevent confounding the assessment of safety. Examples include alendronate (Fosamax), zolendronic acid (Reclast), risedronate (Actonel), and denosumab (Prolia).

6.7 Dose Modifications and Stopping Rules

6.7.1 Dose-Limiting Toxicity (Dose Escalation)

DLTs will be graded according to NCI CTCAE, Version 5.0. The DLT evaluation period is 28 days of treatment, which must include 7 days of follow-up after the second dose. A DLT is defined as any of the following during the DLT evaluation period if considered not clearly and incontrovertibly due to the underlying disease or extraneous causes by either the investigator or the sponsor:

- Any death not clearly due to the underlying disease or extraneous causes
- ≥ Grade 3 non-hematologic toxicity, with the following exceptions:
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade 2 or less within 72 hours with adequate supportive care
  - ≥ Grade 3 electrolyte or serum chemistry abnormality that resolves to Grade 2 or less within 72 hours, unless the participant has clinical symptoms, in which case these abnormalities are considered DLTs regardless of duration

  - ≥ Grade 3 amylase/lipase elevation not associated with signs/symptoms of pancreatitis that resolves to ≤ Grade 2 or baseline within 72 hours
  - Grade 3 IRRs that resolve to ≤ Grade 1 within 24 hours with or without intervention
    - In the event of a Grade 3 IRR in ≥ 20% of participants, all subsequent participants will require pre-medication and/or modification of infusion approach per Section 6.1.1. For subsequent participants, any ≥ Grade 3 IRR will be considered a DLT
- The abnormality meets the definition of drug-induced liver injury (DILI) as defined in Section 8.4.3.3
- Grade 4 anemia or Grade 3 anemia lasting > 7 days (transfusions permitted)
- Grade 4 neutropenia lasting > 7 days
- Grade 4 thrombocytopenia lasting > 7 days, or ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- ≥ Grade 3 febrile neutropenia (ANC < 1000/µL with a single oral temperature measurement of ≥ 38.3ºC [101ºF] or a temperature of ≥ 38ºC [100.4ºF] sustained over a 1-hour period)
- Dose delay ≥ 14 days due to toxicity that is not clearly related to the underlying disease or extraneous causes

Participants who experience AEs meeting DLT criteria may continue study treatment if the toxicity resolves to Grade 1 or baseline, and the investigator and sponsor judges the participant may benefit from further therapy. Subsequent doses will be defined by the Medical Monitor in discussion with the site investigator in the context of the type of AE observed and may be given at the same or a reduced dose level. Re-consent is not required unless deemed necessary by the applicable Institutional Review Board (IRB).

6.7.2 Dose Modification Guidance and Stopping Criteria

In Dose Escalation, intraparticipant dose modifications such as increase or decrease of GEN1160 dosage are not allowed; only dose delay is allowed.

In Expansion, dose modifications such as increase or decrease of GEN1160 dosage and dose delay are allowed.

6.7.2.1 Dose Escalation Part

- If a participant experiences a DLT, GEN1160 treatment will need to be interrupted, and further doses withheld while managing the DLT. The investigator is required to notify the sponsor's Medical Monitor promptly and conduct a full assessment of the event and benefit-risk for the participant. The participant may continue treatment with GEN1160, if the toxicity recovers to ≤ Grade 2 or baseline within 4 weeks from occurrence of the DLT. Continuous treatment with GEN1160 must be approved by the sponsor's Medical Monitor. GEN1160 treatment will be permanently discontinued, 1) in the event the DLT

is not resolved to ≤ Grade 2 or baseline within 4 weeks, or 2) in the event a participant experiences a second episode of a DLT with GEN1160. Following a DLT of Grade 4 non-hematologic toxicity, GEN1160 treatment should be immediately interrupted, and proper management of the AE should be initiated promptly. Resumption of GEN1160 may be considered under the following conditions after discussion with the Medical Monitor: 1) Grade 4 AE has improved to Grade 2 or better; or 2) participant has shown clinical benefit from the GEN1160 treatment.

- If a participant experiences toxicity that would have qualified as a DLT, but the event occurs after the DLT evaluation period, the participant's benefit-risk must be thoroughly assessed by the investigator. Continuous treatment with GEN1160 must be approved by the sponsor's Medical Monitor.
- For the participant who receives treatment beyond the DLT evaluation period, all corresponding AEs that would have met the DLT criteria will be considered for the purpose of determining the expansion dose and/or MTD (if reached). For the declaration of the expansion dose from the Dose Escalation part for further development of GEN1160 in the Expansion part, the totality of the data including safety, tolerability, immunogenicity, PK, pharmacodynamics, and preliminary efficacy will be evaluated.
- During Dose Escalation, a planned dose of GEN1160 can be postponed for up to 4 weeks due to an AE whether it is considered drug-related or not.

In case of dose delay of more than 4 weeks from the last trial drug administration due to toxicity (not a DLT), continuous GEN1160 treatment may be considered if the participant is clearly benefiting from GEN1160 treatment (eg, imaging indicating clinical activity of GEN1160). Resuming GEN1160 must be approved by the sponsor's Medical Monitor.

During the trial, the GEN1160 dose can be held for the following laboratory results:

a. If platelet count is $< 50 \times 10^9$/L, hold dose until platelet count is $\geq 50 \times 10^9$/L.
b. If febrile neutropenia is $< 0.5 \times 10^9$/L, hold dose until neutrophil count is $\geq 0.5 \times 10^9$/L.
c. If hemoglobin is < 8 g/dL (< 80 g/L), hold dose until hemoglobin is ≥ 8 g/mL (≥ 80 g/L).

Note: If the investigator deems any of the above cytopenia as bone marrow involvement due to the disease, continuation of GEN1160 treatment can be discussed with the sponsor's Medical Monitor.

G-CSF use is mandated at the onset of Grade 3 or Grade 4 neutropenia. Transfusion with blood products may be administered, per institutional standards.

If a dose delay occurs, then PK CCI assessments should be performed on or relative to the actual day of trial drug administration, not on the original scheduled administration day.

Refer to Table 12 for dose modification guidelines for specific AEs (including guidance for permanent discontinuation of treatment).

Table 12: Dose Modification Guidelines for Adverse Events

	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0 Except Cairo-Bishop for TLS/CTLS)	Adverse Event Management
Hematologic	Neutrophil counts decreased/ Neutropenia	Grade 3 or 4	• Hold GEN1160 dosing until neutrophil count recovers to $\geq 1.0 \times 10^9$/L • G-CSF is mandated at the onset of Grade 3 or Grade 4 neutropenia • Closely monitor ANC for count recovery • Consider G-CSF prophylaxis for subsequent cycles
		Recurrent Grade 4 neutropenia	• Hold GEN1160 dosing and manage with G-CSF until neutrophil count recovers to $\geq 1.0 \times 10^9$/L • Consider dose reduction to 90 mg/m^2 for each occurrence or • Consider discontinuation
	Platelet count decreased/ thrombocytopenia	Grade 3 or 4	• Hold GEN1160 dosing until platelet count recovers to $\geq 50 \times 10^9$/L • Platelet transfusions should be administered per institutional standards
	Anemia	Grade 3 or 4	• Hold GEN1160 dosing until hemoglobin improves to ≥ 8 g/L • Red blood cell transfusions should be administered per institutional standards.
	TLS/CTLS	Any grade	• Hold GEN1160 dosing until resolution of TLS/CTLS event
Non-hematologic	Nausea, vomiting, diarrhea, ALT/AST elevations	Grade 3 or 4	• Hold GEN1160 dosing until improvement to $\leq$ Grade 1
		Grade 3 or 4, recurrent	• Hold GEN1160 dosing until improvement to $\leq$ Grade 1 • Initiate proper management of the AE • Permanently discontinue GEN1160 if no improvement within 14 days • Consider dose reduction to 90 mg/m^2 if improved to $\leq$ Grade 1 within 14 days

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; CTLS=clinical tumor lysis syndrome; G-CSF=granulocyte colony-stimulating factor; TLS=tumor lysis syndrome.

6.7.2.2 Expansion Parts A and B

Dose modification guidance used in the Dose Escalation part (see Section 6.7.2.1) will be applied to the Expansion Parts A and B, as appropriate, CCI [redacted]

6.7.2.3 Dose Delays of GEN1160 Due to COVID-19 Infection

During the trial, GEN1160 should be withheld in participants with a suspected COVID-19 infection or with a positive viral test. GEN1160 may be resumed if the following criteria are met:

- Symptomatic participants:
  - Participant has recovered, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (eg, cough, shortness of breath), AND participant has obtained 2 negative molecular (eg, PCR) tests or negative antigen tests with results ≥ 24 hours apart, and it has been 7 to 10 days after the second negative test.
- Asymptomatic participants:
  - Participant has obtained 2 negative molecular (eg, PCR) tests or negative antigen tests with results ≥ 24 hours apart and it has been 7 to 10 days after the second negative test.

6.7.3 Safety Stopping Guidance for the Trial

The trial can/will be stopped for unacceptable toxicity as per recommendations from SMC in Dose Escalation or Safety Committee in the Expansion part(s) and based on a benefit-risk assessment. Fatal events considered related to GEN1160 should always be assessed by the SMC in Dose Escalation or Safety Committee in the Expansion part(s).

6.7.3.1 Safety Stopping for Dose Escalation

If a participant death is considered related to GEN1160 by the sponsor, enrollment will be paused at that dose level and all higher dose levels until:

- The case is reviewed by the investigator, the sponsor, and the SMC
- The sponsor has notified applicable regulatory authorities of the outcome of the safety assessment and justification for restarting enrollment in the affected cohorts. If necessary, according to local regulatory requirements, the sponsor has received approval to resume enrollment.

6.7.3.2 Safety Stopping for Expansion Part A and B

Pocock's flexible alpha-spending method will be used as a stopping guidance for each Expansion part similar to the method described by (Ivanova et al., 2005), but in a more stage-wise manner. For each individual cohort, the overall significance level to stop further treatment due to a safety concern is set to CCI [redacted]. Table 13 and Table 14 provide stopping guidance for Expansion Parts A

and B, respectively. The alpha spent will be adjusted if the information rates deviate from the planned rates.

For the Grade 4 treatment-related AEs, the same acceptable rate of CCI is adopted for all Expansion parts. If data indicate a treatment-related death rate exceeding CCI, stopping the Expansion part(s) will be considered.

If any of the boundaries in Table 13 and Table 14 are crossed for an Expansion part, a prompt comprehensive review of the safety data will be conducted to determine if the trial should be stopped.

Table 13: Stopping Guidance for Expansion Part A

Number of Participants Dosed at Dose Level	5	10
Grade ≥ 4 Treatment-related Adverse Event (stop if ≥)	3	4
Treatment-related Death (stop if ≥)	1	2

Table 14: Stopping Guidance for Expansion Part B

Number of Participants Dosed at Dose Level	10	15	25
Grade ≥ 4 Treatment-related Adverse Event (stop if ≥)	4	5	6
Treatment-related Death (stop if ≥)	2	2	2

6.8 Management of Overdose

An overdose of GEN1160 is defined as administration of ≥ 20% of the intended dose. In the event of an overdose of GEN1160, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of GEN1160.
- Notify the Medical Monitor within 24 hours of the overdose, to discuss details of the overdose (eg, exact amount of GEN1160 administered, participants' body surface area [BSA]) and any AEs.
- Any AE associated with an overdose should be recorded on the AE electronic case report form (eCRF) with the diagnosis of the AE.

7 DISCONTINUATION OF TREATMENT AND DISCONTINUATION FROM TRIAL

7.1 Discontinuation of Treatment

Participants can decline to continue receiving GEN1160 treatment and/or other protocol-required therapies or procedures at any time during the trial but continue participation in the trial. Participants who have discontinued GEN1160 treatment and/or other protocol-required therapies or procedures should not be automatically removed from the trial. Whenever safe and feasible, it is imperative that participants remain on-trial to ensure safety surveillance and/or collection of outcome data (ie, continue efficacy evaluations according to the trial protocol).

The participant may discontinue both GEN1160 treatment and further participation in trial activities; however, they may continue to be followed for survival (see Section 7.1.4) and are not considered discontinued from the trial (see Section 7.2).

Reasons for discontinuation from GEN1160 treatment may include any of the following:

- Disease progression according to response criteria outlined in Section 10.11
- Clinical progression
- Absence of clinical benefit
- Unacceptable AE(s) requiring treatment discontinuation
- Initiation of non-GEN1160 anticancer therapy
- Participant requests to discontinue trial drug treatment
- Sponsor or investigator decision
- Participant noncompliance
- Pregnancy
- Lost to follow-up

7.1.1 End of Treatment

For Dose Escalation, an end of treatment (EOT) visit should occur 30 days after the last dose of GEN1160 unless delayed due to an AE or conducted earlier due to the start of another anticancer therapy. If EOT evaluations are completed before 30 days after the last study treatment, the participant will be contacted 30 days (via phone screen) following the last treatment to assess any AEs.

Participants will be asked to attend the EOT visit and complete the assessments per the Schedule of Activities (see Section 1.3).

For Expansion, the EOT visit should be conducted as soon as possible after the decision to end treatment or upon treatment completion before initiation of non-protocol therapy. The visit should be done within 7 days from the date the decision is made by the investigator to

discontinue study drug. The date of the last dose and the reason for end of treatment must be documented.

7.1.2 Safety Follow-up Visit(s)

Participants in Expansion discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the participant receives the last dose of GEN1160. If the decision for treatment discontinuation is made at least 30 days after the last dose of trial treatment, the 30-day safety follow-up visit can be combined with the end of treatment visit.

If the participant initiates new anticancer treatment within 30 days of the last dose of GEN1160, the safety follow-up visit should be performed prior to starting new anticancer treatment unless the first safety follow-up visit was completed < 30 days prior.

7.1.3 Post-Treatment Follow-up

Upon permanent discontinuation of GEN1160 prior to disease progression, post-treatment assessments for efficacy should continue until disease progression or start of new anticancer therapy. Assessments will be performed based on the schedules described in Section 1.3.

7.1.4 Survival Status Follow-up

For Dose Escalation, a first follow-up visit will occur 12 weeks (± 1 week) from the most recent prior response evaluation. Subsequent follow-up visits will be scheduled 12 weeks (± 1 week) after the previous follow-up visit.

All participants who discontinue treatment with GEN1160 will remain on the study for follow-up and continue to be assessed for survival status and collection of first subsequent anticancer treatment information until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Participants who discontinue treatment prior to disease progression will continue to be assessed for efficacy for up to 12 months after EOT until progressive disease (PD) is documented or a new therapy is initiated. Response will be assessed by CT, PET/CT scan (if diagnostic-quality CT scan included, and/or MRI scan of the chest, abdomen, and pelvis (and neck if tumor involvement in this region is either documented or suspected) with IV contrast unless contraindicated.

Participants who have initiated a subsequent anticancer therapy will not be assessed for response but will be followed for survival.

In Expansion, survival status will be assessed every 12 weeks (±14 days), beginning from the day the participant receives the last trial administration and continuing until the participant dies, withdraws consent for survival status follow-up, or the trial ends. Survival status may be requested more frequently around the time of a database lock or other trial milestones. Refer to Section 7.3 for guidance regarding participants lost to follow-up.

Site personnel, or an independent third party, will attempt to collect the survival status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not receive trial treatment. Participants may be contacted by telephone, email, or visit. Additionally, survival status may be collected through medical records, national registries, or publicly available information, as allowed per local regulation. If survival status is determined as deceased, this will be documented.

7.2 Withdrawal From the Trial

Reasons for discontinuation of a participant from the trial are:

- Death
- Lost to follow-up
- Sponsor decision
- Participant withdraws consent from trial participation
- Maximum trial duration met

If the reason for discontinuation from the trial is withdrawal of consent, then no additional assessments are allowed, but the sponsor may retain and continue to use any data collected before such a withdrawal of the consent. When a participant withdraws before completing the trial, the reason for withdrawal should be documented.

If a participant withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must notify the sponsor accordingly (see Section 10.4 for further details).

7.3 Lost to Follow-up

A participant will be considered as lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be reached by the trial site. The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have discontinued from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of all assessments applicable to this trial.

All assessments in Dose Escalation and Expansion should be performed prior to GEN1160 administration unless otherwise indicated in the Schedule of Activities. Sample collections for PK and biomarker assessments should be kept within the allowed visit windows.

Instructions for the collection, handling, storage, and shipment of samples can be found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be conducted under the specified, and where applicable, temperature-controlled conditions as indicated in the Laboratory Manual.

8.1 Demography and Baseline Assessments

8.1.1 Demographics

The following demographic details will be collected at screening, where permitted by local regulations:

- Gender and sex assigned at birth
- Age at time of screening
- Race
- Ethnicity

Rationale for collecting race and ethnicity in all participants: Clinical development of a drug requires an understanding of the optimal dose and/or exposure–effect relationship. To understand the relationship between exposure and safety/efficacy, PK of the drug needs to be characterized in a participant population, which includes quantitative characterization of interindividual variability (IIV). Specifically, understanding of IIV at the population level can be achieved using population PK modeling, where the PK of a drug is characterized in the target participant population and IIV is investigated by assessing the effect of different covariates on PK parameters. Historically, race and ethnicity are important demographic variables contributing to IIV (Gill et al., 2016; Johnson, 1997; Johnson, 2000; Xie et al., 2001), and therefore this information will be helpful to assess the impact of exposure on safety and efficacy.

8.1.2 Diagnosis and Disease Status

A participant's history relating to the underlying disease including primary diagnosis, date of diagnosis, as well as disease status at trial entry, staging, and genetic alterations will be recorded. The following should be recorded at screening:

- Date of diagnosis
- Subtype

- Staging at diagnosis and at screening, including constitutional symptoms (B symptoms) (Section 8.1.7)

To confirm eligibility, the local pathology report will be collected. The report should include relevant markers associated with the B-NHL subtype assessed by histology, cytogenetics, fluorescent in situ hybridization, or PCR. The local pathology reports containing the relevant information must be sent to the Medical Monitor, or designee, prior to enrollment. In absence of a local pathology report, enrollment requires preapproval by the Medical Monitor or delegate.

Additionally, if known, local-assessed cancer-associated mutations, gene signatures, and immune therapy prognostic targets may also be recorded.

8.1.3 Medical History

Participant medical history (which includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications) will be assessed at screening.

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of trial treatment 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 treatment should only be reported if it is an AE assessed by the investigator to be related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of trial treatment will be documented as an AE. See additional reporting details in Section 10.2.

8.1.4 Prior and Concomitant Medication

Prior and concomitant medication given within 28 days prior to screening and throughout the trial should be documented. Once a participant moves into survival follow-up, only new anticancer treatment information will be collected.

Concomitant medication and therapies are described in Section 6.6.3.

8.1.5 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 participant's medical history.

Blood transfusions will also be documented.

8.1.6 Prior Cancer Therapy and Surgery

Administration of prior anticancer therapies (including surgery, radiotherapy, chemo-radiotherapy, systemic treatment regimens, etc) for the treatment of NHL, RCC, or NPC from the time of diagnosis until enrollment in this trial must be reported in the appropriate section of the eCRF. Best response and stop reason along with dates of administration and progression should be reported.

8.1.7 Constitutional Symptoms

Constitutional symptoms will be evaluated and documented for all participants as indicated in the Schedule of Activities (Section 1.3). Constitutional symptoms include night sweats, weight loss >10% over 6 months, extreme fatigue and/or fever without infection.

8.1.8 Pregnancy Testing

For participants of reproductive potential, a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline (Day -14 to Day 1 [Dose Escalation]; Day -21 to Day -1 [Expansion]). After the first cycle, urine pregnancy tests may be performed within 7 days prior to Day 1 of each cycle and at the EOT visit and any positives should be confirmed by serum test. A negative pregnancy result is required within 24 hours before the participants may receive study drug. Pregnancy tests may also be repeated, as requested per IRB/Independent Ethics Committee (IEC) or if required by local regulations.

8.2 Efficacy Assessments

Efficacy assessments will be conducted at the time points specified in the Schedule of Activities (Section 1.3).

Imaging assessment schedules in both the Dose Escalation and Expansion are: at screening, Week 6 ± 7 days, Week 12 ± 7 days, Week 18 ± 7 days, Week 24 ± 7 days, Week 30 ± 7 days, Week 36 ± 7 days, Week 42± 7 days, Week 48 ± 7 days, and then every 6 months (± 14 days) until participant has disease progression, starts new anticancer therapy, withdraws from trial, or dies, whichever comes first. Disease assessment and imaging assessment should not be delayed when there is a treatment cycle delay, ie, imaging assessment time points are counted from the date of the first dose of GEN1160 by calendar days, not by treatment cycles. Disease evaluation and response assessment may be conducted more frequently if clinically indicated. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. Please refer to Schedule of Activities (Section 1.3) for specified time points. Copies of imaging reports must be made available for sponsor’s review upon request.

8.2.1 Evaluations

Disease assessments by radiological imaging, physical examination, laboratory testing, and other procedures should be performed at the site level throughout the trial as shown in the Response

assessment in the Schedule of Activities (Section 1.3), or more frequently if clinically indicated. For imaging assessments, the same radiographic modality used at screening for disease evaluation should be used throughout the trial for consistent response evaluations.

8.2.1.1 Radiographic Assessments

Radiographic Assessment for NHL

A combined fluorodeoxyglucose (FDG)-PET/CT scan (or CT/MRI and FDG-PET when PET-CT scan is not available) must be performed within 28 days before Cycle 1 Day 1 (Dose Escalation) and within 21 days before Cycle 1 Day 1 (Expansion). Imaging assessments performed as SOC prior to the participant signing of informed consent may be submitted as screening assessment, if assessment is performed within 42 days of Cycle 1 Day 1.

As all participants are anticipated to have FDG-avid tumors at screening, subsequent disease assessments will include FDG-PET using the 5-point scale (see Section 10.10; (Barrington et al., 2014)). 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 participant 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 participant.

Participants 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 participants who are 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 (see Section 1.3) and performed during the trial only if clinically indicated.

Radiographic Assessment for RCC and NPC

Tumor evaluation will be performed by CT, PET/CT scan (if diagnostic-quality CT scan included, and/or MRI scan of the chest, abdomen, and pelvis). Imaging of the neck must also be obtained if there is documented or suspected involvement in this region. Scans must be of diagnostic quality, and IV contrast must be used unless medically contraindicated. For each assessed lesion, the same modality should be used throughout the duration of the study. For participants unable to tolerate contrast-enhanced CT assessments, MRI imaging is acceptable. MRI scans may not be appropriate to assess lung parenchymal lesions and CT without contrast enhancement is acceptable in such situations. If any other radiographic or disease assessment examination is conducted per SOC, the assessment information will be documented.

8.2.1.2 Bone Marrow Assessment

For participants with known bone marrow involvement or whose disease is suspected to have bone marrow involvement, fresh bone marrow biopsy and/or bone marrow aspirate must be obtained at screening and to confirm CR or suspected CR, or as clinically indicated. However, archival bone marrow biopsy obtained as routine SOC taken within 42 days before the first dose of GEN1160 is acceptable. Bone marrow evaluation must include morphological examination and either flow cytometry or immunohistochemistry, if warranted, to confirm the presence or absence (complete remission) of lymphoma.

8.2.1.3 Assessment of Disease Response and Progressive Disease

All response assessments should be conducted throughout the trial until disease progression, starts new anticancer therapy, withdrawal of consent from trial participation, or death, whichever comes first. Response assessments will be performed by the investigators at the local site to make decisions for continuation of the study treatment.

For time points when FDG-PET assessment (metabolic response) is available, the FDG-PET (metabolic response) assessment trumps the CT-response in FDG-avid histologies. For time points when only CT is available, following a prior FDG-PET assessment, CT assessments may be affected by the prior PET-CT assessment (eg, CT-based PR at current time point, with no worsening, does not preclude prior FDG-PET CR [metabolic response] and response can stay as CR).

Tumor response for NHL participants will be based on the Lugano criteria (Cheson et al., 2014). Tumor response for RCC and NPC will be based on RECIST Version 1.1.

8.3 Safety Assessments

Any clinically relevant untoward events occurring during the trial must be documented as AEs. Any clinically significant abnormalities persisting at the end of the trial/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached (see Section 8.4.6).

The trial will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Section 1.3).

8.3.1 Physical Examination

A complete (full) physical exam (according to SOC) should be performed during the screening period and at the time points specified in the Schedule of Activities (Section 1.3). Physical examinations should include assessments of the following body systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Abnormalities identified during physical examination should be recorded. Any relevant findings during screening should be reported as medical history, and as AE if caused by a protocol-mandated procedure (eg, tumor biopsy or CT/MRI scan). At subsequent visits, the investigator or qualified designee will perform a symptom directed/clinically indicated, brief physical examination prior to trial treatment administration.

After the first dose of trial treatment, new or worsening findings since the last assessment should be documented as AEs.

8.3.2 Body Measurements

Height (without shoes) must be measured at screening/baseline and rounded to the nearest centimeter or inch. Body weight (without overcoat and shoes) will be measured as indicated in the Schedule of Activities (Section 1.3) and rounded to the nearest kilogram.

8.3.3 Vital Signs

Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature. Vital signs will be measured and recorded prior to the start of GEN1160 administration and at additional time points specified in Section 1.3.

8.3.4 Electrocardiograms

Standard 12-lead safety ECGs will be conducted in triplicate for all participants at screening and at time points specified in Section 1.3. In addition, all participants will receive on-treatment 12-lead ECGs conducted in triplicate with PK correlation to monitor for changes in cardiac repolarization (Section 1.3). Standard ECG parameters will be measured and collected, including RR, PR, QT intervals, and QRS duration, etc.

All ECGs should be performed after the participant has been resting for at least 10 minutes and obtained within 30 minutes prior to PK blood collections unless otherwise specified (eg, within 15 minutes after the end of the infusion; see Section 1.3).

Waiting periods between each ECG are not required. Electronic or paper copies of the tracings may be submitted to the sponsor or its designee for possible central assessment.

8.3.5 ECOG Performance Status

The grading scale for ECOG performance status is shown in Section 10.5. ECOG assessment will be completed according to Section 1.3.

At screening and Cycle 1 Day 1, ECOG PS must be within 0-1 (Dose Escalation) or within 0-2 (Expansion), or the participant cannot receive trial drug. However, the Cycle 1 Day 1 ECOG PS should not be performed if the screening ECOG PS was obtained within the previous 5 days.

8.3.6 Clinical Laboratory Assessments

The laboratory assessments outlined in Table 15 (Dose Escalation) and Table 16 (Expansion) will be performed by the local laboratories at scheduled time points (see Section 1.3) during the study. Other safety tests may be conducted as clinically indicated, at the discretion of the investigator.

Table 15: Clinical Laboratory Assessments (Dose Escalation)

Category	Test
Glycemic control:	• fasting glucose • Hgb A1c
Serum chemistry (biochemistry):	• albumin • alkaline phosphatase • ALT • AST • blood urea nitrogen • calcium • carbon dioxide • creatinine • chloride • lactate dehydrogenase • phosphorus • potassium • sodium • total bilirubin
Blood hematology:	• red blood cell count • white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) • absolute neutrophil count • platelet count • Hgb • hematocrit
Fasting lipid panel:	• total cholesterol • LDL • HDL • triglycerides
Pancreatic function:	• amylase • lipase
Coagulation:	• PT/aPTT/INR
Urinalysis:	• standard urinalysis (with reflexive microscopy for abnormal results) • urine protein and urine creatinine for UPC ratio
Pregnancy:	• Baseline serum β-hCG pregnancy test for participants of reproductive potential. Post baseline urine pregnancy test is acceptable and any positive should be confirmed by serum.
Viral serology:	• HIV • Hepatitis B surface antigen • HCV RNA test by PCR

Abbreviations: ALT=alanine transaminase; aPTT=activated partial thromboplastin time; AST=aspartate transaminase; β-hCG=beta human chorionic gonadotropin; HCV=hepatitis C virus; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; Hgb=hemoglobin; Hgb A1c=hemoglobin A1c; INR=international normalized ratio; LDL=low-density lipoprotein; PCR=polymerase chain reaction; PT=prothrombin time; UPC=urine protein creatinine.

Table 16: Clinical Laboratory Assessments (Expansion Part A and Part B)

Local Laboratory	
Test Category	**Test Name**
Hematology	Hematocrit, hemoglobin, platelets, reticulocytes (RBC indices: MCH, MCHC, MCV, % reticulocytes), white blood cells including differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes (absolute values for differential are preferred).
Biochemistry	Albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, blood urea nitrogen or urea, calcium, chloride, creatinine and estimated creatinine clearance, gamma-glutamyl transferase, glucose (non-fasting), lactate dehydrogenase, lipase, magnesium, inorganic phosphorus (phosphate), potassium, sodium, total and direct bilirubin, total protein, uric acid.
Tumor lysis sample	Uric acid, potassium, inorganic phosphorus (phosphate), calcium, and creatinine.
Coagulation	International normalized ratio, activated partial thromboplastin time, prothrombin time.
Serology/Molecular Testing	HBsAg and HBcAb. If either are positive, PCR for HBV-DNA to be performed. HCV antibody. If positive serology PCR for HCV RNA to be performed. HIV (per local regulations or institutional guidelines). CMV serology (IgG and IgM) at screening. If positive serology, CMV PCR to be performed.
Additional tests	Beta2-microglobulin (at screening only). Immunoglobulins: IgA, IgE, IgG and IgM.
Urinalysis	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase/leukocytes, specific gravity.
Pregnancy Test	For female participants with reproductive potential, a serum pregnancy test will be performed at Screening; a urine or serum test will be conducted at the start of each cycle and at other visits as indicated in Section 1.3.
Bone Marrow Biopsy and/or Aspirate	Required at screening for participants with known bone marrow involvement or whose disease is suspected to have bone marrow involvement; and to confirm CR or suspected CR; otherwise as clinically indicated. Bone marrow evaluation must include morphological examination and either flow cytometry or immunohistochemistry, if warranted, to confirm the presence or absence of lymphoma.

Abbreviations: CMV=cytomegalovirus; CR=complete response; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell.

8.4 Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Information in this section should be used in conjunction with the additional details provided in Section 10.2.

8.4.1 Definition of Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, as well as attribution definitions; severity criteria; and procedures, are provided in Section 10.2.

8.4.2 Adverse Event Reporting

The safety reporting periods are defined in Table 17. The safety reporting period starts once the participant has signed the ICF and ends 30 days after the last dose of trial treatment, participant withdraws consent, starts new anticancer treatment, or dies, whichever comes first.

Table 17: Reporting Period and Requirements

Safety Reporting Period	Reporting Requirements
Signing of ICF until first dose of trial treatment	AEs, if assessed by the investigator to be related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.
First dose through 30 days after the last dose of trial treatment (EOT visit in Dose Escalation / the safety follow-up visit in Expansion)	All AEs (see definitions in Section 10.2), regardless of causality, will be documented.
After the safety reporting period through end of trial/after end of trial	There is no requirement to monitor participants for SAEs following the protocol-required safety reporting period or after end of trial. However, if the investigator becomes aware of an SAE, it must be reported if judged by the investigator as related to trial treatment.
Refer to Section 10.2.2 for additional guidance for recording and reporting AEs and Section 7.1.2 for timing of safety follow-up visit(s).	

Abbreviations: AE(s)=adverse event(s); CT=computed tomography; EOT=end of treatment; ICF=informed consent form; SAE(s)=serious adverse event(s).
NOTE: Any second primary malignancy(ies) regardless of relatedness to trial treatment, should be reported as an SAE at any time during or after the trial if the investigator becomes aware of such an event (see Section 8.4.3.1.2).

For details regarding follow-up of AEs and SAEs, see Section 8.4.6. Refer to Section 6.2 for guidance regarding product complaints.

8.4.3 Events Requiring Immediate Reporting

Refer to Section 10.2.2 for additional guidance for recording and reporting AEs.

8.4.3.1 Serious Adverse Events

8.4.3.1.1 Serious Adverse Events

All SAEs occurring during the safety reporting period must be reported from the trial site to the sponsor no later than 24 hours following principal investigator's or any investigator personnel's awareness, including receipt of relevant test results.

Updated information regarding previously reported SAEs must be submitted as it becomes available.

8.4.3.1.2 Second Primary Malignancy

Second primary malignancy(ies) (not a metastasis of the cancer under trial; 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 within 24 hours of knowledge of the event (at any time during or after the trial).

8.4.3.2 Special Reporting Situations

8.4.3.2.1 Overdose

All cases of overdose (as defined in Section 6.8), whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event (see additional details in Section 10.2).

8.4.3.2.2 Medication Errors

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of trial treatment, whether associated with an AE or not, should be reported to the sponsor within 24 hours of knowledge of the event.

8.4.3.2.3 Pregnancy

Pregnancy is not allowed in this trial. However, any pregnancy which occurs during trial participation must be reported using the pregnancy reporting paper form available in the investigator site file.

All reports of pregnancy, occurring during the trial or 6 months after the last dose of trial drug, in female participants or partners of male participants must be reported to the sponsor within 24 hours of knowledge of the event. In the case of pregnancy in the partner of a male participant, a separate ICF will be obtained from the female partner for collection of information regarding the pregnancy.

The pregnancy must be followed up to determine the 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. Spontaneous abortions will always be considered an SAE.

Pregnant trial participants must be withdrawn from treatment immediately, whereas male participants may continue in the trial should pregnancy of female partners occur.

8.4.3.3 Potential Drug-induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a trial treatment may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential DILI in the clinical setting(s) being studied. However, finding one Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

8.4.3.3.1 Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 × ULN,

AND

2. Total bilirubin >2 × ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.4.3.3.2 Reporting Requirements

Any potential Hy's Law case should be handled as an SAE and reported promptly to the sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

8.4.3.3.3 Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to > 3 × ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding trial treatment. If DILI is ruled out, treatment with trial drug can be resumed. With a confirmed case of DILI, the participant cannot be rechallenged with trial drug.

Regional guidelines should be followed. Additional information is provided in FDA Guidance for Industry, DILI: Premarketing Clinical Evaluation, 2009.

8.4.3.4 Adverse Events of Special Interest or Other Events of Interest

Not applicable to this trial.

8.4.4 Regulatory Reporting Requirements

8.4.4.1 Reporting Requirements for Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local health 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 participants are met.

The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) is documented and reported as soon as possible, but within a maximum of 15 calendar days (fatal or life-threatening SUSARs within a maximum of 7 calendar days) of first knowledge by the sponsor or designee, to the health authorities and/or to the IEC/IRB according to the applicable local regulatory requirements. Relevant follow-up information of SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will submit SUSARs aggregated in line listings in periods as warranted by any local health authority.

The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods and according to local regulations.

The investigator must be aware of reporting regulations/requirements for their local IEC/IRB. The CRO 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 and agreement with the investigators. SUSARs aggregated in line listings will be distributed in periods as warranted by the IEC/IRB. The investigator must review such safety information in a timely manner and signoff for the review as instructed by the sponsor, to document the awareness about the latest safety updates that may impact on the investigator's responsibilities for participant care.

8.4.5 Disease-related Events/Outcomes and Other Events/Procedures Not Qualifying as Adverse Events or Serious Adverse Events

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

- Events that are clearly consistent with the expected pattern of the underlying disease or its progression 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 may be reported as AEs or SAEs if the symptom 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.

- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.2.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.
- Unrelated Procedures: Diagnostic and therapeutic noninvasive 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).

8.4.6 Follow up of Adverse Events and Serious Adverse Events

All AEs must be followed until they are resolved or until the safety follow-up visit or the start of new anticancer treatment, whichever comes first.

All SAEs that are ongoing at the follow-up visit(s) should continue to be followed on a regular basis until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

8.4.7 Precautions and Warnings

Refer to the IB for detailed information for precautions and warnings. Additional relevant safety information collected between IB updates will be communicated in the form of investigator notifications. Significant information will be included in the ICF and should be discussed with the participant during the trial.

8.5 Pharmacokinetic and Immunogenicity Assessments

Pharmacokinetics will be assessed based on GEN1160-related analyte concentrations measured at defined time points (see Section 1.3).

GEN1160 conjugated-exatecan, total antibody (TAb), and unconjugated exatecan concentrations in plasma will be determined using validated assays. The assays may include enzyme-linked immunosorbent assay (ELISA) or liquid chromatography with tandem mass spectrometry (LC-MS/MS), as well as other assays if further characterization is required.

Analysis of GEN1160 ADC concentrations may be run in a subset of samples in an exploratory way using non-validated methods. Remaining PK samples will be archived for possible analysis of other GEN1160-related species.

A qualified electrochemiluminescence assay will be used to assess levels of antidrug antibody (ADA) against GEN1160 in serum. Samples will be archived for future ADA assessment(s) including, but not limited to, neutralizing ADA assays.

8.6 Biomarker and Pharmacodynamic Assessments

Biomarker and pharmacodynamic assessments will be performed in peripheral blood and tumor tissue as outlined below in samples collected as per the time points specified in the Schedule of Activities (Section 1.3). Exploratory, predictive, and prognostic biomarkers associated with

response, resistance, or safety observations will be monitored before and during treatment with GEN1160. Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

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

8.6.1 Biomarker Assessments in Tumor Samples

A fresh tumor biopsy should be collected before administration of GEN1160 (ie, during the screening period) for all participants with accessible tumors, unless medically unfeasible. Alternatively, an archival tumor biopsy, which is the most recently collected tumor biopsy acquired within 6 months prior to enrollment, may be provided in lieu of a fresh sample. Aspirates are not acceptable. An acceptable archival tumor biopsy may consist of formalin-fixed paraffin-embedded (FFPE) tumor tissue block; freshly cut unstained slides are also acceptable. If fresh or archival (from most recent progression and taken within 6 months) tumor biopsies cannot be provided, site may submit an older archival tumor biopsy (most recent available, and preferably no older than 2 years counted from the first dose of GEN1160) representative of the histology under which the participant will be enrolled in the trial. Further details on the collection, processing, storage and shipment of tumor tissue samples will be provided in separate documents (eg, sample handling sheets or laboratory manual).

Biomarker assessments in tumor biospecimens may include, but are not limited to, CD70 expression, measurements of GEN1160 and its potential metabolites such as exatecan, as well as characterization of the tumor microenvironment, drug target(s), tumor subtyping, profiling of somatic mutations and/or gene expression. Assays may include, but are not limited to, LC-MS/MS, immunohistochemistry (IHC), ELISA, electrochemiluminescence, and next generation sequencing of ribonucleic acid (RNA) and DNA. If tissue is available from a standard clinical care biopsy collected after enrollment, it may also be examined.

8.6.2 Biomarker Assessments in Blood Samples

Pharmacodynamic assessments in blood will include, but not be limited to, cytokine levels, disease associated biomarkers, and circulating nucleic acids, in the plasma. Correlative studies will be conducted to gain a better understanding of target expression-response relationship, predictive/prognostic biomarkers, mechanism of action (MOA), resistance mechanisms, and pharmacodynamics.

Biospecimen Repository

In the US, for participants who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by the sponsor and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

9 STATISTICAL CONSIDERATIONS

The statistical analysis of the data collected in this trial is the responsibility of the sponsor. A description of the statistical methods to be used to analyze the data is outlined below. The analyses will be detailed further in the statistical analysis plan (SAP).

9.1 Statistical Hypotheses

This trial is exploratory, and no formal statistical hypothesis is defined.

9.2 Population for Analyses

Analysis Set	Definition
Full Analysis Set (FAS)	The FAS includes all participants who receive any amount of GEN1160. Participants are analyzed according to actual treatment (dose level).
Safety Analysis Set (SAS)	Same as FAS. Participants are analyzed according to actual treatment (dose level).
DLT-evaluable Analysis Set (DAS)	The DAS includes all treated participants who either experienced a dose-limiting toxicity (DLT) or were followed for the full DLT evaluation period.
Response-evaluable Analysis Set (RES)	The RES includes all treated participants who had a baseline and at least 1 postbaseline disease assessment according to RECIST Version 1.1/Lugano Classification, or who had documented disease progression at any time after the first dose of GEN1160.
Pharmacokinetic Analysis Set (PAS)	The PAS includes all participants who receive any amount of GEN1160 and have at least one postbaseline concentration measurement.
Immunogenicity Analysis Set (IAS)	The IAS will include all participants who receive at least one dose of GEN1160 and have a baseline and at least one evaluable on-treatment ADA sample.

9.3 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General Considerations

Data from the Dose Escalation and Expansion parts will be presented separately. Data from each disease cohort in the Dose Escalation part will be presented separately, if not otherwise specified. Data from each cohort in the Expansion part(s) will be presented separately, if not otherwise specified.

Descriptive statistics will be provided for selected demographics, safety, and PK data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and

percentages. Data will be presented and summarized by cohort and DL, and also by time, as appropriate.

Baseline is the last available measurement prior to first dosing, if not otherwise specified.

9.3.2 Analysis of the Dose Escalation Part

9.3.2.1 Primary Endpoint Analysis

The primary endpoints for the Dose Escalation part of the trial are the incidence and severity of AEs and laboratory abnormalities and the incidence of DLTs. For analysis of AEs and laboratory abnormalities, see Section 9.3.4.

The incidence of DLTs will be presented for the DLT-evaluable analysis set (DAS) using descriptive statistics.

9.3.2.2 Secondary Endpoint Analysis

For the Dose Escalation part of the trial the following secondary endpoints are presented (see below).

9.3.2.2.1 Efficacy

All efficacy endpoints will be summarized using the full analysis set (FAS) and the response evaluable analysis set (RES).

9.3.2.2.2 Objective Response Rate

The objective response rate (ORR), as assessed by the investigator for NHL, will be classified according to Lugano criteria (Cheson et al., 2014).

The ORR, as assessed by the investigator for RCC/NPC, will be classified according to RECIST Version 1.1 (Eisenhauer et al., 2009).

The ORR is defined as the proportion of participants with a best overall response of CR or PR. All other categories, including not-evaluable are considered non-response.

Best overall response (BOR) will be summarized in conjunction with the ORR. The estimated ORR and the exact 2-sided 95% CI using the Clopper-Pearson method will be presented.

9.3.2.2.3 Disease Control Rate

The disease control rate (DCR) is defined as the percentage of participants having stable disease (SD) or achieving a PR or CR (DCR = SD + PR + CR). The estimated DCR and the exact 2-sided 95% CI using the Clopper-Pearson method will be presented.

9.3.2.2.4 Progression-Free Survival

PFS is defined as the time from Cycle 1 Day 1 to first documented progressive disease or death due to any cause, whichever occurs earlier.

PFS will be defined for all participants and presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

PFS will be assessed by investigator by the Lugano criteria (Cheson et al., 2014) for NHL and by RECIST Version 1.1 (Eisenhauer et al., 2009) for RCC/NPC.

9.3.2.2.5 Duration of Objective Response

Duration of objective response (DOR) is defined as the time from the first documentation of response (CR or PR) to the date of progressive disease or death, whichever occurs earlier. DOR will be analyzed as described for PFS.

9.3.2.2.6 Pharmacokinetics

For reporting of PK concentrations and parameters, see Section 9.3.7.

PK data may also be used to create a population PK model that will be reported separately.

9.3.2.2.7 Immunogenicity

Incidence of ADAs will be presented as described in Section 9.3.8.

9.3.2.3 Exploratory Endpoint Analysis

9.3.2.3.1 Overall survival

OS is defined as the time from Cycle 1 Day 1 to the date of death due to any cause. Participants who withdrew consent to the trial or are lost to follow-up will be censored at the latest date the participant was known to be alive (on or before the cutoff date).

OS is presented as described for PFS.

9.3.2.3.2 Biomarkers

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters may be explored. Correlations between pharmacodynamic assessments and PK parameters will be explored in concentration-QT plots and regression analysis. Relationships and associated data that are determined to be of interest may be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.3 Analysis of Expansion Parts A and B

All efficacy endpoints will be summarized using the full analysis set (FAS) and the response evaluable analysis set (RES).

9.3.3.1 Primary Endpoint Analysis

The objective response rate (ORR), as assessed by the investigator for NHL, will be classified according to Lugano criteria (Cheson et al., 2014).

The ORR, as assessed by the investigator for RCC/NPC, will be classified according to RECIST Version 1.1 (Eisenhauer et al., 2009).

The ORR is defined as the proportion of participants with a best overall response of CR or PR. All other categories, including not-evaluable are considered non-response.

Best overall response (BOR) will be summarized in conjunction with the ORR. The estimated ORR and the exact 2-sided 95% CI using the Clopper-Pearson method will be presented.

9.3.3.2 Secondary Endpoint Analysis

9.3.3.2.1 Complete Response Rate

The complete response rate (CRR) is defined as the percentage of participants having achieved a CR. The estimated CRR and the exact 2-sided 95% CI using the Clopper-Pearson method will be presented.

9.3.3.2.2 Duration of Objective Response

DOR is defined as the time from the first documentation of response (CR or PR) to the date of progressive disease or death, whichever occurs earlier and will be presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

9.3.3.2.3 Time To Response

Time to response (TTR) is defined as the time from Cycle 1 Day 1 to first documentation of objective response (CR or PR) in participants achieving PR or CR. Time to response will be presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

9.3.3.2.4 Progression-Free Survival

PFS is defined as the time from Cycle 1 Day 1 to first documented progressive disease or death due to any cause, whichever occurs earlier.

PFS will be defined for all participants and presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

PFS will be assessed by investigator by the Lugano criteria (Cheson et al., 2014) for NHL and by RECIST Version 1.1 (Eisenhauer et al., 2009) for RCC/NPC.

9.3.3.2.5 Overall Survival

OS is defined as the time from Cycle 1 Day 1 to the date of death due to any cause. Participants who withdrew consent to the trial or are lost to follow-up will be censored at the latest date the participant was known to be alive (on or before the cutoff date). OS will be defined for all participants and presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

9.3.3.2.6 Incidence of AEs

For reporting of AEs, see Section 9.3.4.

9.3.3.2.7 Immunogenicity

Incidence of ADAs will be presented as described in Section 9.3.8.

9.3.3.2.8 Pharmacokinetics

For reporting of PK concentrations and parameters, see Section 9.3.7.

PK data may also be used to create a population PK model that will be reported separately.

9.3.3.3 Exploratory Endpoint Analysis

Exploratory endpoints will be presented descriptively.

9.3.4 Safety Analyses

Safety analysis will be done for both Dose Escalation and Expansion part(s) of the trial using the safety analysis set (SAS).

9.3.4.1 Adverse Events

The on-treatment period is defined as the time from Cycle 1 Day 1 until the end of safety follow-up.

TEAEs are events that occur during the on-treatment period or are AEs that start before Cycle 1 Day 1 and worsen during the on-treatment period.

Adverse events will be graded according to the NCI CTCAE as described in Section 10.2.

All TEAEs and treatment-emergent SAEs will be presented descriptively.

Analysis of AEs will be summarized using the SAS with the exception of deaths, which will be presented for the FAS.

9.3.4.2 Clinical Laboratory Tests

Grading of laboratory values will be assigned programmatically according to the NCI CTCAE v5.0. The calculation of NCI CTCAE grades will be based on the observed laboratory values only; clinical assessment will not be considered. CTCAE Grade 0 will be assigned for all non-missing values not graded 1 or higher.

Laboratory tests that are graded by NCI CTCAE are presented in a shift table presenting baseline grade versus worst on-treatment grade.

Laboratory tests that cannot be graded by NCI CTCAE are presented in a shift table presenting baseline low/normal/high classification versus worst on-treatment value.

The number of participants with at least 1 Grade 3 or higher on-treatment laboratory test will be summarized.

9.3.4.3 ECOG

ECOG will be presented descriptively.

9.3.4.4 ECG

Evaluation of ECG by investigator will be presented as normal/abnormal and not clinically significant/abnormal clinically significant.

9.3.4.5 Vital Signs

Vital signs will be presented by descriptive statistics.

9.3.5 Other Analyses

For selected endpoints, exploratory subgroup analyses may be conducted including but not limited to the following categories: prior therapies, disease subtype, and CD70 level.

9.3.6 Planned Analyses

9.3.6.1 Primary Analysis

The primary analysis will be conducted when all participants have discontinued treatment and have completed all required follow-up visits or following study termination by the sponsor. At this time, a final data sweep will be performed to determine the survival status of previously discontinued participants.

9.3.6.2 Interim Analysis Expansion Part A

As outlined in Section 4.1.2, data from 10 participants with R/R DLBCL belonging to the RES who received GEN1160 CCI from the Dose Escalation and/or from Expansion Part A, will be reviewed by the Safety Committee when they have completed ≥ 2 cycles of treatment. If [redacted] or more out of the 10 participants respond to treatment with GEN1160, Expansion Part B could be initiated.

If the true underlying response rate is CCI, then the probability of observing [redacted] or more responders in 10 participants is CCI. Hence, it is very unlikely to only observe CCI [redacted] responders (out of 10 participants) if the underlying response rate is CCI.

9.3.7 Pharmacokinetic Analyses

9.3.7.1 Dose Escalation Part

Individual curves of concentrations of GEN1160 conjugated-exatecan, TAb, and unconjugated exatecan, including information on actual dose, will be presented for all participants. All available data will be shown in these figures. PK endpoints will be calculated based on appropriate methods and presented separately per the first 3 doses. Predose values will be summarized and presented graphically for all trial days where measured.

Descriptive statistics of PK endpoints will include arithmetic and geometric means, standard deviation, coefficient of variation (CV) %, median, minimum, and maximum values. Concentration values below the lower limit of quantification (LLOQ) will be handled as LLOQ/2 in summary statistics and reported as is in data listings. Any missing PK endpoint data will not be imputed. The pharmacokinetic analysis set (PAS) will be used.

9.3.7.2 Expansion Part A and B

Trough and peak values will be presented with descriptive statistics over time. The PAS will be used.

9.3.8 Immunogenicity Analyses

The results from the analysis of immunogenicity samples (Expansion Parts A and B) are given as ADA positive, ADA negative, or missing. The ADA positive results are then to be confirmed with a given titer value.

Data will therefore be categorized as one of the following:

- ADA confirmed
- ADA not confirmed (ie, negative samples and not-confirmed positive samples)
- Missing samples

The number of participants having at least 1 confirmed ADA during treatment will be presented and the largest titer value will be presented for participants having at least 1 confirmed ADA sample. The immunogenicity analysis set (IAS) will be used for immunogenicity analyses.

9.4 Sample Size Determination

Given the exploratory nature of the trial no formal sample size calculation will be done for the Dose Escalation part, but approximately 50 participants are expected to be enrolled.

No formal sample size calculation will be done for Expansion Part A. A sample of 10 participants per cohort per DL is deemed enough to provide a preliminary assessment of efficacy and is in line with recommendations in the FDA's Guidance on expansion cohorts (FDA Guidance for Industry, 2022).

No formal sample size calculation will be done for Expansion Part B, but assuming a 40% ORR the exact 95% CI is (21%, 61%) with 25 participants in the Expansion part. When assuming a 30% ORR, the exact 95% CI is (12%, 49%).

10 APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

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

ICH GCP E6(R3) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial participants 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 IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants. 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.

10.1.2 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6(R3), and applicable regulatory and country-specific requirements. This includes supervision of the trial and staff. Delegation of responsibilities should be to only qualified staff and should be documented. In case the investigator is unavailable (eg, on vacation), the investigator should ensure that a qualified, trained deputy physician is available for medical care of the participants. The investigator shall notify the sponsor immediately of any suspected serious breach of ICH GCP E6(R3), the protocol, or any regulation where required.

NOTE: a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

10.1.3 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given written approval of the final protocol, amendments to the protocol (if applicable), the ICF, applicable recruiting materials, participant compensation programs, and other applicable documents that are part of the

regulatory package, and the sponsor has received a copy of this written 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 participants, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and written approval before implementation of the change(s).

The IB and updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, serious breaches, serious noncompliance, annual written summaries of the trial status, and deviations to the protocol implemented to eliminate immediate hazards to the participants must be submitted to the IEC/IRB.

Interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator, where applicable, 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, within the required timelines.

10.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.5 Administrative Procedures

10.1.5.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (eg, change in the sponsor's medical officer or contact information). 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 deviation from the protocol is unavoidable, the investigator or other physician in attendance will contact the sponsor (see the separate sponsor Contact Information page, which will be provided separately from the protocol). Except in emergency situations, this contact should be made before implementing any deviations 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 electronic

case report form (eCRF) and source documents will reflect any deviation from the protocol, and the source documents will describe this departure and the circumstances requiring it.

10.1.5.2 Regulatory Documentation

This protocol and any amendments must be submitted to the appropriate regulatory authorities in each respective country, in accordance with local regulations. A trial may not be initiated until all local regulatory requirements are met.

10.1.5.3 Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification log to permit easy identification of each participant during and after the trial. This document will be reviewed by the sponsor trial-site contact for completeness.

The participant identification log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the sponsor or any third parties. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the trial will identify participants by their unique participant identifier.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the trial. The participant screening log will be filed in the Investigator Site file and the Trial Master File.

10.1.6 Informed Consent Process

The ICF(s) that is/are used must be approved by the reviewing IEC/IRB and be in a language that the participant can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, ICH GCP E6(R3), 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail.

Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason and without penalty or loss of benefits to which participants are otherwise entitled. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of their disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by IRB/IEC and Regulatory Authorities, and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF the participant is authorizing such access, including permission to obtain information about survival status, and agrees to allow their trial physician to re-contact the participant for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about survival status.

The participant will be given sufficient time to read the ICF and the opportunity to enquire about details of the trial prior to deciding whether to participate in the trial. After this explanation and before any trial-specific procedure is performed, consent should be appropriately documented by means of the participant's personally dated signature.

Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, European regulation 536/2014 for clinical studies, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA), and European Union (EU) General Data Protection Regulation (GDPR) requirements, where applicable, and the IRB/IEC or trial center. The investigator or authorized person obtaining the informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

The sponsor will, on an ongoing basis, assess whether reconsent of participants is needed and revise the ICF whenever any important new information becomes available that may be relevant to the participant's consent.

Participants who are rescreened are required to sign a new ICF.

10.1.7 Data Protection

The investigator will ensure that the confidentiality of all participants' data will be preserved. In the electronic case report form (eCRF) or any other documents submitted to the sponsor/sponsor's representative, the participants will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential participant identification code and the signed ICF 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 participants 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 are only stored on information technology (IT) systems and networks that are protected against virus, malware, and unauthorized access.

- Data are 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 participants and authorities, has been established in order to mitigate any adverse impact on the participants.

Additional technical security measures implemented include that:

- All data are encrypted when at rest.
- Data have 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 participants 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 participants confidential.

The informed consent obtained from the participant 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 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 participant 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), and 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.

10.1.8 Committees Structure

Safety Monitoring Committee

The SMC will monitor the safety of GEN1160 throughout the study. The SMC is comprised of the study medical monitor, active study site Investigators, and the study Sponsor. The committee will monitor the safety of participants in this study, through regular and/or ad hoc meetings that include review of data pertaining to dose escalation decisions and treatment-emergent toxicities. At a minimum, SMC meetings will be held during the Dose Escalation part of the study after all patients in a cohort have completed the DLT evaluation period. The SMC will review clinical data from enrolled patients for safety assessment and for DLT determination. The SMC will make recommendations on dose level and cohort size. Dose levels will not be skipped. The SMC will also meet approximately quarterly during Part B of the study for cumulative patient data review.

In addition to determination of DLTs and dose escalation recommendations, the SMC may make 1 or more of the following recommendations during the study, as applicable:

- Further evaluation of safety at a given dose
- CCI
- Evaluation of a lower or intermediate dose level during Dose Escalation
- Evaluation of a longer interval between doses (cycle length)
- Recommendation on the dose(s) and dosing interval(s) to be evaluated in the Expansion part(s) based on activity and tolerability of dose levels during escalation.
  - To identify a recommended dose and schedule for Expansion, the SMC will comprehensively review cumulative safety and efficacy data from all patients at all dose levels. The SMC assessment will include evaluation of cumulative toxicity outside of the DLT window, as well as review of any available PK data.

Safety Committee

The sponsor's Safety Committee is a cross-functional committee that evaluates the evolving safety profile of the product, supports assessment of the product's benefit/risk profile and recommends risk management strategies to ensure safety of participants who participate in Genmab sponsored clinical trials or participants treated with marketed Genmab drugs. For Dose Escalation Phase, the Safety Committee will consider the recommendation made by the SMC regarding the expansion dose/MTD/MAD and make the final decision regarding the proposed dose for further development in the Expansion phase. The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in participant benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

Decisions with the potential to affect participant safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and health authorities, as required.

10.1.9 Dissemination of Clinical Trial Data

The protocol information will be registered in a publicly accessible database (eg, clinicaltrials.gov, Clinical Trials Information System (CTIS), and/or other national registries/health authority websites). In addition, after trial completion (defined as last participant last visit globally) and finalization of the study report, the results of this trial will be submitted for disclosure and posted in a publicly accessible database of clinical trial results as required by local regulations (eg, clinicaltrials.gov, CTIS).

10.1.10 Data Quality Assurance, Record Retention, Monitoring, and On-Site Audits

10.1.10.1 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 sponsor's delegate), and direct transmission of clinical laboratory data from a central laboratory, ECG data from the ECG vendor, and review of radiographic scans and pathology reports (as applicable) from the central imaging vendor (Expansion only) into the sponsor's data base. 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 (CRO) 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, the data will be reviewed for accuracy and consistency with the data sources.

10.1.10.2 Record Retention

In compliance with ICH GCP E6(R3), 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 participant, 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. Medical records (participants' hospital record) are retained/archived according to applicable local regulation.

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.

10.1.10.3 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 (ie, the first participant has signed the ICF) has begun. At these visits, the monitor will verify 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, or 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 with the purpose of verifying that the data recorded 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 contact can occur. It is expected that during these remote contacts, trial-site personnel will be available to provide an update on the progress of the trial at the site.

10.1.10.4 On-Site Audits and Inspections

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. Participant privacy must, however, be respected. The principal 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 designee(s).

Similar procedures for inspections 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 they have been contacted by a regulatory agency concerning an upcoming inspection. Regulatory inspectors must be allowed direct access to original medical records (source data/documents).

10.1.11 Source Documents and Case Report Form Completion

10.1.11.1 Source Documentation

Source documents provide evidence for the existence of the participant 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 participant should be consistent with that commonly documented at the trial site as a basis for standard medical care.

Source documents are original documents, data, and records from which the participant's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. The author of an entry in the source should be identifiable.

Source documents may also include data captured in the IRT system (if used, such as the unique participant identifier and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). For this trial, the CRF entry may be considered as source for the following: demographic data (race, ethnicity, sex at birth). Additionally, source data may be recorded directly electronically (eg, ECGs, COAs). Such data are considered source data and are accessible by both the investigator and sponsor. Specific details required as source data for the trial will be reviewed with the investigator before the trial, described in the monitoring guidelines (or equivalent), and captured in a source data verification log at site.

For each participant, the investigator must indicate in the hospital/medical source records that the participant participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the participant at the time the participant 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 ICFs will be stored in the investigator site file and archived according to local requirements.

In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each participant:

- participant's name and date of birth
- screening/participant/randomization number
- trial identification

- confirmation of eligibility for participation in the trial, including diagnosis
- medical history
- date of each visit
- any assessment performed eg, results of safety and efficacy evaluations
- concomitant medications
- occurrence of any AEs/SAEs (including description and duration)
- status of the participant at the end of trial
- reason for treatment discontinuation/trial withdrawal, if applicable

Information included in the participant'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.

10.1.11.2 Case Report Form Completion

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

Data relating to the trial must be documented and reported in English. Trial site personnel must complete the case report form (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, response 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 subinvestigator and who is delegated this task on the Delegation of Authority Form.

Corrections to the eCRF after data entry can be done as follows (corrections must be verified and approved by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form.):

- 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.

10.1.12 Trial and Site Start and Closure

The trial start date will be the first act of recruitment (ie, the first participant that signs the ICF).

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. Trial sites will be closed upon trial completion. A

trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given to the sponsor 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(R3), and applicable regulatory requirements.
- Inadequate recruitment of participants by the investigator
- Discontinuation of further GEN1160 development.

The sponsor may, based on available data, discontinue further development of GEN1160.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant(s) and should ensure appropriate participant therapy and/or follow-up.

10.1.13 Publication Policy

All information, including but not limited to information regarding GEN1160 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 exploratory research data, 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. CROs involved in the trial are not permitted to publish without the sponsor’s prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1160, and thus may be shared as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trial to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

Trial participant 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, 2010; ICMJE, 2019) the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the prespecified and approved publication plan. 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 current version of 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' (ICMJE Recommendations, http://www.icmje.org/recommendations/), 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.

10.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, and Reporting

10.2.1 Definitions

10.2.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a participant or clinical trial participant, 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.

10.2.1.2 Definition of Serious Adverse Event

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

- Is fatal or life-threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent 1 of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - Hospitalizations for the following reasons should not be reported as SAEs:
    - Routine treatment or monitoring of the underlying disease, not associated with any deterioration in the condition
    - Solely due to progression of the underlying cancer
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the ICF
    - Social reasons and respite care in the absence of any deterioration in the participant’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 an SAE given above.

10.2.2 Procedures for Recording and Reporting

10.2.2.1 Recording

All AEs, serious or nonserious, must be documented.

- The diagnosis/cause of an AE should be documented rather than the symptoms of the AE.
- If no diagnosis is available, then each sign and symptom should be documented as an individual AE.
- All AEs that occur during the AE reporting period must be documented, whether or not the event is considered treatment-related.
- All AEs should be documented and reassessment made at each visit (or more frequently, if necessary).
- Final assessment of AEs must be performed by a medically qualified person.

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial drug(s) should be documented as an AE.

- Whenever possible, a diagnosis should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation for the abnormality is found.
- NOTE: A CTCAE Grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

10.2.2.2 Reporting

The primary mechanism for reporting an SAE to the sponsor is the EDC tool. In order to report pregnancies and if the EDC tool is unavailable to report SAEs, then the site must use the respective paper report forms via secure transmission to ensure the event is reported within 24 hours following first knowledge of the event.

Once the trial has ended, if the investigator learns of a second primary malignancy or a treatment-related SAE, the event should be reported using the paper forms via secure transmission.

10.2.3 Evaluation of Adverse Events

10.2.3.1 Severity

Toxicities will be graded for severity according to the NCI CTCAE, v5.0. Clinical tumor lysis syndrome (CTLS) will be evaluated according to the Cairo-Bishop classification (Coiffier et al., 2008).

10.2.3.2 Relationship to the Investigational Medicinal Product

The investigator must assess whether or not the event is related to the trial drug(s). The relationship is to be judged using the following terms:

- Related
- Not related

If the relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the event is being reported.

A suspected adverse reaction is one in which there is a reasonable possibility that the trial drug(s) caused the AE, this means there is evidence to suggest a causal relationship between the trial drug(s) and the AE (ie, considered related). Refer to the GEN1160 IB.

10.3 Appendix 3: Definition of Reproductive Potential and Contraception

Male and female participants of reproductive potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of GEN1160.

If relevant (based on treatment regimen) and allowed by local regulations, if male and female participants of reproductive potential plan to father a child or become pregnant after the trial ends, consider discussing option for semen banking or cryopreservation prior to dosing.

10.3.1 Definition of Reproductive Potential

In this trial, female participants are considered to have reproductive potential unless they are postmenopausal or permanently sterile:

- A postmenopausal state is defined as no menses in participants >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 postmenopausal state in participants 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.

In this trial, male participants will be considered to be of reproductive potential unless they have permanent azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

10.3.2 Contraception Methods for Female Participants

Adequate contraception is defined as highly effective methods of contraception (see Table 18). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.

All female participants must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of GEN1160.

Table 18: Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable[a]

- Intrauterine device[a]
- Intrauterine hormone-releasing system[a]
- Bilateral tubal occlusion[a]
- Vasectomized partner[a,b]
- Sexual abstinence[c]

Adapted from "Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1." (CTFG, 2020).

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

[b] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female participant of reproductive potential (ie, the trial participant) and that the vasectomized partner has received medical assessment of the surgical success.

[c] 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 participant.

10.3.3 Contraception Methods for Male Participants and Female Partners of Male Participants

Male participants of reproductive potential must use a condom during treatment and for 6 months after the last dose of GEN1160.

The female partner should consider using an acceptable method of effective contraception such as: hormonal IUD, intrauterine hormonal-releasing system (IUS), female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the participant's sole female partner is of nonchildbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the trial.

10.4 Appendix 4: Sample Storage and Destruction

Any sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to trial participants. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the trial. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the trial. Results are stored in a secure database to ensure confidentiality.

Exploratory biomarker research may also be performed to investigate and better understand R/R B-NHL, R/R DLBCL, and RCC/NPC, the dose response and/or prediction of response to GEN1160, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained; but are not necessarily reported as part of this study. Samples can be retained for up to 5 years.

Since the evaluations are not expected to benefit the participant directly or to alter the treatment course, the results of any exploratory biomarker research are not placed in the participant's medical record and are not to be made available to the participant, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The participant retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the participant, the investigator is to provide the sponsor with the required trial and participant number so that any remaining samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction will be retained by Genmab.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the participant through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The participant has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 10.1.7 for participant confidentiality.

10.5 Appendix 5: ECOG Performance Status

Score	Definition
0	Fully active, able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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 out any self-care. Totally confined to bed or chair.
5	Dead.

Source: (Oken et al., 1982)

10.6 Appendix 6: New York Heart Association Criteria

The table below describes the most commonly used classification system for heart failure, the New York Heart Association (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).

10.7 Appendix 7: Estimation of Glomerular Filtration Rate Using Cockroft-Gault Formula

Glomerular filtration rate (GFR) may be estimated using the Cockroft-Gault formula

$$GFR = \frac{(140 - age) \times weight \times F_S}{Serum\ Creatinine \times 72}$$

Units: GFR [mL/min], age [years], weight [kg], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0.85$

10.8 Appendix 8: Classification of Laboratory and Clinical Tumor Lysis Syndrome

The presence of TLS is not clearly defined by Common Terminology Criteria for Adverse Events (CTCAE). For this trial the Cairo-Bishop classification will be used to define the presence of TLS. Laboratory tumor lysis syndrome (LTLS) (Table 19) will not be considered as presence of TLS in the absence of the specified clinical complications (Coiffier et al., 2008). Clinical TLS should be graded according to Table 20. Individual symptoms should be graded according to CTCAE.

In laboratory TLS, 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 (CTLS) requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Table 19: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Laboratory parameter	Value	Change From Baseline
Uric acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 1.45 mmol/L	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: 2 or more laboratory changes within 3 days before or 7 days after treatment with GEN1160.
Source: Based on (Coiffier et al., 2008).

Table 20: Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine*†	1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 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)	

Abbreviations: ADL=activities of daily living; CHF=congestive heart failure; ULN=upper limit of normal.
* Not directly or probably attributable to GEN1160.
† If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.
Source: Based on (Coiffier et al., 2008).

10.9 Appendix 9: 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)[a]
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

[a] 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.

10.10 Appendix 10: PET Positivity Evaluation Using the 5-Point Scale

Evaluation of fluorodeoxyglucose (FDG)-positron emission tomography (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.

10.11 Appendix 11: Lugano Response Criteria for Malignant Lymphoma

Target and Non-target Lesions

Target lesions should consist of up to 6 of the largest dominant nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters and should preferably be from different body regions representative of the participant'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 6 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, gastrointestinal (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. 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 response**	**Complete radiologic response** *(all of the following)*
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5-PS[b] 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

Response	Site	PET-CT–Based Response	CT-Based Response
	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 response**	**Partial remission** *(all of the following)*
	Lymph nodes and extralymphatic sites	Score 4 or 5[b] 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[b] 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	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or	PPD progression:

Response	Site	PET-CT–Based Response	CT-Based Response
	masses, extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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

Abbreviations: 5-PS=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=product of the perpendicular diameters; SDi=shortest axis perpendicular to the LDi; SPD=sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many participants 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 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 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).

[b] PET 5-PS: 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)

10.12 Appendix 12: RECIST Version 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Term	Definition
Complete Response (CR)	• Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm • Cannot previously have met criteria for PD
Partial Response (PR)	• A ≥ 30% decrease in the sum of diameters of target lesions (longest for non-nodal target lesions and the short axes for nodal target lesions), taking as reference the baseline sum diameters • Cannot have previously met criteria for PD
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study • Cannot have previously met criteria for PD
Progressive Disease (PD)	• A ≥ 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase ≥ 5 mm • The appearance of 1 or more new lesions is also considered progression

Source: (Eisenhauer et al., 2009)

10.13 Appendix 13: CYP3A and CYP1A2 Inhibitors

NOTE: Additional strong CYP3A and CYP1A2 inhibitors may become available while the clinical trial is ongoing. The following statements would apply to those medications in addition to those listed in the table below.

The systemic exposure of exatecan has not been characterized. During Dose Escalation, strong inhibitors of CYP3A and CYP1A2 are prohibited to minimize potential for increased exatecan exposure.

Strong CYP3A Inhibitors	Strong CYP1A2 Inhibitors
boceprevir	ciprofloxacin
clarithromycin	enoxacin
cobicistat	fluvoxamine
conivaptan	
danoprevir and ritonavir	
diltiazem	
elvitegravir and ritonavir	
grapefruit juice	
idelalisib	
indinavir and ritonavir	
itraconazole	
ketoconazole	
lopinavir and ritonavir	
nefazodone	
nelfinavir	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	
posaconazole	
ritonavir	
saquinavir and ritonavir	
telaprevir	
tipranavir and ritonavir	
troleandomycin	
voriconazole	

Note: Any additional strong CYP3A and CYP1A2 inhibitors that are identified or become commercially available while the clinical trial is ongoing should also be closely monitored for adverse reactions.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Amendment 2 (04 June 2025)

The main rationale of the amendment is to support enrollment needs in the NHL study population, with the high-level changes impacting:

- Study design (Dose Escalation, Expansion Part A, and Expansion Part B) with respective objectives and endpoints
- Eligibility criteria and response assessment tailored to R/R DLBCL for Expansion Part A and Part B
- Based on the overall safety data, modified guidance for adverse event management
- Included Dose Escalation data summary for RCC/NPC and NHL with benefit-risk assessment
- Introduced interim analysis for Expansion Part A and randomization for dose optimization for Expansion Part B

Due to the Genmab acquisition of ProfoundBio, the protocol amendment resulted in conforming the protocol to the Genmab template. The following table lists all **substantive** changes. The synopsis has been updated to align with global protocol edits. Additional minor changes have also been incorporated throughout the protocol to provide clarity and consistency.

Description of Changes:

Section	Description of Change	Brief Rationale
Global	Throughout the protocol, the trial number has been updated from PRO1160-001 to GCT1160-01 and the Investigational Product number has been updated from PRO1160 to GEN1160. Safety Committee, as appropriate for Expansion Part A and B, added.	To align with Genmab's Investigational Product and trial numbering schema, as well as nomenclature.
Global	Converted legacy protocol language and section numbering to Genmab template.	To align with Genmab protocol template requirements.

Section	Description of Change	Brief Rationale
Cover page	Converted to Genmab template, updated study number to reflect Genmab study number, updated compound name to reflect Genmab compound description, added short (brief) title, updated sponsor name, updated protocol approver, updated sponsor information, and updated the confidentiality statement.	ProfoundBio was acquired by Genmab and protocol template alignment.
Sponsor Information Page	Added.	Protocol template alignment.
Investigator Agreement	Added.	Protocol template alignment.
Section 1.2	Updated study design schema.	Updated with appropriate details highlighting Dose Escalation in NHL and Expansion DLBCL Part A and Part B.
Section 1.3	Updated schedule of activities.	To include Expansion DLBCL Part A and Part B.
Section 2.1.4	Added details for summary of clinical trials.	Updated with appropriate details.
Section 2.2	Added details for trial rationale.	Updated with appropriate details.
Section 2.3	Added details for benefit-risk assessment.	Updated with appropriate details.
Section 3	Added objectives and related endpoints for Dose Escalation and Expansion Part A and Part B.	Updated with appropriate details.
Section 4.1	Added details for trial design description related to Dose Escalation and Expansion Part A and Part B.	Updated with appropriate details.
Section 4.2	Added details for updated trial design rationale.	Updated with appropriate details.
Section 4.3	Added details for updated dose and schedule rationale.	Updated with appropriate details.
Section 4.4	Added details for primary completion date, estimated trial duration, and end of trial definitions.	Updated with appropriate details per Genmab protocol template.
Section 5.1 Section 5.2	Added details summarizing trial population eligibility for Dose Escalation and Expansion Parts A and B.	Updated with appropriate details.
Section 5.3	Added details for participant enrollment.	Updated with appropriate details per Genmab protocol template.
Section 5.4	Added details for screen failures.	Updated with appropriate details per Genmab protocol template.

Section	Description of Change	Brief Rationale
Section 6.1	Added details for IMP.	Updated with appropriate details per Genmab protocol template.
Section 6.2	Added details for product complaints.	Updated with appropriate details per Genmab protocol template.
Section 6.3	Added details for preparation, handling, storage, and accountability.	Updated with appropriate details per Genmab protocol template.
Section 6.4	Added details for randomization and blinding.	Updated with appropriate details.
Section 6.5	Added details of treatment compliance.	Updated with appropriate details.
Section 6.6	Added details, for prior and concomitant therapies for Expansion Parts A and B.	Updated with appropriate details per Genmab protocol template.
Section 6.7	Added details for GEN1160 dose modifications and stopping rules.	Updated with appropriate details.
Section 6.8	Added details for GEN1160 overdose management.	Updated with appropriate details per Genmab protocol template.
Section 7	Added details of discontinuation of treatment, discontinuation from trial, and lost to follow-up.	Updated with appropriate details per Genmab protocol template.
Section 8	Added trial assessments and procedures including adverse event definitions and reporting.	Updated with appropriate details per Genmab protocol template.
Section 9	Added a comprehensive statistical considerations section summarizing analysis populations, hypotheses, and other general considerations for Dose Escalation and Expansion Parts A and B.	Updated with appropriate details.
Section 10.1	Added details regarding other supporting documentation and operational considerations	Updated with appropriate details per Genmab protocol template.
Section 10.2	Added details for adverse event recording, evaluating, and reporting.	Updated with appropriate details per Genmab protocol template.
Section 10.3	Added contraception details.	Updated with appropriate details per Genmab protocol template.

Section	Description of Change	Brief Rationale
Section 10.4	Added details for sample storage and destruction.	Updated with appropriate details per Genmab protocol template.
Section 10.5	Replaced ECOG definitions.	Updated with appropriate details per Genmab protocol template.
Section 10.6 Section 10.7 Section 10.8 Section 10.9 Section 10.10	Added study-specific appendices.	Updated with appropriate details per Genmab protocol template.