CLINICAL TRIAL PROTOCOL

Protocol Title	A Phase 1/2a, Open-Label, Dose Escalation Trial of GEN3017 With Expansion Cohorts in Relapsed or Refractory CD30+ Classical Hodgkin Lymphoma and CD30+ Non-Hodgkin Lymphoma		
Protocol Number	GCT3017-01		
Compound	GEN3017		
Brief Title	A first-in-human trial of safety and efficacy of GEN3017 in subjects with Hodgkin lymphoma or non-Hodgkin lymphoma		
Trial Phase	1/2a		
Sponsor Name	Genmab*		
Regulatory Agency Identifier Numbers	**EU CT No.**	2023-503348-15-00	
	NCT No.	NCT06018129	
Protocol Approver**	**Name**	PPD , MD, PhD	
	Title	PPD	
Protocol Version History	**Version**		**Approval Date**
	Original; v1.0		02 May 2023
	Amendment 1; v2.0		28 June 2023
	Amendment 2; v3.0		18 October 2023

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** This protocol was approved via electronic signature on the approval page appended to the document.

CONFIDENTIALITY STATEMENT

Sponsor Information Page

Sponsor information for countries in the European Economic Area, Switzerland, and the United Kingdom	Genmab A/S Carl Jacobsens Vej 30 2500 Valby Denmark
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 trial responsible medical officer, as well as the CRO(s), laboratory(ies) (names and addresses), and other technical/medical services used.

Investigator Agreement

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

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), the principles in the Declaration of Helsinki, the Japanese Ministerial Ordinance on GCP, 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 trial. I will discuss this material with them to ensure that they are fully informed regarding the trial treatment, the conduct of the trial, 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 trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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List of Abbreviations and Definitions

Abbreviation	Definition
Ab	antibody
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
CCI	CCI
ALCL	anaplastic large cell lymphoma
CCI	CCI
AMP	auxiliary medicinal product
anti-HBc	antibodies to the hepatitis B core antigen
anti-HBs	antibodies to the hepatitis B surface antigen
aPTT	activated partial thromboplastin time
ASTCT	American Society for Transplantation and Cellular Therapy
AU	Australia
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to last quantifiable sample
BOIN	Bayesian optimal interval design
bsAb	bispecific antibody
BV	brentuximab vedotin
C	cycle
CAR-T	chimeric antigen receptor T cell
CD	cluster of differentiation
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CHOEP	cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLIA	Clinical Laboratory Improvement Amendment
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CTFG	Clinical Trials Facilitation Group
CTLS	clinical tumor lysis syndrome
C_{trough}	predose trough concentration
D	day
DEC	Dose Escalation Committee
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
CCI	CCI
EBV	Epstein-Barr virus
EC_{50}	concentration at which 50% of the maximum effect is observed
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
CCI	CCI
EoT	end of treatment
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
EU	European Union
FAS	Full Analysis Set
Fc	crystallizable fragment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
HTLV-1	human T-cell leukemia virus type 1
HTLV-2	human T-cell leukemia virus type 2
IB	investigator's brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
IgG	immunoglobulin G
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRT	interactive response technology
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose
MMAE	monomethyl auristatin E
MOA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
CCI	CCI [redacted]

Abbreviation	Definition
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell(s)
PCR	polymerase chain reaction
PD	pharmacodynamic
PD-1	programmed cell death protein 1
CCI	CCI
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
CCI	CCI
CCI	CCI
QA	quality assurance
QTcF	corrected QT interval by Fridericia's formula
RES	Response Evaluable Set
RP2D(s)	recommended phase 2 dose(s)
R/R	relapsed/refractory
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SOC	standard of care
CCI	CCI
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TCL	T-cell lymphoma
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to reach C_{max}
TNFR	tumor necrosis factor receptor
Trial drug(s)	specifically refers to IMP(s)

Abbreviation	Definition
Trial treatment	any IMP, AMP, or medical device(s) intended to be administered to a trial subject according to the trial protocol
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
WHO	World Health Organization
yo	years old

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Protocol Title:	A Phase 1/2a, Open-Label, Dose Escalation Trial of GEN3017 With Expansion Cohorts in Relapsed or Refractory CD30+ Classical Hodgkin Lymphoma and CD30+ Non-Hodgkin Lymphoma
Brief Title:	A first-in-human trial of safety and efficacy of GEN3017 in subjects with Hodgkin lymphoma or non-Hodgkin lymphoma
Phase:	1/2a
Indication:	CD30+ classical Hodgkin lymphoma and CD30+ non-Hodgkin lymphoma

Rationale:

In recent years, anti-programmed cell death protein 1(PD-1) checkpoint inhibitors (ie, nivolumab, pembrolizumab) and anti-cluster of differentiation (CD)30 antibody-drug conjugate (ie, brentuximab vedotin [BV]) have advanced the clinical outcome of relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL). However, a significant portion of patients will progress while on these therapies. Although allogeneic hematopoietic stem cell transplant (HSCT) is potentially curative, its application is still limited and post-transplant relapse is common. As checkpoint inhibitors (CPIs) and BV are moving up in the cHL treatment paradigm, patients who are relapsed after or refractory to these treatment modalities are in dire need of new treatment options. Lymphoma is one of the most common cancers in pediatric patients. For the 15- to 19-year-old age group, cHL is the single most common malignancy. While the overall cure rate for the majority of pediatric cHL patients is high, there is a small group whose disease is highly refractory to the current treatment regimens. Reducing long-term morbidity and mortality secondary to intensive chemotherapy and/or radiotherapy for cHL in young patients who have decades of life ahead of them is of high unmet medical need. Among T-cell lymphomas (TCL), prognosis remains poor for most subtypes CCI [redacted].

cHL Reed-Sternberg cells invariably express high levels of CD30 antigen. CCI [redacted]

T-cell-based immunotherapy such as CD30-directed CAR-T cell and bispecific T-cell engagers such as GEN3017 represents a promising approach among advanced R/R cHL and CD30+ TCL patients whose disease no longer responds to standard therapies including chemotherapy, BV, and HSCT.

In vitro, GEN3017 showed potent tumor cell killing in cHL and ALCL cell lines associated with T-cell activation and proliferation. Repeated dose toxicity studies in cynomolgus monkeys tested GEN3017 via subcutaneous (SC) and intravenous (IV) administrations up to CCI [redacted]. The no observed adverse effect level (NOAEL) was determined to be CCI [redacted].

The purpose of this phase 1/2a trial is to characterize the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics profiles, and assess preliminary anti-tumor activity of GEN3017 (DuoBody®-CD3xCD30) in subjects with R/R CD30+ cHL or R/R CD30+ TCL.

Objectives and Endpoints:

Objectives	Endpoints
Dose Escalation	
Primary	
Determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) and recommended phase 2 dose (RP2D), or dose(s) to be studied in the expansion part	Incidence of dose-limiting toxicities (DLTs)
Evaluate the safety and tolerability of GEN3017	Incidence and severity of adverse events (AEs)
Secondary	

Characterize the pharmacokinetic (PK) properties of GEN3017	Noncompartmental PK parameters: • Maximum concentration (C_{max}) • Time to C_{max} (t_{max}) • Predose trough concentration (C_{trough}) • Area under the concentration-time curve from time 0 to last quantifiable sample (AUC_{last}) and from time 0 to infinity (AUC_{inf}) • Elimination half-life ($T_{1/2}$) • Clearance • Volume of distribution
Evaluate immunogenicity	• Anti-GEN3017 antibodies
Assess the preliminary anti-tumor activity of GEN3017	Anti-tumor activity based on the Lugano criteria as assessed by investigator: • Objective response rate (ORR) • Duration of response (DOR) • Time to response (TTR)
Expansion	
Primary	
Assess the preliminary anti-tumor activity of GEN3017	ORR based on the Lugano criteria as assessed by independent review committee (IRC)
Secondary	
Assess the anti-tumor activity and efficacy of GEN3017	Anti-tumor activity based on the Lugano criteria as assessed by IRC and investigator: • ORR (investigator only) • CR (complete response) rate • DOR • TTR • PFS (progression-free survival) • OS (overall survival)
Evaluate safety and immunogenicity of GEN3017	• Safety: Incidence and severity of AEs and serious adverse events (SAEs) • Immunogenicity: Anti-GEN3017 antibodies
Characterize the PK of GEN3017	PK parameters (clearance; volume of distribution; AUC_{last}; AUC_{inf}; C_{max}; T_{max}; C_{trough}; and $t_{1/2}$)

Trial Design and Duration:

This is a phase 1/2a, open-label, multicenter, trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of GEN3017 in subjects with R/R CD30+ cHL or R/R CD30+ TCL.

The trial will be conducted in 2 parts: dose escalation (phase 1) and expansion (phase 2a).

Each part will consist of the following:

1. Screening period (up to 21 days prior to Cycle 1 Day 1),
2. Treatment period (Cycle 1 Day 1 until GEN3017 treatment discontinuation),
3. Follow-up period (ie, 60-day safety follow-up from the last dose of GEN3017 or before the initiation of a new anticancer treatment, whichever comes first; post-treatment follow-up for subjects who discontinue GEN3017 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).

CCI [redacted]

The MTD of each disease cohort, if reached, along with the MAD and RP2D of each disease cohort will be determined based on the totality of the data of each disease cohort.

During dose escalation, a Dose Escalation Committee (DEC) will review the preliminary data from subjects treated at a specific dose level (DL) according to DEC Charter and evaluate potential DLTs. The DEC will make recommendations on escalating to the next DL and/or propose the RP2D/MTD/MAD to the Safety Committee, who will have to endorse the proposed DL before subjects at the next DL can be enrolled, as well as the dose(s) selected for expansion.

During expansion, the Safety Committee will assess the totality of safety information of the trial and identify additional safety signals.

The estimated trial duration for an individual subject is approximately 2 years, consisting of a 21-day screening period, an estimated 1-year treatment period (the duration of treatment may vary for each subject), a 60-day safety follow-up period, post-treatment follow-up for subjects who discontinue GEN3017 prior to disease progression, and a survival follow-up period (the duration of follow-up may vary for each subject).

Number of Subjects:

Approximately 120 subjects (60 in each disease cohort) are expected to be enrolled in the dose escalation part of the trial and approximately 120 subjects are expected to be enrolled in the expansion part of the trial.

Summary of Key Eligibility Criteria:

Key Inclusion Criteria:

Dose Escalation

- Must be at least 18 years of age. For subjects in the R/R cHL Cohort in the United States (US) and Australia, must be at least 16 years of age.
- Histologically confirmed R/R cHL or R/R TCL according to the 2016 World Health Organization classification.
- Subjects must have at least 1 measurable lesion according to the 2014 Lugano criteria.
  - An fluorodeoxyglucose- positron emission tomography (FDG-PET) scan demonstrating positive lesion compatible with computed tomography (CT)- or magnetic resonance imaging (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)
- Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1 for subjects 18 years of age and above. For subjects ≥16 and <18 years of age (US and Australia only), Karnofsky score of >60% per Karnofsky performance scale.
- Confirmed CD30-positivity in tumor biopsy prior to the first dose of GEN3017. Subjects must have documented CD30 expression by immunohistochemistry or flow cytometry as assayed in a local Clinical Laboratory Improvement Amendments (CLIA) certified (or local equivalent) hematopathology laboratory. A fresh biopsy is recommended to demonstrate CD30 expression if clinically feasible and not considered as a high-risk procedure.

R/R cHL Cohort in Dose Escalation

- Must have relapsed or progressive cHL after receiving at least 3 prior lines of therapy CCI [redacted]

OR

- Refractory to the second line of therapy.

TCL Cohort in Dose Escalation

- CCI [redacted]
  - CCI [redacted]

CCI

- CCI

Expansion

- Eastern Cooperative Oncology Group (ECOG) performance status score 0, 1, or 2 for subjects 18 years of age and above. For subjects ≥16 and <18 years of age (US and Australia only), Karnofsky score of >60% per Karnofsky performance scale. For subjects ≥12 and <16 years of age) (US and Australia only), Lansky score of CCI per Lansky play-performance scale.

R/R cHL in Expansion

- Must have relapsed or progressive cHL after receiving at least 3 prior lines of therapy CCI

  OR

  Refractory to the second line of therapy.
- For subjects in the R/R CD30+ cHL (US and Australia only), age ≥12 and <18 years

R/R TCL in Expansion

- CCI
  - CCI
  - CCI

Key Exclusion Criteria for Dose Escalation and Expansion:

- CCI
- 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 CD30-targeting therapy, CCI (except BV).
  - Autologous HSCT within 60 days (applies to both cHL and TCL). Allogeneic HSCT within 90 days (applies to cHL) prior to the first dose of GEN3017.
  - Chemotherapy within 2 weeks or major surgery within 4 weeks of the first dose of GEN3017.
  - Curative radiotherapy within 4 weeks or palliative radiotherapy within 2 weeks prior to the first dose of GEN3017.
  - Treatment with an investigational drug within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of GEN3017 or currently receiving any other investigational agents.
  - Prior treatment with live, attenuated vaccines within 30 days prior to the first dose of GEN3017. 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 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 GEN3017.

Trial Treatment:

CCI

- CCI
- CCI

CCI

CCI

In expansion, 1) for adult subjects, GEN3017 will be administered as an CCI injection with CCI at the DL determined by the data from the dose escalation part. 2) For adolescent subjects with R/R cHL (US and Australia only; Cohort 2), GEN3017 will be administered as an CCI

Other Trial Treatment:

Prophylactic premedication to mitigate the risk and severity of CRS will consist of corticosteroids (IV dexamethasone 20 mg or methylprednisolone 100 mg [or equivalent]), antihistamine (diphenhydramine 50 mg orally (PO) or IV [or equivalent]), and/or antipyretics (paracetamol/acetaminophen 650 mg to 1000 mg PO [or equivalent]) 30 minutes to 2 hours prior to the administrations of GEN3017.

Tocilizumab may be used for the management of CRS, when indicated. In such cases, the dose of tocilizumab is 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period.

Siltuximab may be used for the management of CRS, when indicated. In such cases, the dose of siltuximab is 11 mg/kg IV over 1 hour, 1 time only.

Anakinra may be used for the management of CRS and ICANS, when indicated. In such cases, the dose of Anakinra is 100 mg SC once/day.

Statistics:

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

No formal sample size calculations will be done for the dose escalation part. With 10 expected DLs, and an average of 6 subjects per DL, 60 subjects are expected to be enrolled in each disease cohort.

No formal sample size calculations will be done for the expansion part. A sample of 20 subjects per cohort per dose level is deemed enough to provide a preliminary assessment of efficacy and in line with recommendations in the Food and Drug Administration (FDA)'s Guidance on expansion cohorts.

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 Dose Determining Set using descriptive statistics.

All secondary efficacy analyses (ORR, DOR, and TTR) will be based on the Full Analysis Set (FAS). The FAS will be used for PK analyses and the Safety Set will be used for immunogenicity analyses.

Expansion:

The primary endpoint for the expansion part of the trial is ORR based on the Lugano criteria as assessed by IRC. The ORR is defined as the proportion of subjects 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.

The Full Analysis Set (FAS) will be used. The Response Evaluable Set (RES) may also be used for sensitivity analysis.

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

1.2 Schema

Figure 1-1 Trial Schema

1.3 Schedule of Activities

Table 1-1 CCI

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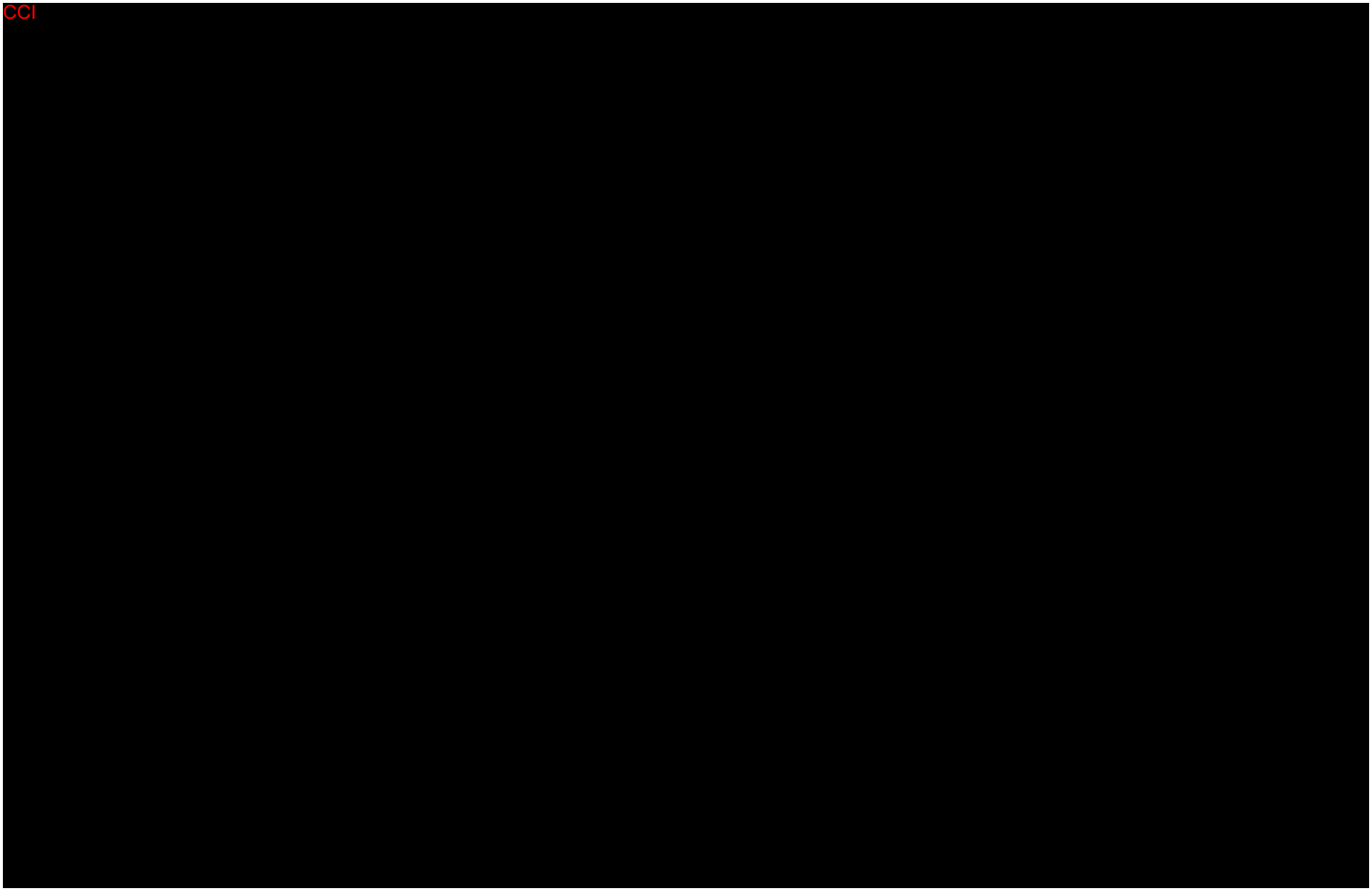
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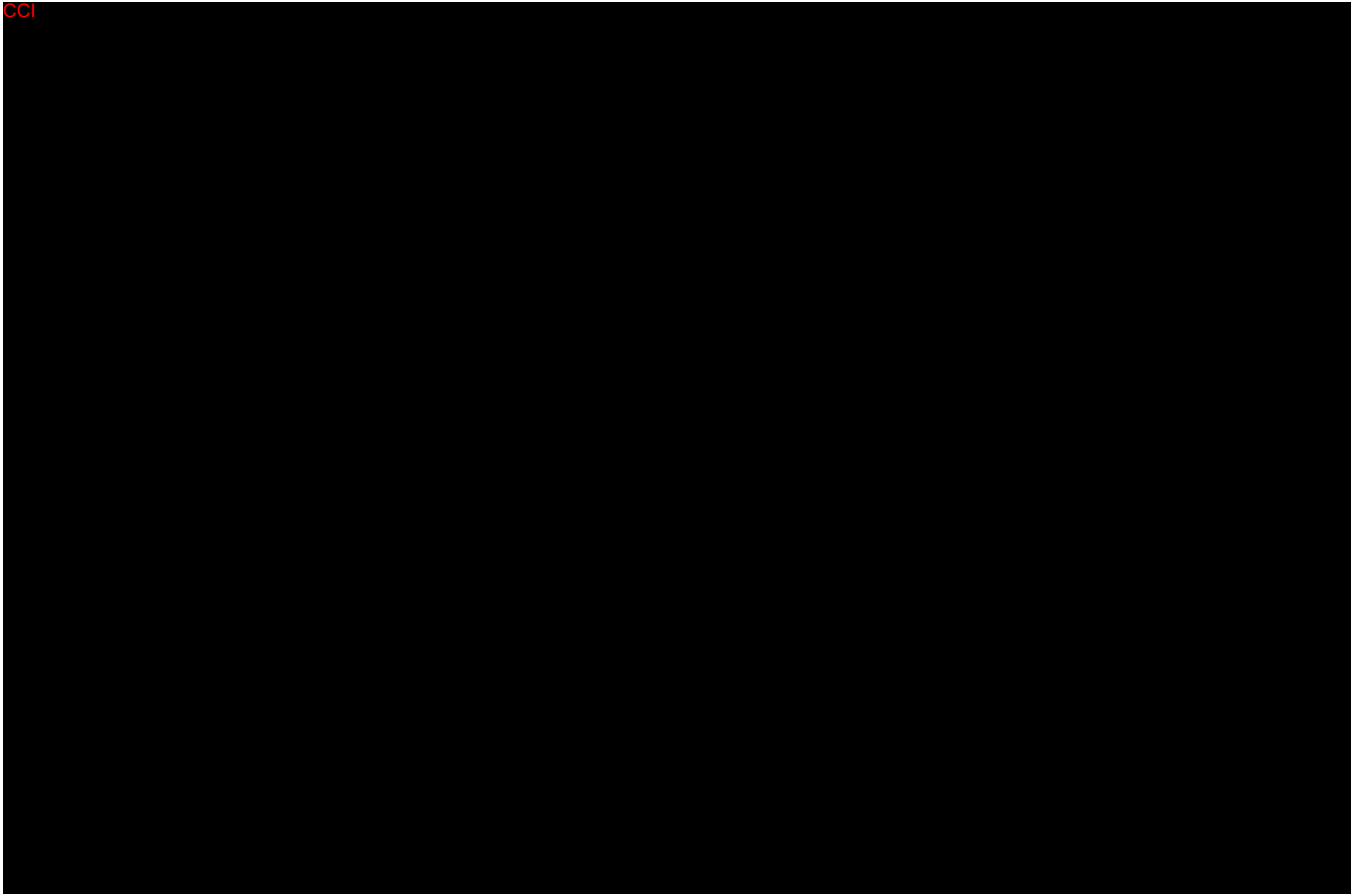

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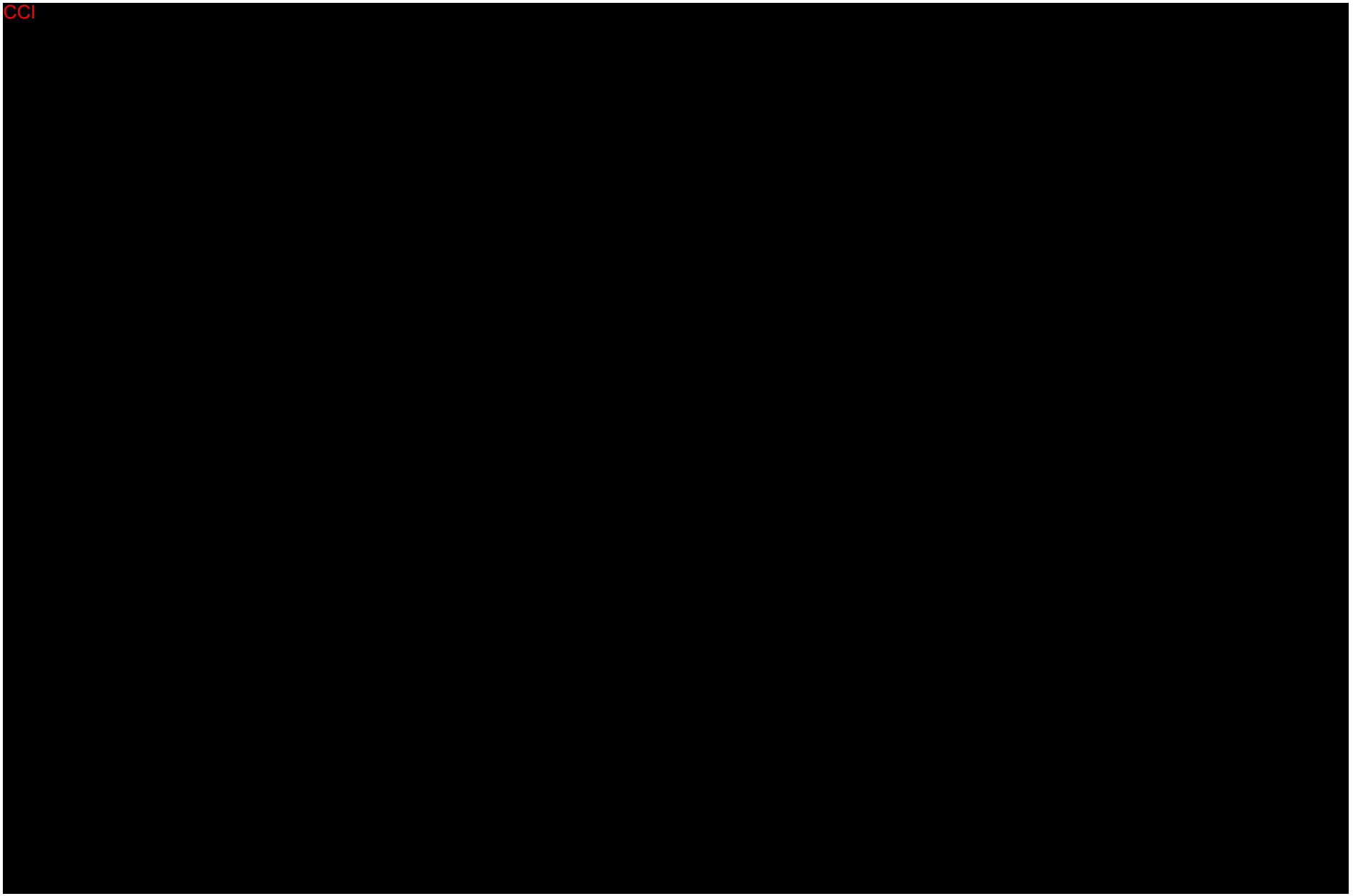

Table 1-2 CCI

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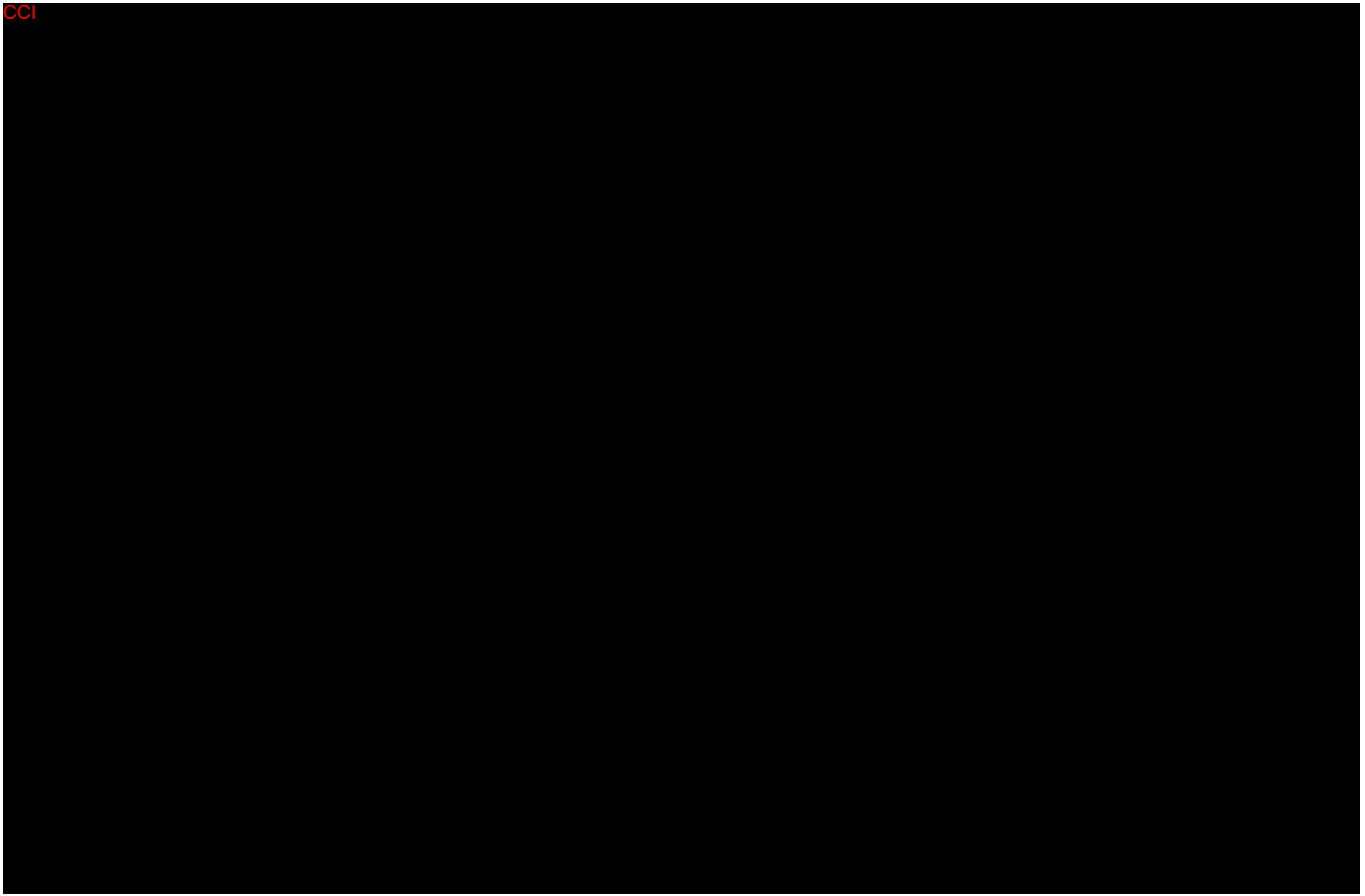
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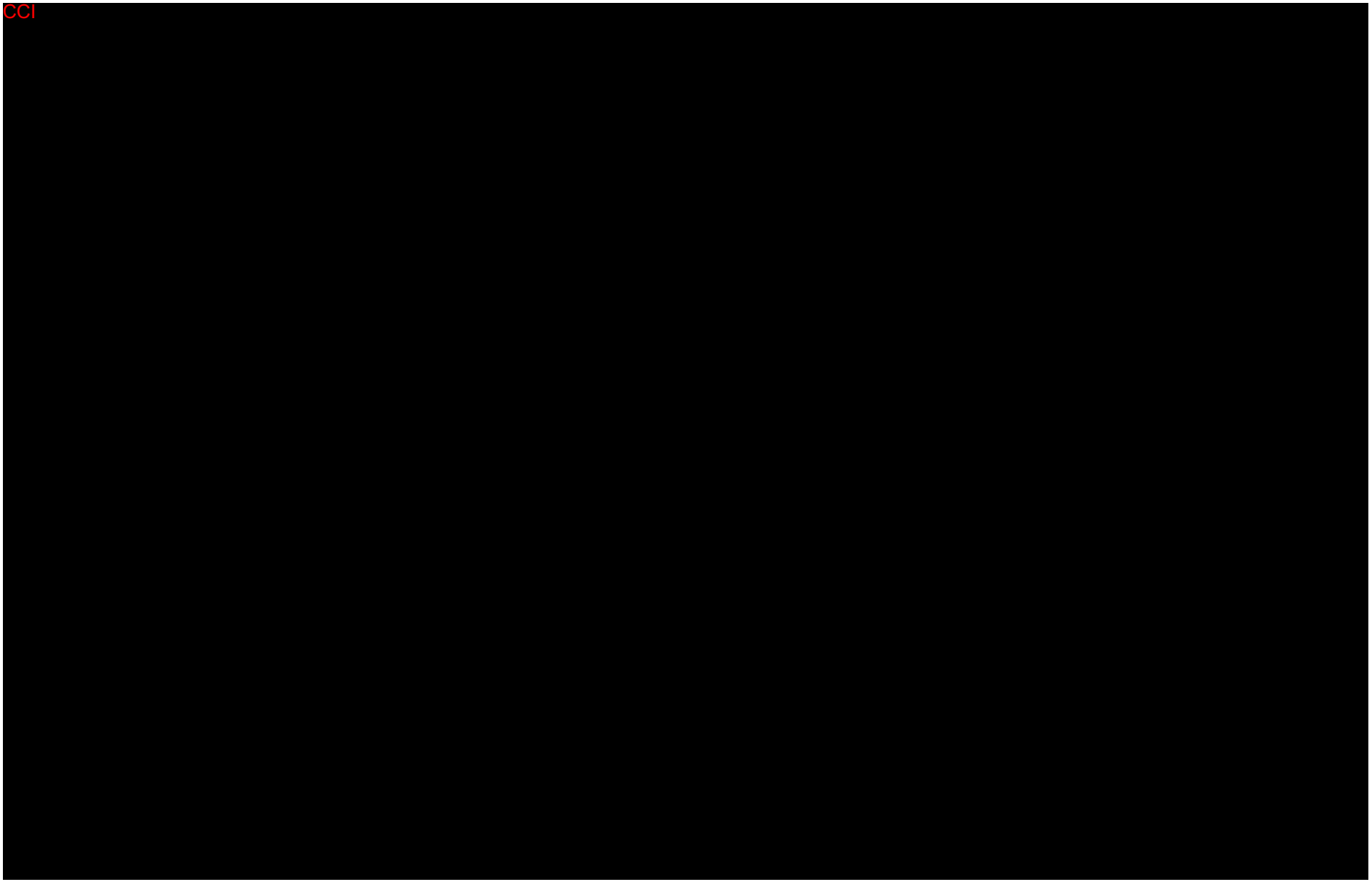

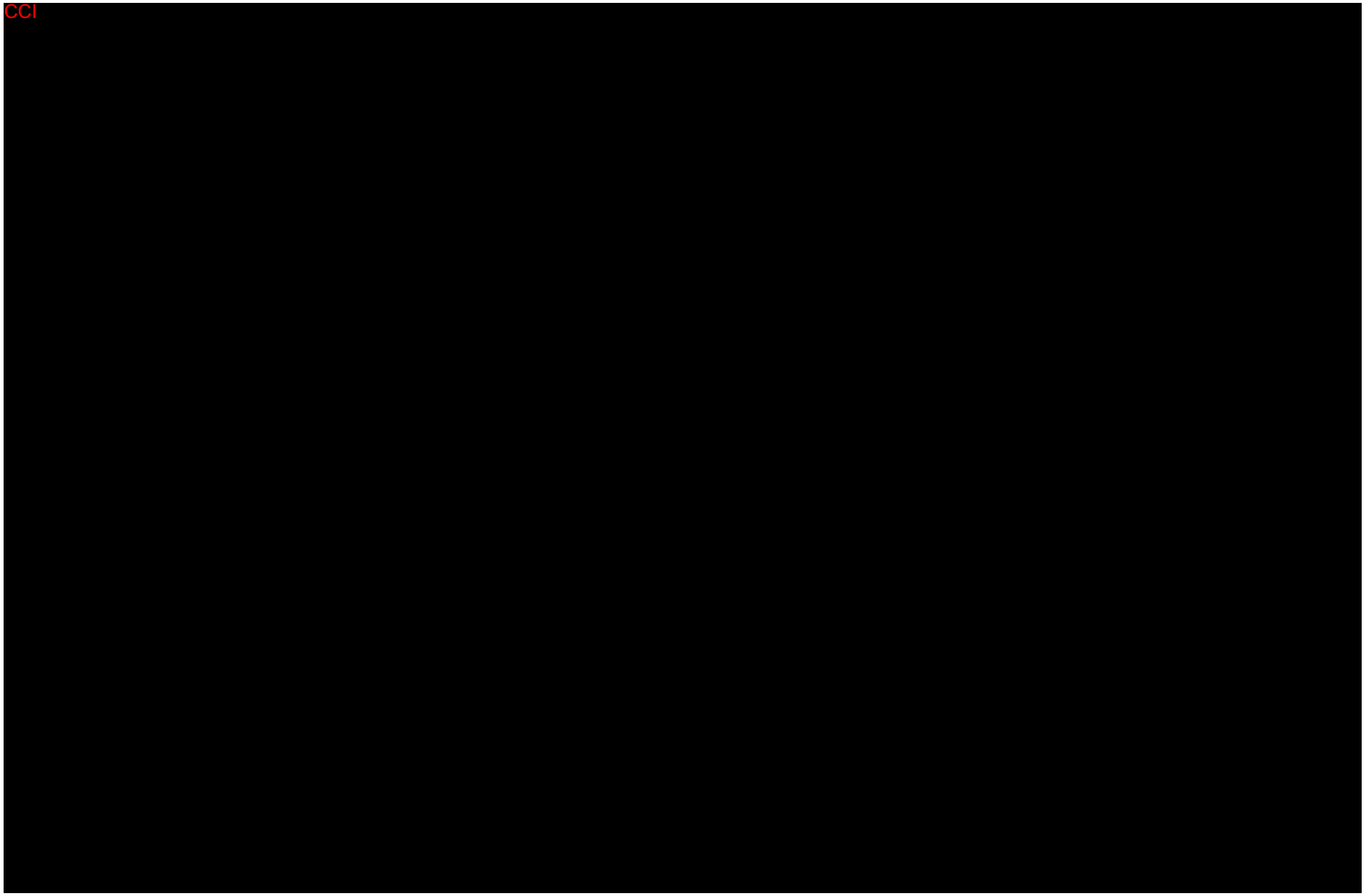
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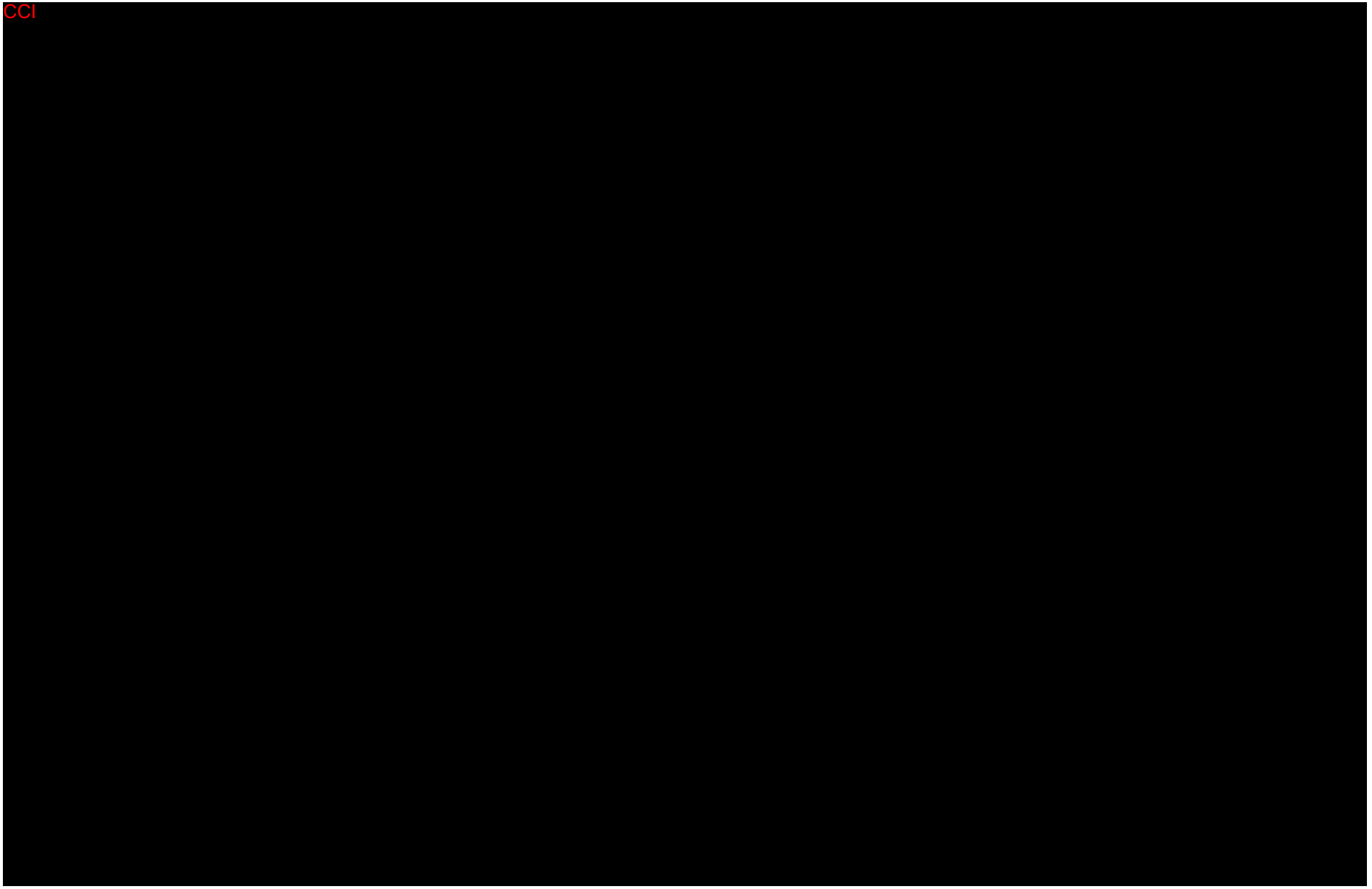
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Table 1-3 CCI

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Table 1-4 CCI

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Table 1-5 CCI

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Diseases

2.1.1.1 Classical Hodgkin Lymphoma

Classical Hodgkin lymphoma (cHL) accounts for 10% to 15% of all lymphomas (Brice et al., 2021). It is characterized by rare malignant Reed-Sternberg (HRS) cells surrounded by extensive yet ineffective inflammatory/immune cells, which enable the immune evasion of tumor cells (Liu and Shipp, 2017; Weniger and Küppers, 2021). The HRS cells of cHL are known to express high cluster of differentiation (CD)30 antigen (Hsu and Hsu, 2000). Most cHL patients are diagnosed between ages 15 and 30 years, followed by another peak in adults ≥55 years. In the United States (US), an estimated 8,540 new cases of cHL will be diagnosed in 2022 with 920 deaths expected (SEER, 2022).

Although cHL has an 85% to 95% complete remission (CR) rate following frontline chemotherapy and radiotherapy, up to 30% of patients will eventually relapse (Chohan and Ansell, 2022). Conventional salvage therapies rely upon high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HSCT). Although allogeneic HSCT is potentially curative, its application is still limited and post-transplant relapse is common.

In the past decade, novel agents such as brentuximab vedotin (BV), pembrolizumab, and nivolumab have dramatically improved the clinical outcome as from salvage therapies for R/R cHL with reduced short- and long-term toxicities. Several clinical trials have assessed the utilization of BV-containing chemotherapy regimens in the frontline setting and anti-programmed cell death protein 1 (PD-1) inhibitors as combination therapies with either chemotherapy or BV in relapsed/refractory (R/R) disease care (ADCETRIS, 2022; Bryan et al., 2023; KEYTRUDA, 2023; Massaro et al., 2022; OPDIVO, 2023). As anti-PD-1 inhibitors and BV are moving up in the cHL treatment paradigm, patients who are relapsed after or refractory to these treatments are in dire need of new treatment options.

Early phase trials of CD30-directed chimeric antigen receptor T cell (CAR-T) cell therapy have shown encouraging anti-tumor activity in heavily pretreated cHL patients: 2 parallel phase 1/2 trials reported an objective response rate (ORR) of 72% with 59% complete response (CR) (Ramos et al., 2020). In a third trial (phase 2), among 15 response-evaluable patients, ORR was 73% with CR 60% (Ahmed et al., 2022). Autologous CD30-directed CAR-T therapy has demonstrated a well-tolerated safety profile: only grade 1 cytokine release syndrome (CRS) was observed and there was no event of immune effector cell-associated neurotoxicity syndrome (ICANS). Some patients have benefited from a second infusion of CD30 CAR-T cells (Ahmed et al., 2022).

Although CD30/CD16A bispecific antibody(bsAB) (AFM13) alone has limited clinical activity against cHL, promising efficacy has been observed in R/R cHL treated with the combination of AFM13 and allogeneic natural killer (NK) cell infusion. Specifically, among 24 patients treated at the recommended phase 2 dose (RP2D), all patients achieved a response (ORR 100%) with CR 70.8%. The safety profile was favorable with no cases of CRS or ICANS (Nieto et al., 2022).

Although T-cell or NK cell therapies represent a promising approach among patients with R/R cHL with high unmet medical need, the extended manufacturing time may preclude patients whose disease is rapidly progressing. Repeated cell infusions with high treatment expense are not ideal. Furthermore, the lymphodepletion regimen may contribute to prolonged cytopenia and high occurrence of infections.

In summary, there is a significant unmet medical need for cHL patients who have exhausted standard of care (SOC) or whose diseases are resistant to prior multi-modality therapies.

2.1.1.2 CD30+ Non-Hodgkin Lymphoma

CCI [redacted]

T-cell lymphoma (TCL), also called T-cell NHL and peripheral T-cell lymphoma (PTCL), is a heterogeneous entity and encompasses clinically/biologically distinct disorders derived from mature T cells with either nodal or extranodal sites of involvement. TCL represent multiple rare subsets of systemic diseases with distinct clinical presentation and accounts for about 10% of NHL. As per World Health Organization (WHO) 2016 (Swerdlow et al., 2016), TCL is further divided into 29 subsets, CCI [redacted]

Anthracycline-based chemotherapy regimens (eg, CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or CHOEP [CHOP + etoposide] or dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin]) are the most commonly used first-line therapy regimens since these are associated with a trend toward significance in mortality reduction (Collins et al., 2019). However, anthracycline-based chemotherapy regimens result in low CR rates and poor progression-free survival (PFS) and overall survival (OS). In an analysis of 341 patients with newly diagnosed PTCL treated with anthracycline-based chemotherapy, the 3-year PFS and OS rates (32% and 52%, respectively) were significantly inferior to the matched cohort of patients with diffuse large B-cell lymphoma and there was no clear benefit for patients undergoing consolidative HSCT (Abramson et al., 2014). CCI [redacted]

BV, an anti-CD30-drug conjugate, has demonstrated encouraging activity as monotherapy in R/R systemic ALCL (Horwitz et al., 2022). BV combination with CHP has become an SOC for newly diagnosed ALCL and CD30-expressing PTCL (ADCETRIS, 2022) and in the relapse settings after anthracycline-based chemotherapy regimens.

In summary, despite intensified approaches in the frontline setting, such as the addition of etoposide to CHOP followed by consolidation with HSCT, TCL remains a distinct challenge

with very high unmet medical need. Although BV as a monotherapy and in combination with chemotherapy has demonstrated significant clinical benefit in CD30+ TCL, toxicities from the payload and cytotoxic agents remain a major concern. CD30-targeting therapies such as GEN3017 may lead to reduced toxicity and improved efficacy therefore is warranted to be explored in patients with advanced NHL whose disease no longer responds to standard therapies.

2.1.2 Introduction to GEN3017

GEN3017 (DuoBody®-CD3xCD30) is a CD3xCD30 bispecific CCI with a silenced Fc domain that was generated with Genmab's proprietary DuoBody technology, also referred to as controlled Fab-arm exchange (Labrijn et al., 2013; Labrijn et al., 2014). GEN3017 is structurally and biochemically similar to conventional immunoglobulin G (IgG)1 molecules. GEN3017 targets the T-cell antigen CD3 and the tumor necrosis factor receptor (TNFR) super family member CD30, which is expressed by certain hematologic diseases. GEN3017 is designed to induce cytotoxic synapse formation and killing of CD30+ target cells by cross-linking CD3 on T cells with CD30 expressed on tumor cells.

CD30, also known as Ki-1 or TNFRSF8, is a transmembrane glycoprotein receptor consisting of an extracellular domain, a transmembrane domain, and an intracellular domain, and is a member of the TNFR superfamily (Falini et al., 1995; Sotomayor et al., 2014). Binding of the CD30 ligand (also called CD153) to CD30 induces trimerization and recruitment of molecules that result in signaling pathway activation. These effects occur when ligand binding is transduced through the receptor to the intracellular portion of CD30, inducing TRAF binding (primarily TRAF2 and TRAF5). The extracellular portion of CD30 is subject to enzymatic cleavage by metalloproteases, resulting in the release of 85-kDa soluble CD30 in the serum and/or bodily fluids. Several studies have now demonstrated that levels of soluble CD30 may be associated with the extent of tumor burden in some malignancies. It is thought that high serum levels of soluble CD30 might provide an independent predictor of disease progression and poor prognosis in patients with CD30+ lymphomas (Sotomayor et al., 2014).

CD30 has emerged as an important molecule in the field of targeted therapy because its expression is generally restricted to specific disease types and states. The major cancers with elevated CD30 expression include cHL and ALCL, and CD30 expression is considered essential to the differential diagnosis of these malignancies (Sotomayor et al., 2014). CCI Over the past several years, several therapeutic agents were developed to target CD30 including antibody-drug conjugates, antibody-based immunotherapies, and cellular therapies. CD30-targeting agents were explored clinically in patients with cHL and in a proportion of those with NHL, with varying success in clinical trials. A major advance in the targeting of CD30 was seen with the development of the antibody-drug conjugate BV, which consists of the anti-CD30 antibody SGN-30 conjugated to the synthetic anti-tubulin agent monomethyl auristatin E and was approved by the US FDA for use in cHL and PTCL (ADCETRIS, 2022).

Even though addition of BV to chemotherapy or immunochemotherapy improved the outcome for patients with cHL or PTCL, disease relapse or progression occurs in many patients. Therefore, there remains a need to develop new therapies.

2.1.2.1 Summary of Nonclinical Studies

A nonclinical pharmacology package demonstrating the potency and mechanism of action (MOA) of GEN3017 in models representing HL and NHL is available. GEN3017 induced potent killing of CD30-expressing tumor cells in vitro using T cells from peripheral blood mononuclear cell (PBMC) obtained from healthy donors or HL or NHL patients as effector cells. Activation and cytotoxic activity of T cells induced by GEN3017 were dependent on the simultaneous binding to both CD3-expressing T cells and CD30-expressing tumor cells. EC_{50} values for GEN3017-induced cytotoxicity toward CD30-expressing HL and NHL cell lines were in the picomolar range as determined in a flow cytometry assay.

The nonclinical safety program for GEN3017 included in vitro assessments as well as in vivo toxicology studies in cynomolgus monkeys. In a GLP-compliant tissue cross reactivity study, GEN3017 showed expected membrane staining on mononuclear cells in lymphoid and non-lymphoid tissues in both human and cynomolgus monkey tissue panels. There was also membrane staining in epithelial cells in human placenta (specifically extravillus trophoblasts) and in epithelial cells in skin (follicular root sheaths of sweat glands), testis (seminiferous tubules), and ureter (mucosa) from cynomolgus monkey. A whole blood cytokine release assay, using concentrations of GEN3017 up to CCI, indicated that GEN3017 was associated with cytokine release at the higher concentrations. The hemolytic potential and plasma compatibility of GEN3017 was determined at concentrations up to CCI without indications of hemolytic potential and with good plasma compatibility.

Repeated dose safety and toxicity studies were performed in cynomolgus monkey. Of 6 animal species commonly evaluated in nonclinical toxicology studies, cynomolgus monkey was the only relevant toxicology species with similar binding affinity to human and cynomolgus monkey CD3 and CD30, and with comparable pharmacological activity in vitro. In the pivotal GLP toxicology study, GEN3017 was administered subcutaneously (SC) and intravenously up to CCI for 5 weeks. In line with the intended immune stimulatory mode of action, GEN3017 administration was associated with activation of immune cell populations and elevated serum levels of proinflammatory cytokines 6 to 12 hours postdosing on Day 1. The cytokine levels returned to baseline levels within 72 hours and were of lower magnitude after the second dose on Day 8. Changes in clinical chemistry, hematology, and coagulation were transient and mostly related to an acute phase response. Histologic assessments were also consistent with the expected MOA, where administration of GEN3017 was associated with an increased incidence of mononuclear or lymphocytic infiltration and increased cellularity, usually of germinal centers, in lymphoid tissues at all doses. There were no adverse findings in urinalysis, ophthalmoscopy, or macroscopic assessment of organ tissue. Safety pharmacology evaluations (electrocardiograms [ECGs]/heart rate, respiratory rates, and neurobehavioral examinations) were performed as part of the study, with no GEN3017-related findings in any parameter. Weekly SC administration of GEN3017 was well tolerated locally.

The first-in-human (FIH) dose selection takes into account the MOA of GEN3017 and is based on estimation of the dose that led to CCI using in vitro nonclinical data and interspecies scaling and modeling (see Section 4.3).

For additional details regarding nonclinical studies, refer to the GEN3017 investigator's brochure (IB).

2.1.2.2 Summary of Clinical Studies

This is an FIH trial, therefore no clinical experience is available.

2.2 Trial Rationale

In recent years, anti-PD-1 checkpoint inhibitors (CPIs) (ie, nivolumab, pembrolizumab) and anti-CD30 antibody-drug conjugate (ie, BV) have advanced the clinical outcome of R/R cHL (ADCETRIS, 2022; KEYTRUDA, 2023; OPDIVO, 2023). However, a significant portion of patients will progress while on these therapies. Although allogeneic HSCT is potentially curative, its application is still limited and post-transplant relapse is common (Chohan and Ansell, 2022). As CPIs and BV are moving up in the cHL treatment paradigm, patients who are relapsed after or refractory to these treatment modalities are in dire need of new treatment options. Lymphoma is one of the most common cancers in pediatric patients. For the 15- to 19-year-old age group, cHL is the single most common malignancy (Siegel et al., 2022). While the overall cure rate for the majority of pediatric cHL patients is high, there is a small group whose disease is highly refractory to the current treatment regimens. Reducing long-term morbidity and mortality secondary to intensive chemotherapy and/or radiotherapy for cHL in young patients who have decades of life ahead of them is of high unmet medical need (Kelly, 2015; Kelly et al., 2013). CCI [redacted]

In cHL, HRS cells invariably express high levels of CD30 antigen (Sotomayor et al., 2014). Among TCLs, ALCL has the most intense CD30 expression; various levels of partial expression of CD30 are found in other TCL subtypes CCI [redacted].

T-cell-based immunotherapy such as CD30-directed CAR-T cell and bispecific T-cell engagers such as GEN3017 represents a promising approach among advanced R/R cHL and CD30+ TCL patients whose disease no longer responds to standard therapies including chemotherapy, BV, and HSCT.

In vitro, GEN3017 showed potent tumor cell killing in cHL and ALCL cell lines associated with T-cell activation and proliferation. Repeated dose toxicity studies in cynomolgus monkeys tested GEN3017 via subcutaneous (SC) and intravenous (IV) administrations up to CCI [redacted]. The no observed adverse effect level (NOAEL) was determined to be CCI [redacted].

CCI [redacted]

The purpose of this phase 1/2a trial is to characterize the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics profiles, and assess preliminary anti-tumor activity of GEN3017 (DuoBody-CD3xCD30) in subjects with R/R CD30+ cHL or R/R CD30+ TCL.

In phase 1 dose escalation, dose-liming toxicities (DLTs) will be monitored to determine the RP2D, and if reached, the maximum tolerated dose (MTD) for R/R CD30+ cHL and R/R CD30+ TCL, respectively. It is expected the safety and efficacy profile of GEN3017 may differ in cHL versus TCL. Therefore, dose escalations will be conducted in 2 disease cohorts, ie, R/R CD30+ cHL Cohort and R/R CD30+ TCL Cohort. The totality of the data including safety,

immunogenicity, PK, pharmacodynamics, and preliminary efficacy will be evaluated to guide further development for expansion.

In phase 2a expansion, the anti-tumor activity of GEN3017 at the RP2D and selected dosage(s) will be assessed together with safety, immunogenicity, PK, and pharmacodynamics in R/R CD30+ cHL subjects including adult (18 years and older) and adolescent (12-17 years old) and in subjects with selected R/R CD30+ TCL subtypes. It is expected that the patient populations to be enrolled in this trial are heavily pretreated. CCI

2.3 Benefit-Risk Assessment

GCT3017-01 is an FIH trial. No clinical data on GEN3017 exists and the safety profile for GEN3017 is yet to be established. The trial population is limited to subjects with R/R cHL or TCL patients who have exhausted standard therapies or are ineligible for standard therapies. The risk to subjects in this trial should be minimized by complying with the eligibility criteria and trial procedures with close monitoring and proper/prompt management of treatment-emergent adverse events (TEAEs).

2.3.1 Potential Benefit

CD30 is a valid therapeutic target in CD30+ lymphomas as demonstrated by BV either as a monotherapy or in combination therapies (ADCETRIS, 2022; Horwitz et al., 2019; Straus et al., 2021).

Anti-CD30 monoclonal antibodies (mAbs) such as SGN-30, unconjugated antibody of BV, only showed minimal clinical activity with one CR reported in one cutaneous ALCL out of 3 R/R CD30+ NHL subjects and 4 stable disease in 21 cHL subjects in a phase 1 study of SGN-30 (Bartlett et al., 2008). In the phase 2 study of SGN-30 in R/R cHL and ALCL, SGN-30 has been demonstrated to be safe; however, objective responses were observed in only 7 out of 41 ALCL subjects and no objective response was observed in the 38 cHL subjects (Forero-Torres et al., 2009). The antibody-drug conjugate BV (SGN-35), which consists of SGN-30 conjugated via a cathepsin cleavable linker to the synthetic anti-tubulin agent monomethyl auristatin E (MMAE), has significantly improved the clinical activity in CD30-expressing lymphomas. CCI

MDX-060 is a human anti-CD30 immunoglobulin [Ig] G1 mAb which constitutes the CD30 arm of GEN3017. Nonclinical data indicate that MDX-060 could kill HL cell lines in vitro and in xenograft tumor models; however, MDX-060 alone had limited clinical activity when administered to patients. In a phase 1/2 trial evaluating MDX-060 in R/R cHL and ALCL, although the safety profile of single agent MDX-060 was favorable at dose levels up to

15 mg/kg, there were only 6 responders out of 72 patients across all DLs including CR in 2 HL and 2 ALCL patients and partial response (PR) in 2 HL patients (Ansell et al., 2007).

Recently, T-cell engager therapies such as CD30-directed CAR-T cell therapy has demonstrated encouraging clinical outcome in R/R cHL and CD30+ TCL patients who have exhausted standard therapies including chemotherapy, BV, CPIs, or autologous or allogeneic transplantation (Ahmed et al., 2022; Caballero Gonzalez et al., 2022; Quach et al., 2022). It is hypothesized that GEN3017 may introduce more potent tumor cell killing by utilizing a novel MOA of T-cell-mediated cytotoxicity in a similar fashion.

Anthracycline-based chemotherapy regimens with or without BV have been considered standard therapy for cHL and TCL. Cardiovascular disease, secondary cancers, endocrine toxicity, neurological sequelae, and fertility issues are the most significant late effects in long-term survivors of cHL due to intensified chemotherapy and radiotherapy (Di Molfetta et al., 2022). Although therapy with a CPI is very promising in R/R cHL, some patients may develop irreversible and life-long immune-related AEs. Use of BV can cause peripheral neuropathy (52-67% in adults), an off-target toxicity of BV due to the MMAE payload and represents the most common extra-hematological and the main clinically significant BV-related toxicity. An increased risk of progressive multifocal leukoencephalopathy associated with BV treatment has been reported and added as a boxed warning in the package insert (ADCETRIS, 2022). GEN3017, on the other hand, is a bsAb and delayed toxicities from chemotherapy, radiotherapy, or irreversible AEs are not expected.

2.3.2 Potential Risks

GEN3017 has not been administered to human subjects; therefore, no clinical data are available. Based on nonclinical studies conducted to date (Section 2.1.2.1) and literature review of clinical data from CD30-targeting therapies including antibody-drug conjugate, CD30 bsAbs, and CD30-directed CAR-T cell therapies, the main risks identified for GEN3017 are CRS and, potentially, ICANS.

CRS and neurologic toxicities are 2 major toxicities observed in T-cell engager therapies such as CAR-T cell therapy and CD3-bispecific antibodies (Dickinson et al., 2022; Hutchings et al., 2021; Kamdar et al., 2022). CRS results in a defined constellation of symptoms including but not limited to chills, fever, hypoxia, and hypotension. Clinical findings from ICANS strongly indicated existence of overactivated peripheral immune response followed by endothelial activation-induced blood-brain barrier dysfunction, which triggers subsequent central nervous system (CNS) inflammation and neurotoxicity (Gu et al., 2022). It usually occurs concurrently with or after CRS onset and may temporarily affect cognitive function, speech, and level of consciousness (Lee et al., 2019). Clinical experience with CD30-directed CAR-T cell therapies in cHL showed the following:

1. CRS was reported in R/R cHL patients with low incidence and severity:

    a) In the pilot segment of phase 2 CHARIOT trial (Ahmed et al., 2022), there was 1 subject with CRS (grade 1) out of 15 enrolled subjects (6.7%);

    b) In the phase 1/2 CD30.CAR EBVSTs trial (Quach et al., 2022), there were 4 subjects with CRS (grade 1) out of 14 subjects (28.6%);

c) In the phase 1 HSP-CAR30 trial (Caballero Gonzalez et al., 2022), there were 6 subjects with CRS (grade 1) out of 10 subjects (60%).

2. No ICANS was reported in cHL patients on the above CAR-T trials.

In summary, CRS/ICANS could potentially occur with treatment of GEN3017; however, low grade and frequency are expected in cHL.

To mitigate the risk of CRS, the protocol has implemented the following modalities:

1. Premedications with corticosteroids, antipyretics, and antihistamines (see Section 6.1.2).
2. CCI [redacted]

Management of CRS and ICANS includes IV hydration, oxygen, corticosteroids, and interleukin (IL)-6 signaling pathway antagonist tocilizumab (see Sections 10.12, 10.13, and 10.14). Hospitalization for CRS monitoring for 24 hours following each GEN3017 administration in CCI [redacted] is mandatory and immediate access to tocilizumab is mandated on site. CRS and/or ICANS should be proactively identified and promptly treated to prevent irreversible effects for which careful monitoring and timely management should follow the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines (Lee et al., 2019).

Tumor flare has been reported in B-NHL with immunotherapies including rituximab or CD3xCD20 bsAb such as glofitamab and epcoritamab; and in cHL with lenalidomide or BV treatment (Chanan-Khan et al., 2006) (Han et al., 2009). In general, tumor flare in lymphomas is of low grade and severity.

Tumor flare could potentially occur with treatment of GEN3017. Therefore, subjects will be monitored for tumor flare reaction (see Section 10.15 and Table 6-4 for dose modification guidance). Prophylactic interventions should be considered in patients with tumors involving critical locations such as the oropharynx and mediastinum. Pain associated with tumor flare can be managed with non-opioid and opioid analgesia, with high-dose corticosteroids reserved for persistent or severe cases (Salvaris et al., 2021).

CCI [redacted] injection of GEN3017 may cause local injection site reactions and systemic administration-related reactions. Subjects will be closely monitored for such reactions after each administration (see Table 6-1 for post-dose observation guidance and Section 6.7.2 and Table 6-4 for dose modification guidance).

Tumor lysis syndrome (TLS) is a known risk when treating hematologic malignancies. Prophylaxis guidelines are provided in Section 6.1.2. Subjects will be closely monitored for laboratory changes suspicious for TLS (see Section 10.15).

A Dose Escalation Committee (DEC) and Safety Committee will be reviewing data from this trial. All subjects enrolled in this trial will be monitored by qualified health care professional(s) who will provide care and evaluate the subject's response to GEN3017, in terms of its safety and efficacy.

2.3.3 Conclusion

Collectively, nonclinical data of GEN3017 and clinical data from other CD30-targeting compounds warrant clinical development of GEN3017 in both cHL and CD30+ TCL. GEN3017 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 subjects might receive from GEN3017.

For more comprehensive information related to the nonclinical studies, potential safety aspects, and the known and expected benefits/risks for GEN3017, refer to the IB.

3 OBJECTIVES AND ENDPOINTS

Table 3-1 Objectives and Endpoints – Dose Escalation

Objectives	Endpoints
Primary	
• Determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) and recommended phase 2 dose (RP2D), or dose(s) to be studied in the expansion part	• Incidence of dose-limiting toxicities (DLTs)
• Evaluate the safety and tolerability of GEN3017	• Incidence and severity of adverse events (AEs)
Secondary	
• Characterize the pharmacokinetic (PK) properties of GEN3017	Noncompartmental PK parameters: • Maximum concentration (C_{max}) • Time to reach C_{max} (t_{max}) • Predose concentration (C_{trough}) • Area under the concentration-time curve from time 0 to last quantifiable sample (AUC_{last}) and from time 0 to infinity (AUC_{inf}) • Elimination half-life ($t_{1/2}$) • Clearance • Volume of distribution
• Evaluate immunogenicity	• Anti-GEN3017 antibodies
• Assess the preliminary anti-tumor activity of GEN3017	Anti-tumor activity based on the Lugano criteria as assessed by investigator: • ORR (objective response rate) • DOR (duration of response) • TTR (time to response)
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3017	• Expression of CCI [redacted] markers on tumor cells at baseline and during treatment
• Assess potential marker of activity of GEN3017	• CCI [redacted]
• To evaluate pharmacodynamic markers linked to the mechanism of action of GEN3017	• Pharmacodynamic markers in blood samples and tumor tissues (on-treatment biopsy), including activation and/or (phenotypical) changes in peripheral blood T cells and/or increased cytokine/chemokine levels
• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity and PK/safety)	• Dose concentration response (biomarkers and/or efficacy, safety) relationship
• Explore the clinical efficacy of GEN3017	• Progression-free survival (PFS) • Overall survival (OS)

Table 3-2 Objectives and Endpoints – Expansion

Objectives	Endpoints
Primary	
• Assess the preliminary anti-tumor activity of GEN3017	• Objective response rate (ORR) based on the Lugano criteria as assessed by independent review committee (IRC)
Secondary	
• Assess the anti-tumor activity and efficacy of GEN3017	Anti-tumor activity based on the Lugano criteria as assessed by IRC and investigator: ◦ ORR (investigator only) ◦ Complete response (CR) rate ◦ Duration of response (DOR) ◦ Time to response (TTR) ◦ Progression-free survival (PFS) • Overall survival (OS)
• Evaluate safety and immunogenicity of GEN3017	• Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Immunogenicity: Anti-GEN3017 antibodies
• Characterize the pharmacokinetics (PK) of GEN3017	• PK parameters (clearance; volume of distribution; area under the concentration-time curve from time 0 to last quantifiable sample [AUC_{last}]; area under the concentration-time curve from time 0 to infinity [AUC_{inf}]; maximum [peak] concentration [C_{max}]; time to reach C_{max} [T_{max}]; predose trough concentration [C_{trough}]; and elimination half-life [$t_{1/2}$])
Exploratory	
• Evaluate the pharmacodynamic profiles of GEN3017	• Pharmacodynamic markers in blood samples and tumor tissues (on-treatment biopsy), including activation and/or (phenotypical) changes in peripheral blood T cells and/or increased cytokine/chemokine levels
• Assess potential biomarkers predictive of clinical response to GEN3017	• Expression of CCI [redacted] markers on tumor cells at baseline and during treatment • Immune cell profiling • Intratumoral and peripheral blood gene expression and genomics: DNA mutation status and gene profile (RNA-seq). Additional analyses of tumor cell spatial transcriptomics and/or proteomics may be conducted.
• Assess potential marker of activity of GEN3017	• CCI [redacted]
• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity and PK/safety)	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a phase 1/2a, open-label, multicenter, trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of GEN3017 in subjects with R/R CD30+ cHL or R/R CD30+ TCL.

The trial will be conducted in 2 parts: dose escalation (phase 1; Section 4.1.1) and expansion (phase 2a; Section 4.1.2). A diagram of the trial design is provided in Section 1.2.

Each part will consist of the following:

1. Screening period (up to 21 days prior to Cycle 1 Day 1),
2. Treatment period (Cycle 1 Day 1 until GEN3017 treatment discontinuation),
3. Follow-up period (ie, 60-day safety follow-up from the last dose of GEN3017 or before the initiation of a new anticancer treatment, whichever comes first; post-treatment follow-up for subjects who discontinue GEN3017 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).

CCI [redacted]

The MTD of each disease cohort, if reached, along with the maximum administered dose (MAD) and RP2D of each disease cohort will be determined based on the totality of the data of each disease cohort.

Approximately 120 subjects (60 in each disease cohort) are expected to be enrolled in the dose escalation part of the trial and approximately 120 subjects are expected to be enrolled in the expansion part of the trial.

In phase 1 (dose escalation), subjects who are not DLT-evaluable will be replaced (see Section 4.1.1.5). In phase 2a (expansion), subjects who discontinue from the trial will not be replaced.

During dose escalation, a DEC will review the preliminary data from subjects treated at a specific dose level (DL) according to DEC Charter and evaluate potential DLTs. The DEC will make recommendations on escalating to the next DL and/or propose the RP2D/MTD/MAD to the Safety Committee, who will have to endorse the proposed DL before subjects at the next DL can be enrolled, as well as the dose(s) selected for 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.

4.1.1 Dose Escalation

In dose escalation, GEN3017 will be tested in 2 disease cohorts:

- R/R CD30+ cHL Cohort (see Sections 5.1 and 5.2 for inclusion and exclusion criteria): Adult subjects 18 years and older will be enrolled. In the US and Australia, subjects 16 to 17 years old will be eligible to participate in the R/R CD30+ cHL dose escalation cohort (Section 10.18.3 and 10.18.4, respectively).

  and

- R/R CD30+ TCL Cohort (see Sections 5.1 and 5.2 for inclusion and exclusion criteria): Adult subjects 18 years and older will be enrolled. CCI [redacted]

Dose escalations for each disease cohort will be conducted independently. The modified Bayesian optimal interval design (mBOIN) design will be applied to guide dose escalations for each disease cohort separately. The MAD, RP2D, and MTD (if reached) for the 2 disease cohorts will be determined based on the observed toxicity with each. Population PK modeling may be explored to facilitate selection of the optimal dosing and dosing schedule.

CCI [redacted]

Dose escalation will start with an accelerated titration with single-subject DLs followed by standard titration of 3-subject DLs. For each disease cohort, up to 3 DLs will enroll 1 subject for the accelerated titration part. The trigger point to expand a 1-subject DL into a 3-subject DL (eg, adding 2 more subjects to a single-subject DL) is the observation of any of the following events during the DLT evaluation period:

- Any hematologic toxicity ≥ grade 2 (according to Common Terminology Criteria for Adverse Events (CTCAE)
- Any non-hematologic toxicity ≥ grade 2 (per CTCAE)
  - Any CRS ≥ grade 2 (per ASTCT criteria (Lee et al., 2019))
  - Any ICANS ≥ grade 2 (per ASTCT criteria (Lee et al., 2019))
- A DLT (see Section 6.7.1)
- Or a DL CCI [redacted] is being explored.

Adverse events (AEs) of specified grades mentioned above, regardless of relationship to GEN3017, should be considered relevant for transitioning from single subject into the standard 3 subjects at the initial single-subject DLs, unless the event can clearly be determined to be unrelated to the drug.

This marks the start of the standard titration part, where the DL sizes by default are 3 subjects each. For the standard titration part, Table 4-2 provides guidance to the DEC for the next DL.

The timeframe for administering CCI [redacted] should proceed as follows:

- For an investigated, non-cleared DL, there should be at least 2 nights between administration of the first dose to the first subject and the second subject within the same DL.
- Any additional subjects enrolled in the investigated, non-cleared DL should receive the first dose at least 1 day apart.
- For a DL cleared for safety as recommended by the DEC and Safety Committee, there is no specific time frame for receiving the first dose among subjects (ie, additional subjects may be treated in parallel at the respective DL that are considered safe (Section 4.1.1.6).

GEN3017 will be tested at DLs ranging from CCI [redacted] in CCI [redacted] cycles. Intrapatient dose escalation will not be allowed. At each DL, DLTs will be assessed in the first treatment cycle CCI [redacted] all subjects are required to be hospitalized for 24 hours after GEN3017 administration (Section 6.1). Additional and prolonged hospitalization for monitoring subject's safety during GEN3017 administration CCI [redacted] may be implemented at investigator's discretion.

Additional dose levels below the currently deemed safe dose level may also be explored for further substantiation of safety, PK, and PD based upon emerging data.

4.1.1.1 Dose Levels and Escalation Steps

The FIH dose of GEN3017 is as follows: CCI [redacted]

Table 4-1 CCI [redacted]

CCI [redacted]

CCI [redacted]

If subjects in a given DL experience a ≥ grade 2 AE (except for AEs unequivocally due to the underlying disease or an extraneous cause) during the DLT period, the next maximum dose increment will be limited to 100%, CCI [redacted] in the next DL.

If subjects in a given DL experience 2 or more ≥ grade 2 AEs (except for AEs unequivocally due to the underlying disease or an extraneous cause) during the DLT period, the next maximum dose increment will be limited to 50%, CCI [redacted] in the next DL.

If subjects in a given DL experience 1 or more DLT during the DLT period, the next maximum dose increment will be limited to 50%, CCI [redacted] in the next DL (Table 4-2).

All other AEs will be evaluated in their totality by the DEC and Safety Committee (see Section 10.1.8 for additional information on the DEC and Safety Committee).

4.1.1.2 Dose Escalation Strategy

An mBOIN will be utilized to propose optimal recommendations at the end of each observed DL.

The MTD is defined as the highest DL with the observed DLT rate lower than the target toxicity level. CCI [redacted]

The corresponding decision table for optimal recommendations of a DL after completion of the DLT period is presented in Table 4-2.

Table 4-2 mBOIN Guidance Table

	Total Number of DLT-Evaluable Subjects	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Guidance Based on Total Number of DLTs	Escalate if # DLT ≤	0	0	0	1	1	1	1
	Remain if # DLT ≤	1	1	1	NA	2	2	2
	Deescalate if # DLT ≥	2	2	2	2	3	3	3
	Terminate a dose level if # DLT ≥	3	3	3	4	4	4	5

DLT=dose-limiting toxicity; mBOIN=modified Bayesian optimal interval design; NA=not applicable

The DEC can at any time propose a lower DL than the mBOIN algorithm recommends as a precaution (see Section 4.1.1.7). The Safety Committee will endorse the proposed DL before subjects can be enrolled into it.

4.1.1.3 Modifications to BOIN

The BOIN algorithm has been modified to include a DL termination criterion (Table 4-2). For DLs with 3 DLT-evaluable subjects, the escalation decision will be consistent with the '3+3' design (ie, escalate if no DLT, remain on same DL if 1 DLT, de-escalate if 2 DLTs, and terminate DL if 3 DLTs).

4.1.1.4 Stopping Rules

The dose escalation stops when there are 9 DLT-evaluable subjects on the current DL and according to the escalation rules, the decision will be to remain on the same DL (Table 4-2).

MTD or MAD may be declared based on 6 DLT-evaluable subjects if the recommendation is to escalate and the next level is not available.

At any time point, based on the totality of the accumulated data, the DEC and Safety Committee may conclude on the dose(s) selected for further development in the expansion part.

4.1.1.5 Number of Subjects Per Dose Level

To limit number of subjects treated with a presumed non-efficacious dose, only 1 DLT-evaluable subject is planned to be recruited for the initial up to 3 DLs. These initial single-subject DLs can be expanded to 3 DLT-evaluable subjects as described in Section 4.1.1 and the mBOIN algorithm will be used to define the next DL. If any single-subject DL is expanded to a total of 3 DLT-evaluable subjects, all subsequent DL(s) will have at least 3 DLT-evaluable subjects.

Over-recruitment by 2 subjects is allowed, so that each 3-subject DL may consist of 3 to 5 subjects who are evaluable for DLTs.

Subjects who are not DLT-evaluable will be replaced.

4.1.1.6 Backfill and Parallel DLs

To better understand the safety, tolerability, PK, pharmacodynamic, or anti-tumor activity, approximately 7 additional subjects in total may be allocated to DLs that are considered safe (ie, DLs that have been cleared by DEC and Safety Committee) for such allocation (DLs at or below the currently investigated one). In total, up to 42 additional subjects may be recruited in this manner. Any DLTs observed in such subjects will not directly contribute to the mBOIN design evaluation of the higher DL being investigated but will be reported to the DEC and Safety Committee who will review the data in totality. However, if the mBOIN algorithm later recommends de-escalation to a lower DL, all subjects treated with GEN3017 at that DL will be counted as part of the mBOIN algorithm. A backfilled subject who is not DLT-evaluable may be replaced.

CCI [redacted]

4.1.1.7 Other Dose Escalation/De-Escalation Procedures

During the dose escalation part of the trial, the sponsor will conduct regular calls with investigators and the study team at sites to review and discuss emergent safety data. If a safety concern of any kind arises, ad hoc investigator safety meeting(s) may be called.

4.1.1.8 Determination of RP2D and Expansion Doses

The RP2D and expansion dose(s) will be determined after review of all available data including safety, PK, pharmacodynamics, and preliminary efficacy activity.

An RP2D may be selected, and expansion cohorts may be initiated, before the MTD has been reached. The RP2D will be declared based on the totality of data and may be lower than the MTD and the MAD, as the aim is to find the optimal therapeutic dose.

4.1.2 Expansion

In the expansion part, the anti-tumor activity of GEN3017 as a monotherapy will be evaluated together with safety, PK, and pharmacodynamics in 6 disease cohorts (see Sections 5.1 and 5.2 for inclusion and exclusion criteria):

- Cohort 1: R/R CD30+ cHL Cohort (adult ≥18 years)
- Cohort 2: R/R CD30+ cHL Cohort (adolescent ≥12 and <18 years; US and Australia only [Section 10.18.3 and 10.18.4, respectively])
- Cohort 3: CCI [redacted]
- Cohort 4: CCI [redacted]
- Cohort 5: CCI [redacted]
- Cohort 6: CCI [redacted]

Adult subjects will receive GEN3017 at CCI [redacted]. For adolescent R/R cHL subjects (US and Australia only; Cohort 2), GEN3017 will be administered as CCI [redacted] will be used and the total dose will not exceed CCI [redacted] used in adults. The dosage(s) and dosing schedule for expansion will be determined at the end of dose escalation. CCI [redacted] of GEN3017 for a minimum of 4 hours and hospitalization for 24 hours for CRS monitoring is required after the CCI [redacted] (Section 6.1). Additional and prolonged hospitalization for monitoring subject's safety during GEN3017 administration CCI [redacted] may be implemented per investigator's discretion.

Each cohort will include up to 20 subjects, testing a minimum of 1 DL. Dose optimization may be built into expansion, and different doses and schedules may be explored. Additional TCL subtypes may be included in the expansion based on clinical data from the dose escalation part. CCI [redacted]

4.2 Trial Design Rationale

This trial is being conducted to identify the MTD and/or MAD, evaluate the RP2D, evaluate safety, and obtain preliminary efficacy of GEN3017 as a single agent in subjects with R/R CD30+ cHL or R/R CD30+ TCL. To this end, the sponsor will conduct a dose escalation part followed by a phase 2a part with expansion cohorts. These data will be used to inform future clinical development of GEN3017.

Escalation and de-escalation in dose escalation will be guided by the mBOIN approach. To collect further data on the safety, tolerability, PK, and anti-lymphoma activity, the selected RP2D of GEN3017 from dose escalation will be studied in expansion. Additional DLS other than RP2D may also be studied for the purpose of dose optimization in expansion.

4.3 Dose and Schedule Rationale

4.3.1 IMP Dose and Schedule Rationale

4.3.1.1 GEN3017

The following considerations were made in defining the FIH starting dose, the dose escalation steps, and the dosing schedule.

1. GEN3017 activates T-cells to kill target cells by binding to CD3 on T cells and CD30 on malignant cells. CD30 is highly expressed in HL and some T-cell lymphomas (Falini et al., 1995; Horwitz et al., 2019) with low-level expression on a subset of healthy, activated T cells and B lymphocytes and a small portion of eosinophils (Falini et al., 1995; Matsumoto et al., 2004). T-cell activation by CD3 bispecific antibodies requires cross-linking, hence, binding to CD3 alone does not lead to T-cell stimulation. Therefore, the tumor is considered the site of pharmacological activity and negligible T-cell activation by GEN3017 is expected outside of the tumor.

2. cHL is characterized by a unique tumor composition in which sparse malignant cells are surrounded by an abundance of immune cells, predominantly T cells. This composition is difficult to mimic in nonclinical experiments. A semi-mechanistic PK/PD model was utilized to guide the selection of the starting dose, which accounts for CCI [redacted]

A physiologically based semi-mechanistic PK/PD model was built to estimate the relationship between dose, exposure, response, and time. CCI [redacted]

The model was used to support key trial design decisions pertaining to dose.

- CCI [redacted]

- The FIH starting dose was based on the estimated dose associated with CCI [redacted].
- GEN3017 is expected to display a biphasic dose-response relationship, with reduced cross-linking beyond an optimum dose range. Smaller escalation steps are taken around the estimated optimum dose range. The upper end of the dose escalation takes into account model uncertainty in identifying the optimum dose range.
- CCI [redacted]
- For adolescent R/R cHL subjects in the expansion part, CCI [redacted].

4.3.2 AMP Dose and Schedule Rationale

4.3.2.1 Dexamethasone or Methylprednisolone (or Equivalent)

To be administered per approved label.

4.3.2.2 Paracetamol/Acetaminophen (or Equivalent)

To be administered per approved label.

4.3.2.3 Diphenhydramine (or Equivalent)

To be administered per approved label.

4.3.2.4 Tocilizumab

To be administered for CRS per Section 10.13 and Section 10.14.

4.3.2.5 Siltuximab

To be administered in cases of CRS per Section 10.13 and Section 10.14. For country-specific information see Section 10.18.2.

4.3.2.6 Anakinra

To be administered in cases of ICANS as well as cases of CRS with concurrent ICANS per Section 10.13 and Section 10.14, respectively. For country-specific information see Section 10.18.2.

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

4.4.1 Primary Completion Date

The primary completion date is defined as the date when the last subject 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. In the case of clinical trials with

more than 1 primary endpoint with different completion dates, this term refers to the date on which data collection is completed for all of the primary endpoints.

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

4.4.2 Estimated Trial Duration

The maximum trial duration is 5 years after the last enrolled subject's first treatment in the trial.

4.4.3 Estimated Trial Duration for an Individual Subject

The estimated trial duration for an individual subject is approximately 2 years, consisting of a 21-day screening period, an estimated 1-year treatment period (the duration of treatment may vary for each subject), a 60-day safety follow-up period, post-treatment follow-up for subjects who discontinue GEN3017 prior to disease progression, and a survival follow-up period (the duration of follow-up may vary for each subject).

A subject is considered to have completed the trial if the subject has completed all periods of the trial including the last visit shown in the Schedule of Activities (Section 1.3).

4.4.4 End of Trial

The end of trial is defined as the date of the last visit of the last subject in the trial globally.

5 TRIAL POPULATION

After obtaining a written informed consent from participating subjects or their guardians, a unique subject identifier will be assigned to each subject and the subject can proceed with screening procedures. Subjects who meet all of the eligibility criteria may be enrolled.

The inclusion and exclusion criteria for enrolling subjects in this trial are described below in Sections 5.1 and 5.2, respectively. The eligibility information will be submitted to the sponsor's MM for review. If the sponsor agrees that the eligibility criteria have been met, the investigator will receive confirmation that the subject may be enrolled into the trial. If the sponsor considers that the eligibility criteria have not been met, then the sponsor will contact the investigator to discuss the subject. If there is a question about these criteria, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the trial.

NOTE: After eligibility approval from the sponsor during screening, investigators are responsible for ensuring subjects to continue meeting eligibility criteria prior to the first dose of GEN3017. Should the subject no longer meet eligibility criteria, investigators are required to inform the sponsor's MM promptly.

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria – Dose Escalation (All Disease Cohorts)

Each potential subject must fulfill all of the following inclusion criteria to be enrolled in the dose escalation part.

1. Must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the trial is taking place).

   1US and 1AU: R/R cHL Cohort: Subjects with R/R cHL must be at least 16 years of age (US and Australia only); assent is required of children capable of understanding the nature of the trial as described in the informed consent form (ICF) (Section 10.18.3 and 10.18.4, respectively).

2. Must sign an ICF by the subject or their legally acceptable representative (not applicable in EU/EEA) 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 subject is willing to participate in the trial. Where required by local or country-specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).

3. Histologically confirmed R/R cHL or R/R TCL according to the 2016 WHO classification (Swerdlow et al., 2016).

4. Subjects must have at least 1 measurable lesion according to the 2014 Lugano criteria (Cheson et al., 2014).

   a. An 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).

5. Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1 for subjects 18 years of age and above.

   5US and 5AU: For subjects ≥16 and <18 years of age (US and Australia only), Karnofsky score of >60% per Karnofsky performance scale (Section 10.18.3 and 10.18.4, respectively).

6. Confirmed CD30-positivity in tumor biopsy prior to the first dose of GEN3017. Subjects must have documented CD30 expression by immunohistochemistry or flow cytometry as assayed in a local Clinical Laboratory Improvement Amendments (CLIA) certified (or local equivalent) hematopathology laboratory. A fresh biopsy is recommended to demonstrate CD30 expression if clinically feasible and not considered as a high-risk procedure.

7. Has acceptable laboratory test results as follows:

CCI

8. CCI

9. Anticipated life expectancy of ≥12 weeks.

10. A female subject with reproductive potential must agree to use adequate contraception during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017. 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 subject experiences menarche), a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in Section 10.3.

11. A female subject with reproductive potential must have a negative serum beta-hCG test at screening.

12. A female subject must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

13. A male subject must agree not to donate sperm during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

14. A male subject 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 GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

15. Male subjects (including males who have had vasectomies) whose partner is pregnant should use condoms for the duration of GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

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

5.1.1.1 Specific Inclusion Criteria for R/R cHL Cohort in Dose Escalation

A.1: Must have relapsed or progressive cHL after receiving at least 3 prior lines of therapy

CCI [redacted]

OR

A.2: Refractory to the second line of therapy.

5.1.1.2 Specific Inclusion Criteria for TCL Cohort in Dose Escalation

CCI [redacted]

CCI

CCI

CCI

5.1.2 Inclusion Criteria – Expansion

Each potential subject must fulfill all of the following inclusion criteria to be enrolled in the expansion part.

1. Must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the trial is taking place).

   1US and 1AU: For subjects in the R/R CD30+ cHL cohort in the US and Australia only, age ≥12 and <18 years; assent is required of children capable of understanding the nature of the trial as described in the ICF (Section 10.18.3 and 10.18.4, respectively).

2. Must sign an ICF by the subject or their legally acceptable representative (not applicable in EU/EEA) 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 subject is willing to participate in the trial. Where required by local or country specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).

3. Histologically confirmed R/R cHL or R/R TCL according to the 2016 WHO classification (Swerdlow et al., 2016).

4. Subjects must have at least 1 measurable lesion according to the 2014 Lugano criteria (Cheson et al., 2014).

   a. An FDG-PET scan demonstrating positive lesion compatible with CT- or 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)

5. ECOG performance status score 0, 1, or 2 for subjects with age of 18 and above.

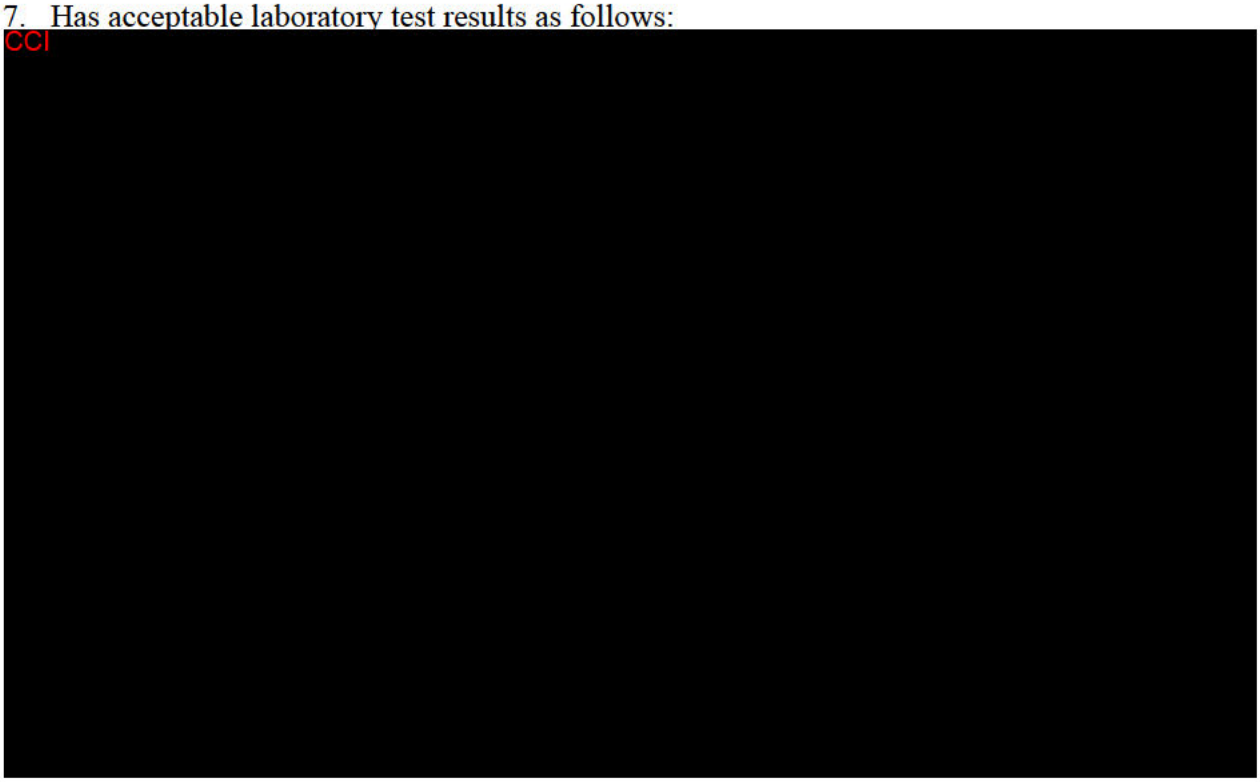
   5US1 and 5AU1: For subjects ≥16 and <18 years old (US and Australia only), Karnofsky score of >60% per Karnofsky performance scale (Section 10.18.3 and 10.18.4, respectively).

   5US2 and 5AU2:For subjects ≥12 and <16 years of age) (US and Australia only), Lansky score of CCI per Lansky play-performance scale (Section 10.18.3 and 10.18.4, respectively).

6. Confirmed CD30-positivity in tumor biopsy prior to the first dose of GEN3017. Subjects must have documented CD30 expression by immunohistochemistry or flow cytometry as assayed in a local CLIA certified (or local equivalent) hematopathology laboratory. A fresh biopsy is recommended to demonstrate CD30 expression if clinically feasible and not considered as a high-risk procedure.

7. Has acceptable laboratory test results as follows:

CCI



8. CCI

9. Anticipated life expectancy of ≥12 weeks.

10. A female subject with reproductive potential must agree to use adequate contraception during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017. 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 subject experiences menarche), a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in Section 10.3.

11. A female subject with reproductive potential must have a negative serum beta-hCG test at screening.

12. A female subject must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

13. A male subject must agree not to donate sperm during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

14. A male subject 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 GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

15. Male subjects (including males who have had vasectomies) whose partner is pregnant should use condoms for the duration of GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

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

5.1.2.1 Specific Inclusion Criteria for R/R cHL in Expansion

A.1.a: Must have relapsed or progressive cHL after receiving at least 3 prior lines of therapy

CCI

OR

A.1.b: Refractory to the second line of therapy.

CCI

CCI

CCI

5.1.2.2 Specific Inclusion Criteria for R/R TCL in Expansion

CCI

CCI

CCI

CCI [redacted]

5.2 Exclusion Criteria

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

5.2.1 Exclusion Criteria – Dose Escalation

1. CCI [redacted]
2. Primary CNS tumor or known CNS involvement.
3. Has been exposed to any of the following prior therapies within the specified timeframes:
   a. Received prior investigational CD30-targeting therapy, CCI [redacted] (except BV)
   b. Autologous HSCT within 60 days (applies to both cHL and TCL). Allogeneic HSCT within 90 days (applies to cHL) prior to the first dose of GEN3017.
   c. Chemotherapy within 2 weeks or major surgery within 4 weeks of the first dose of GEN3017
   d. Curative radiotherapy within 4 weeks or palliative radiotherapy within 2 weeks prior to the first dose of GEN3017
   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 GEN3017 or currently receiving any other investigational agents.
   f. Prior treatment with live, attenuated vaccines within 30 days prior to the first dose of GEN3017. 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 severe acute respiratory syndrome coronavirus 2 (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 GEN3017.
4. CCI [redacted]

5. CCI
   a. CCI
   b. CCI
   c. CCI
6. CCI
7. Active GVHD requiring immune suppression regardless of grade.
8. Active infection requiring antibiotic/antifungal/antiviral treatment.
9. Active infection with human T-cell leukemia virus (HTLV-1) or HTLV-2.
10. Has a known history of seropositivity for HIV. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
11. Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig therapy):
    a. Positive test for antibodies to the hepatitis B core antigen (anti-HBc)

    AND

    b. Negative test for antibodies to the hepatitis B surface antigen (anti-HBs).
12. Known medical history or ongoing hepatitis C infection that has not been cured.
13. CCI
    a. CCI
    b. CCI
    c. CCI
    d. CCI
    e. CCI

14. Has known allergies, hypersensitivity, or intolerance to mAbs, human proteins, or other product excipients.

15. Is a female who is pregnant, breastfeeding, or planning to become pregnant during GEN3017 treatment and within 4 months after the last dose of GEN3017.

16. Is a male who plans to father a child during GEN3017 treatment and within 4 months after the last dose of GEN3017.

17. 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.

18. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Additionally, vulnerable subjects or subjects under guardianship, curatorship, judicial protection or deprived of liberty, are excluded from participation in this trial.

19. CCI [redacted]

5.2.2 Exclusion Criteria – Expansion

1. CCI [redacted]

2. Primary CNS tumor or known CNS involvement.

3. Has been exposed to any of the following prior therapies within the specified timeframes:

   a. Received prior investigational CD30-targeting therapy, CCI [redacted] (except BV).

   b. Autologous HSCT within 60 days (applies to both cHL and TCL). Allogeneic HSCT within 90 days (applies to cHL) prior to the first dose of GEN3017.

   c. Chemotherapy within 2 weeks or major surgery within 4 weeks of the first dose of GEN3017.

   d. Curative radiotherapy within 4 weeks or palliative radiotherapy within 2 weeks prior to the first dose of GEN3017.

   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 GEN3017 or currently receiving any other investigational agents.

   f. Prior treatment with live, attenuated vaccines within 30 days prior to the first dose of GEN3017. 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 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 GEN3017.

4. CCI [redacted]
5. CCI [redacted]
   a. CCI [redacted]
   b. CCI [redacted]
   c. CCI [redacted]
6. CCI [redacted]
7. Active GVHD requiring immune suppression regardless of grade.
8. Active infection requiring antibiotic/antifungal/antiviral treatment.
9. Active infection with HTLV-1 or HTLV-2
10. Has a known history of seropositivity for HIV. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
11. Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig therapy):
    a. Positive test for antibodies to anti-HBc

       AND

    b. Negative test for antibodies to anti-HBs
12. Known medical history or ongoing hepatitis C infection that has not been cured.
13. CCI [redacted]

a. CCI [redacted]
b. CCI [redacted]
c. CCI [redacted]
d. CCI [redacted]
e. CCI [redacted]

14. Has known allergies, hypersensitivity, or intolerance to mAbs, human proteins, or other product excipients.

15. Is a female who is pregnant, breastfeeding, or planning to become pregnant during GEN3017 treatment and within 4 months after the last dose of GEN3017.

16. Is a male who plans to father a child during GEN3017 treatment and within 4 months after the last dose of GEN3017.

17. Has any other serious, life-threatening or unstable pre-existing medical conditions, or uncontrolled intercurrent illness, including but not limited to active infection including COVID-19 infection.

18. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Additionally, vulnerable subjects or subjects under guardianship, curatorship, judicial protection or deprived of liberty), are excluded from participation in this trial.

19. CCI [redacted]

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (refer to Sections 5.1 and 5.2) as assessed during screening. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to follow ICH guidelines, meet the CONSORT publishing requirements, and to respond to queries from regulatory authorities. Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, or other reasons), and any AEs related to a protocol-mandated procedure (eg, CT scan), including washout or discontinuation of prior medications.

Individuals who do not meet the criteria for participation in this trial (ie, screen failures) may be rescreened one time. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be reassessed at the rescreening visit. Previous baseline assessments (eg, imaging scans, certain labs) may be used for rescreening purposes if they are considered within the protocol required screening window for the newly planned C1D1 date. If updates have been made to the ICF since the subject's last

signed ICF, rescreened subjects are required to sign a new ICF before rescreening procedures can be initiated.

6 TRIAL TREATMENT

6.1 Investigational and Auxiliary Medicinal Products

Trial treatment is defined as any IMP, auxiliary medicinal product (AMP), or medical device(s) intended to be administered to a trial subject according to the trial protocol. IMP(s) specifically are referred to as trial drug(s).

Trial treatment should be administered as described in Table 6-1 and Table 6-2 until 1 or more of the discontinuation criteria in Section 7 are met.

Detailed dose modification guidance is provided in Section 6.7. Information regarding concomitant therapy is provided in Section 6.6.

Table 6-1 Investigational Medicinal Product

Trial Drug Name	GEN3017 (DuoBody® CD3xCD30)[a,b]
Dosage Formulation	Concentrate for solution for CCI injection
Dose (including schedule and cycle length)	CCI
Route of Administration	CCI
Dosing Instructions	CCI In expansion, 1) for adult subjects, GEN3017 will be administered as a CCI injection with CCI at the DL determined by the data from the dose escalation part. 2) For adolescent subjects with R/R cHL (US and Australia only; Cohort 2), GEN3017 will be administered as an CCI CCI Refer to Section 6.1.2 for premedication and post-GEN3017 treatment requirements. Refer to the IMP Manual for detailed instructions including drug dilution and injection volume.
Hospitalization/ Monitoring Guidance	During dose escalation in treatment Cycle 1, all subjects are required to be hospitalized for 24 hours after each GEN3017 administration. Subjects must be instructed to contact the investigator should signs or symptoms of CRS and/or ICANS occur following discharge from the hospital. During dose expansion in treatment Cycle 1, all subjects are required to remain at the clinic for monitoring CCI of GEN3017 for a minimum of 4 hours and hospitalization for 24 hours for CRS monitoring is required after CCI . Additional and prolonged hospitalization for monitoring subject's safety during GEN3017 administration CCI may be implemented per investigator's discretion. As data accumulate, increased (or reduced) monitoring may be implemented for additional dose administrations if recommended by the sponsor's Safety Committee.
Packaging	GEN3017 will be provided in 2R Glass Vials

Labeling	Trial drug labels will contain information to meet the applicable regulatory requirements. For further details see the IMP Manual

CD=cluster of differentiation; cHL=classical Hodgkin lymphoma; CRS=cytokine release syndrome; D=day; DL=dose level; EU=European Union; ICANS= immune effector cell-associated neurotoxicity syndrome; IMP=investigational medicinal product; CCI ; R/R=relapsed/refractory; CCI .

a. Refer to the IMP Manual for further details.
b. Refer to Section 10.18.1 for EU authorization status.

Table 6-2 Auxiliary Medicinal Product(s)

AMP Name	Dexamethasone or methylprednisolone (or equivalent)	Paracetamol/ acetaminophen (or equivalent)	Diphenhydramine (or equivalent)	Tocilizumab	Siltuximab[a]	Anakinra[a]
Use	CRS Premedication; CRS/ICANS management	CRS Premedication	CRS Premedication	CRS	CRS	CRS/ICANS
Dosage/ frequency	Premedication: dexamethasone 20 mg, or methylprednisolone 100 mg, or equivalent 30 minutes to 2 hours prior to administration of GEN3017. CRS/ICANS management: dexamethasone 10-20 mg every 6 hours, or methylprednisolone 1000 mg/day	650 to 1000 mg, or equivalent 30 minutes to 2 hours prior to administration of GEN3017	50 mg, or equivalent 30 minutes to 2 hours prior to administration of GEN3017	8 mg/kg over 1 hour. Repeat after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period.	11 mg/kg	100 mg to 200 mg once a day
Route of Administration	IV	PO	IV or PO	IV	IV	SC
Dosing Instructions	See Section 6.1.2 and Table 6-3; See Section 10.13 and Section 10.14	See Section 6.1.2 and Table 6-3	See Section 6.1.2 and Table 6-3	See Section 10.13 and Section 10.14	See Section 10.13 and Section 10.14	See Section 10.13 and Section 10.14
Packaging	N/A	N/A	N/A	Vials	N/A	N/A
Labeling	AMP labels will contain information to meet the applicable regulatory requirements.					

a. Refer to Section 10.18.1 for EU authorization status. Refer to Section 10.18.2 for country-specific information.

6.1.1 GEN3017 Dosing Schedule

CCI

- CCI
- CCI

CCI

6.1.2 Premedication and Post-GEN3017 Monitoring

The purpose of the prophylactic premedication is to mitigate risk and severity of CRS by GEN3017. It is mandatory to premedicate subjects with corticosteroids, antihistamines, and/or antipyretics 30 minutes to 2 hours prior to the administration of GEN3017. Corticosteroid administration for premedication should be administered via IV infusions (Table 6-3) with the recommended dose or equivalent (Section 10.9).

CRS and/or ICANS should be proactively identified and promptly treated to prevent irreversible effects for which careful monitoring and timely management should follow ASTCT guidelines (Lee et al., 2019); Section 10.13 and Section 10.14). Investigators and study personnel must instruct subjects to contact the site if they experience signs and symptoms of CRS or ICANS (eg, fever, chills, dizziness, lightheadedness, syncope, dyspnea, neurologic symptoms, or altered mental status) for guidance on whether the subject must visit the study site or an alternative healthcare facility with experience in treating CRS/ICANS for further assessment and/or management (see Section 10.13 for CRS and Section 10.14 for ICANS assessments). Immediate access to tocilizumab is mandated on site.

Table 6-3 CCI

CCI

CCI

- CCI
- CCI
- CCI

CCI

- CCI

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. Timely, accurate, and complete reporting and analysis of complaint information from trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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 serious adverse event (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 8.4). 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 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 subjects 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 dose escalation, once a specific DL is open for enrollment, subjects will be assigned to that DL using an interactive response technology (IRT) system. Site personnel must contact the contract research organization (CRO) and the sponsor when a potential subject 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 subject should the subject require immediate anticancer treatment; otherwise, the subject may be placed on the waiting list, and the site will be alerted once an opening has become available.

During expansion, subjects will be allocated to individual disease cohorts (see Section 5.1.2) using an IRT system.

6.5 Compliance

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

Treatment start and stop dates, including dates for trial drug(s) delays 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 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 5.2 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 administration of the first dose of trial drug must be documented. Any SARS-COV-2 vaccines and seasonal flu vaccinations received within 3 months prior to the first dose of GEN3017 must be documented.

Refer to Section 5.2 for details regarding prohibited prior therapies or washout periods for prior therapies.

6.6.3 Concomitant Therapies

Subjects must be told to notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) they take after the start of GEN3017. All medications (other than GEN3017) 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 GEN3017 until 30 days after the last dose of GEN3017) 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 GEN3017 only in conjunction with worsening AEs or new SAEs related to GEN3017.

6.6.3.1 Permitted Concomitant Therapies

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

1. SARS-CoV-2 vaccine is generally permitted, including 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 subject's vaccination status and subjects should, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating treatment.

2. 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. In the case of ≥ grade 3 neutropenia, use of growth factors is mandated in dose escalation and at the investigator's discretion in expansion.

3. Red blood cell and platelet transfusions, if clinically indicated.

4. Multivitamins, vitamin D, calcium, and supplements for prevention of weight loss.

5. Prescribed medicinal cannabinoids as palliative therapy.

6. Medications to prevent or treat CRS and ICANS are permitted. Please refer to Section 6.7.2 for AE management guidelines and mitigation plans.

7. It is recommended that high-risk subjects (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg, rehydration, diuretics, allopurinol 300 mg daily, and medication to increase urate excretion). All subjects should be monitored for symptoms of TLS (see Section 10.15). Management of TLS, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended.

8. Anti-infection prophylaxis for bacterial, viral, fungal, or pneumocystis infections is allowed and should be given per institutional practice.

9. Intravenous immunoglobulins are allowed to manage hypogammaglobulinemia at the investigator's discretion per institutional practice. Note, immunoglobulins administered at doses on the order of 1 g/kg body weight have the potential to alter the clearance of other antibodies. Investigators should therefore be aware that the efficacy of antibody-based agents, including GEN3017, may be decreased when administering immunoglobulins at these doses, eg, for the treatment of immune thrombocytopenia, or other immune, inflammatory, or paraneoplastic conditions.

10. 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).

11. Subjects 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 C1D1 until 30 days after last dose of GEN3017 unless otherwise specified:

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

   Note: Radiation therapy is prohibited during the first treatment cycle. After the first cycle, radiation is permitted for palliative use only if documented radiographic disease progression is ruled out first.

2. 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 (excluding corticosteroids given as GEN3017 pre-infusion medication as prophylaxis as described in Section 6.1.2).

3. Live vaccines received within 30 days of the first dose of GEN3017, at any time during GEN3017 treatment, and for 3 months following the last dose of GEN3017.

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

4. In the dose escalation part, administration of SARS-CoV-2 vaccine during the screening period and DLT period is not permitted.

5. Participation in any other investigational or interventional studies is not permitted.

Subjects who require the use of any of these agents will be discontinued from GEN3017 treatment. The sponsor must be notified. Subjects who are discontinued from GEN3017 treatment will be followed for safety outcomes for 60 days following the last dose of GEN3017 or until the subject 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 MM if questions arise regarding medications not listed above.

6.7 Dose Modification and Stopping Rules

6.7.1 Dose-Limiting Toxicity (Dose Escalation of GEN3017)

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

Treatment delays during the first CCI of the start of the DLT window are allowed if they are less than 1 cycle in length; under these circumstances, the DLT window can be extended up to CCI .

All DLTs are required to be reported to the sponsor within 24 hours of occurrence.

All AEs including DLTs will be graded for severity according to the National Cancer Institute (NCI)-CTCAE, v5.0 unless otherwise specified. CRS and ICANS will be evaluated according to the ASTCT criteria (Lee et al., 2019). Clinical tumor lysis syndrome (CTLS) will be evaluated according to the Cairo-Bishop classification ((Coiffier et al., 2008); Section 10.15).

The occurrence of any of the toxicities outlined in this section will be considered as a DLT except those that are clearly due to the underlying disease or extraneous cause:

- All grade 5 toxicities
- Hematological toxicities listed below:
  - Grade 4 neutropenia (ie, absolute neutrophil count $<0.5\times10^9$ cells/L [<500/µL]) lasting >7 days not attributable to underlying disease
  - Grade 3 and grade 4 febrile neutropenia (neutrophil count $<1.0\times10^9$ cells/L with a single temperature of >38.3 °C [100.9 °F] or with a sustained temperature of ≥38 °C [≥100.4 °F] for more than 1 hour) lasting >2 days
  - Grade 4 thrombocytopenia (platelet count $\leq25.0\times10^9$ platelets/L [<25,000/µL]) for >7 consecutive days not attributable to underlying disease, or ≥ grade 3 thrombocytopenia ($<50.0\times10^9$ platelets/L) of any duration with clinically significant bleeding or ≥ grade 3 thrombocytopenia requiring a platelet transfusion
  - Grade 4 anemia
- Non-hematological toxicities listed below:
  - Grade 4 CRS according to ASTCT criteria (Lee et al., 2019)
  - Grade 3 CRS according to ASTCT criteria (Lee et al., 2019) which has not resolved to ≤ grade 2 within 48 hours following adequate intervention
  - Grade 4 ICANS according to ASTCT criteria (Lee et al., 2019)
  - Grade 3 ICANS according to ASTCT criteria (Lee et al., 2019) which has not resolved to ≤ grade 2 within 48 hours following adequate intervention
  - TLS grade 3 that has not resolved within 5 days
  - TLS grade 4
  - Any ≥ grade 3 (severe or life-threatening) non-hematological toxicities, **excluding** the following:
    - Laboratory values out of normal range that do not have any clinical consequence, are clinically transient in nature, and that resolve within 7 days (including electrolyte abnormalities that respond to medical intervention)
    - Grade 3 aspartate transaminase and/or grade 3 alanine transaminase returning to grade 1 or baseline in ≤10 days

- Grade 3 nausea that responds to optimal antiemetic treatment in ≤3 days
- Grade 3 vomiting that responds to optimal antiemetic treatment in ≤3 days
- Grade 3 diarrhea that responds to optimal antidiarrheal treatment in ≤3 days
- Grade 3 fatigue/asthenia when fatigue/asthenia was present at baseline or that lasts for <14 days after the last dose of GEN3017
- Grade 3 amylase or lipase that is not associated with symptoms, or clinical manifestations, or radiological imaging of pancreatitis

Note: AEs of specified grades, regardless of relationship to GEN3017, should be considered relevant for dose escalation decisions, unless the event can clearly be determined to be unrelated to the drug. All of the AEs of specified grades should be classified as DLTs except those that are clearly and incontrovertibly due to the underlying disease or extraneous causes.

Frequent laboratory monitoring of complete blood count, including differential, should be initiated to document start and resolution of hematological AEs. All GEN3017-related AEs will be monitored and included in the evaluation of the toxicity profile of GEN3017 unless the event is clearly determined to be unrelated to GEN3017. AEs clearly not related to GEN3017 such as disease progression, environmental factors, unrelated trauma, etc, should not be considered as a toxicity event.

6.7.2 Dose Modification Guidance and Stopping Criteria

Dose modification such as increase or decrease of GEN3017 is not permitted for this trial. Dose delay of GEN3017 is permitted for this trial, as described below.

6.7.2.1 Dose Escalation Part (GEN3017 Monotherapy)

- If a subject experiences a DLT, GEN3017 treatment will need to be interrupted and further doses withheld while managing the DLT. The investigator is required to notify the sponsor's MM promptly and conduct a full assessment of the event and benefit-risk for the subject. The subject may continue treatment with GEN3017, if the toxicity recovers to ≤ grade 2 or baseline within 4 weeks from occurrence of the DLT. Continuous treatment with GEN3017 must be approved by the sponsor's MM. GEN3017 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 subject experiences a second episode of a DLT with GEN3017. Following a DLT of grade 4 non-hematologic toxicity, GEN3017 treatment should be immediately interrupted, and proper management of the AE should be initiated promptly. Resumption of GEN3017 may be considered under the following conditions after discussion with the MM: 1) grade 4 AE has improved to grade 2 or better; or 2) subject has shown clinical benefit from the GEN3017 treatment.

- If a subject experiences toxicity that would have qualified as a DLT but the event occurs after the DLT evaluation period, the subject's benefit-risk must be thoroughly assessed by the investigator. Continuous treatment with GEN3017 must be approved by the sponsor's MM.

- For the subject 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 RP2D and/or MTD (if reached). For the declaration of the RP2D from the dose escalation for further development of GEN3017 in expansion, the totality of the data including safety, tolerability, immunogenicity, PK, pharmacodynamics, and preliminary efficacy will be evaluated.

- During dose escalation, a planned dose of GEN3017 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 GEN3017 treatment may be considered if the subject is clearly benefiting from GEN3017 treatment (eg, imaging indicating clinical activity of GEN3017). Resuming GEN3017 must be approved by the sponsor's MM. CCI [redacted]

- During the trial, the GEN3017 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 or <4.9 mmol/L), hold dose until hemoglobin is ≥8 g/dL (≥80 g/L or ≥4.9 mmol/L).

  Note: If the investigator deems any of the above cytopenia as bone marrow involvement due to the disease, continuation of GEN3017 treatment can be discussed with the sponsor's MM. Transfusion with blood products and/or administration with G-CSF is permitted if clinically indicated.

If a dose delay occurs, then PK and biomarker 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 6-4 for dose modification guidelines for specific AEs (including guidance for permanent discontinuation of treatment).

Table 6-4 Dose Modification Guidelines for Specific Adverse Events

	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0 Except ASTCT for CRS/ICANS and Cairo-Bishop for TLS/CTLS)	Adverse Event Management
Immune system disorder		Grade 1 and grade 2	Withhold GEN3017 until resolution of CRS event. Provide supportive therapy and manage per current practice guidelines.

	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0 Except ASTCT for CRS/ICANS and Cairo-Bishop for TLS/CTLS)	Adverse Event Management
	CRS (see Section 10.12 and Section 10.13. If CRS is refractory to management, consider other causes including macrophage activation syndrome and hemophagocytic lymphohistiocytosis)		If grade 2 CRS occurs with CCI or beyond, administer CRS prophylaxis with the next dose until an GEN3017 dose is given without subsequent CRS (of any grade).
		Grade 3	Withhold GEN3017 until resolution of CRS event. Ensure CRS symptoms are resolved for at least 72 hours prior to the next dose of GEN3017. If grade 3 CRS occurs CCI or beyond, administer CRS prophylaxis with the next dose until a GEN3017 dose is given without subsequent CRS (of any grade). Hospitalize for the next dose of GEN3017.
			Recurrent grade 3 CRS: Permanently discontinue GEN3017. Manage CRS per current practice guidelines (Section 10.13) and provide supportive therapy, which may include intensive care.
		Cytokine blockade-refractory[a] grade 3 for >72 hours or grade 4	Permanently discontinue GEN3017. Manage CRS per current practice guidelines (Section 10.13) and provide supportive therapy, which may include intensive care.
	ICANS (see Section 10.14)	Grade 1 and grade 2	Withhold GEN3017 until resolution of ICANS event to ≤ grade 1 for at least 72 hours. Provide supportive therapy and manage per current practice guidelines.
		Grade 3	Withhold GEN3017 until resolution of ICANS event to ≤ grade 1 for at least 72 hours. Provide supportive therapy, which may include intensive care, consider neurology evaluation, and manage per current practice guidelines. Recurrent grade 3 ICANS: Permanently discontinue GEN3017.
		Grade 4	Permanently discontinue GEN3017. Provide supportive therapy, which may include intensive care, consider neurology evaluation, and manage per current practice guidelines.
Hematological (see Section 6.7.2.1 for details)[b]	Platelet count decreased/ thrombocytopenia	≥ Grade 3	Withhold GEN3017 until platelet count is ≥50 × 10^9/L. Platelet infusions may be administered per institutional standards.
	Neutropenia and febrile neutropenia	≥ Grade 3	Withhold GEN3017 until neutrophil count is ≥0.5 × 10^9/L. Use of growth factors is mandated.
	Anemia	≥ Grade 3	Withhold GEN3017 until hemoglobin is ≥8 g/dL (≥80 g/L or ≥4.9 mmol/L). Red blood cell infusions should be administered per institutional standards.

	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0 Except ASTCT for CRS/ICANS and Cairo-Bishop for TLS/CTLS)	Adverse Event Management
Other non-hematologic	TLS/CTLS	Any grade	Withhold GEN3017 until resolution of TLS/CTLS event.
	Tumor flare reaction	Grade 3 and 4	Withhold GEN3017 until improvement to ≤ grade 1. Monitor for signs and symptoms of compression or obstruction due to mass effect secondary to tumor flare, and institute appropriate treatment (Section 10.15).
	All other non-hematologic AEs	Grade 3[a]; first occurrence	Withhold GEN3017 until improvement to ≤ grade 2 or resolution to baseline.
		Grade 3[a]; recurrent	Second episode of the same AE considered related to GEN3017: Withhold GEN3017 until improvement to ≤ grade 2 or resolution to baseline. Permanently discontinue GEN3017 if no improvement within 14 days unless otherwise agreed upon with the sponsor's medical monitor.
		Grade 4[a]; first occurrence	Withhold GEN3017. Initiate proper management of the AE. Resume GEN3017 after discussion with the medical monitor and improvement to ≤ grade 2 or resolution to baseline, or subject has shown clinical benefit from GEN3017 treatment.
		Grade 4[a]; recurrent	Second episode of the same AE considered related to GEN3017: Permanently discontinue GEN3017 unless otherwise agreed upon with the sponsor's medical monitor.

AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TLS=tumor lysis syndrome.

a. This may exclude any asymptomatic isolated laboratory abnormalities without any clinical consequences such as hypoalbuminemia, hypophosphatemia, hyponatremia, etc.
b. If recurrent grade 3/4 hematological toxicities are not manageable and no treatment effect from GEN3017 has been observed after Day 42, GEN3017 may be discontinued at the investigator's discretion. In subjects benefiting from GEN3017 treatment, there is no limit to the number of hematological toxicities as long as they can be managed.

6.7.2.2 Expansion Part (GEN3017 Monotherapy)

Dose modification guidance used in the dose escalation part (see Section 6.7.2.1) will be applied to expansion GEN3017 monotherapy cohorts as appropriate and will be modified based on emerging data. CCI [redacted]

6.7.2.3 Dose Delays of GEN3017 Due to COVID-19 Infection

During the trial, GEN3017 should be withheld in subjects with a suspected COVID-19 infection or with a positive viral test. GEN3017 may be resumed if the following criteria are met:

- Symptomatic subjects:

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

- Asymptomatic subjects:
  - Subject has obtained 2 negative molecular (eg, polymerase chain reaction [PCR]) tests or negative antigen tests with results ≥ 24 hours apart and it has been 7-10 days after the 2nd negative test.

6.7.2.4 Tumor Flare or Pseudoprogression

Pseudoprogression, a phenomenon with an influx of immune responsive cells into a lesion that causes clinical and imaging findings during treatment suggestive of progressive disease despite evidence of clinical benefit, has been reported in lymphomas treated with immunotherapies such as rituximab (Han et al., 2009; Skoura et al., 2016), immunomodulatory drugs (eg, lenalidomide (Witzig et al., 2011)), anti-PD-1 inhibitors (Ansell et al., 2015; Lesokhin et al., 2016; Westin et al., 2014), and bispecific antibodies (eg, glofitamab (Dickinson et al., 2022)). It is important to differentiate pseudoprogression from true tumor progression to avoid the premature discontinuation of GEN3017.

6.7.2.4.1 Criteria for Continuing GEN3017 Treatment During Suspected Pseudoprogression

During the trial, when the investigator believes that a subject is deriving clinical benefit from GEN3017 treatment despite radiographic evidence of progressive disease, investigators are encouraged to continue GEN3017 treatment until the next scheduled imaging assessment, provided the following criteria are met:

- There is an absence of symptoms and signs (including worsening of laboratory values) indicating progression of disease.

- There is no decline in ECOG performance status (Section 10.5).

- There is an absence of tumor progression at critical anatomical sites including the central airway, the great vessels, and other organs or tissues where compromised function secondary to tumor progression would be expected to result acutely in severe and/or irreversible disability or death.

Subjects continuing GEN3017 therapy, despite apparent radiographic progression, will be encouraged to undergo a repeat tumor biopsy to assess whether increases in tumor volume are due to immune cell infiltration or neoplastic proliferation, provided that such a biopsy can be performed safely on a non-target lesion.

In subjects categorized as having suspected pseudoprogression, it is mandatory to obtain a repeat imaging in the next scheduled imaging assessment (Section 1.3) or earlier if clinically indicated.

6.7.2.4.2 Retreatment After Discontinuing From GEN3017 Treatment Due To Suspected Pseudoprogression

Subjects discontinued from GEN3017 treatment due to suspected pseudoprogression, who later achieve PR or CR without receiving any other anticancer therapy after the last dose of GEN3017, will be allowed to enter the "post-treatment follow-up" period for efficacy. These subjects may be eligible for retreatment if, after discussion with the sponsor's MM, the MM agrees to retreat the subject and the subject meets eligibility criteria.

6.7.2.5 Monitoring of Rapid Tumor Progression

Rapid tumor progression (ie, an acceleration of disease activity with disease progression according to the 2014 Lugano classification prior to completion of 3 cycles of GEN3017 treatment) will be closely monitored. If a subject experiences rapid tumor progression per the investigator's assessment, the investigator should promptly discuss this with the sponsor's MM and the subject should be discontinued from GEN3017 treatment.

During the conduct of the trial, and after at least 3 subjects have been treated with GEN3017 and received at least one dose of GEN3017, if >33% of subjects (regardless of the DL or if during phase 1 or phase 2a) experience rapid progression, trial accrual will be halted and a full review of these events will be performed by the DEC and Safety Committee for phase 1 and Safety Committee for phase 2a, respectively. Patient accrual will not resume until approved by the DEC and Safety Committee (phase 1) or Safety Committee (phase 2a).

6.7.3 Safety Stopping Guidance for the Trial

The trial can/will be stopped for unacceptable toxicity as per recommendations from DEC and Safety Committee in dose escalation or Safety Committee in expansion and based on a risk-benefit assessment. Fatal events considered related to GEN3017 should always be assessed by the DEC and Safety Committee in dose escalation or Safety Committee in expansion.

In order to ensure subject safety during dose escalation, if any of the boundaries in Table 6-5 are crossed for a DL in 1 of the indications (considered independently), a prompt comprehensive review of the safety data will be conducted to determine if the trial should be stopped. In particular, for treatment-related grade 5 AEs, if the boundary is crossed the enrollment into any dose escalation DL is paused and a subsequent review will occur.

Table 6-5 Safety Stopping Guidance in Study GCT3017-01

Number Dosed at DL	1	2	3	4	5	6	9	12
Grade 3 or greater CRS/ICANS[a]	-	-	3	≥3	≥3	-	≥5	≥5
Grade 4 or greater CRS/ICANS	-	2	≥2	≥2	≥2	≥2	≥3	≥3
Treatment-related grade 5 AEs	1	≥1	≥1	≥1	-	≥2	≥2	≥2

AE=adverse event; CRS=cytokine release syndrome; DL=dose level; ICANS=immune effector cell-associated neurotoxicity syndrome.
a. Which has not resolved to ≤ grade 2 within 48 hours following adequate intervention.

The boundaries assume acceptable incidences of:

- 15% incidence for grade 3 or greater CRS/ICANS

- 5% incidence for grade 4 or greater CRS/ICANS
- 1% incidence for treatment-related grade 5 AEs

When given an acceptable incidence, the probability for crossing the boundary at any monitoring time is approximately 5%.

6.8 Treatment of Overdose

For this trial, an overdose is defined as a subject receiving a dose of GEN3017 in excess of 10% of that specified in this protocol.

Sponsor does not recommend specific treatment for an overdose.

In case of overdose, medication errors, misuse, and/or abuse of GEN3017, subjects should receive supportive care according to local guidelines and potential side effects of GEN3017 should be treated symptomatically.

In the event of an overdose, the investigator should:

- Contact the sponsor's MM (or delegate) immediately (see Section 8.4.3).
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Obtain a serum sample for PK analysis if requested by the sponsor's MM.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Continued Access to Trial Drug After the End of the Trial

For subjects with a potential treatment benefit, subjects may be eligible for continued treatment with Genmab IMP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Genmab reserves the unilateral right, at its sole discretion, to determine whether to supply Genmab IMP(s) and by what mechanism, after termination of the trial and before the product(s) is/are available commercially.

7 DISCONTINUATION OF TREATMENT AND DISCONTINUATION FROM TRIAL

7.1 Discontinuation of Treatment

Subjects can decline to continue receiving GEN3017 treatment and/or other protocol required therapies or procedures at any time during the trial but continue participation in the trial. Subjects who have discontinued GEN3017 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 subjects remain on-trial to ensure safety surveillance and/or collection of outcome data (ie, continue efficacy evaluations according to the trial protocol).

The subject may discontinue both GEN3017 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 GEN3017 treatment may include any of the following:

- Disease progression according to response criteria outlined in Section 10.11 (for treatment after disease progression, especially in cases of pseudoprogession, see Section 6.7.2.4)
- Clinical progression
- Absence of clinical benefit
- Unacceptable AE(s) requiring treatment discontinuation
- Initiation of non-GEN3017 anticancer therapy
- Subject requests to discontinue trial drug treatment
- Sponsor or investigator decision
- Subject noncompliance
- Pregnancy

7.1.1 End of Treatment

The end of treatment (EoT) visit should be conducted as soon as possible after the last dose of GEN3017 and no more than 7 days from the decision to end the GEN3017 treatment. If the subject initiates new anticancer treatment right after the last dose of GEN3017, the EoT visit should be performed prior to the initiation of the new anticancer treatment.

7.1.2 Safety Follow-up Visit(s)

Subjects discontinuing from treatment for any reason will have a safety follow-up visit 60 days (+14 days) after the subject receives the last dose of GEN3017. If the subject initiates new anticancer treatment within 60 days of the last dose of GEN3017, the safety follow-up visit should be performed prior to the initiation of the new anticancer treatment.

7.1.3 Post-Treatment Follow-up

Upon permanent discontinuation of GEN3017 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 8.2. Subjects will then enter survival status follow-up (Section 7.1.4).

7.1.4 Survival Status Follow-up

Survival status will be assessed every 12 weeks (±14 days), beginning from the day the subject received the last dose of GEN3017 and continuing until the subject 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 subjects lost to follow-up.

Site personnel will attempt to collect the survival status of the subject within legal and ethical boundaries for all enrolled subjects. Information about survival status may be given by the

subject or a family member. 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 along with a date of death, if available.

7.2 Discontinuation From the Trial

Reasons for discontinuation of a subject from the trial are:

- Death
- Lost to follow-up
- Sponsor decision
- Subject 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 subject withdraws before completing the trial, the reason for withdrawal should be documented.

If a subject 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 subject will be considered as lost to follow-up if the subject 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 subject fails to return to the clinic for a required trial visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the subject 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 should be performed prior to GEN3017 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, controlled temperature 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:

- Age at time of screening
- Sex at birth
- Race
- Ethnicity

8.1.2 Diagnosis and Disease Status

A subject's history relating to the underlying disease including primary diagnosis, date of diagnosis, as well as disease status at trial entry, Ann Arbor staging, and risk category will be recorded.

To confirm eligibility, the local pathology report including CD30 status (eg, CD30 expression on tumor tissue) will be collected and reviewed by the sponsor's MM. The report should include relevant markers associated with the cHL or TCL subtype assessed by flow cytometry, immunohistochemistry staining, fluorescent in situ hybridization, or PCR.

8.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of GEN3017 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 GEN3017 should only be reported as AEs if they were assessed by the investigator to be caused by a protocol mandated procedure (eg, CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of GEN3017 will be documented as an AE. See additional reporting details in Section 8.4 and Section 10.2.

8.1.4 Concomitant Procedures

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

8.2 Efficacy Assessments

Efficacy assessments will be conducted at the time points specified in the Schedule of Activities (Section 1.3). Imaging must be performed at screening, Week 6 ± 7 days, Week 15 ± 7 days, Week 24 ± 7 days, Week 33 ± 7 days, Week 48 ± 7 days, and then every 6 months (± 14 days) until subject 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 GEN3017 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.

For time points when FDG-PET assessment (metabolic response) is available, the FDG-PET (metabolic response) assessment is preferred over 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).

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 tables (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

A combined FDG-PET/CT scan (or MRI/CT and FDG-PET when PET-CT scan not available) must be performed within 21 days before Cycle 1 Day 1. Assessments performed as SOC prior to the subject signing informed consent may be submitted as the screening assessment if assessment is performed within 42 days of Cycle 1 Day 1. FDG administration for PET should be limited to 370 MBq.

As all subjects are anticipated to have FDG-avid tumors at screening, subsequent disease assessments will include FDG-PET using the 5-point scale (Barrington et al., 2014) (Section 10.10). For subjects with non-avid or variably FDG-avid tumors, CT scan with IV contrast of neck, chest, abdomen, pelvis, and additional known lesions will be performed. The CT component of the PET-CT may be used in lieu of a standalone MRI/CT, 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 MRI/CT and a standard FDG-PET should be performed. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET is recommended to be performed prior to the CT with IV contrast in order not to compromise PET results. The PET-CT acquisition methodology (eg, administration of intravenous contrast) should remain consistent between screening and subsequent assessments for any given subject.

Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast. MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT, for subjects 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. For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. An MRI scan or CT scan of the brain should be performed if CNS involvement is suspected at screening and during the trial.

8.2.1.2 Bone Marrow Assessment

For subjects 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 (ie, within 3 weeks prior to the first dose of GEN3017) 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 GEN3017 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 Response and Progressive Disease

In dose escalation, tumor response will be determined by the investigator based on the Lugano criteria (Cheson et al., 2014). In expansion, tumor response will be determined by both the independent review committee (IRC) and the investigator based on the Lugano criteria (Cheson et al., 2014). PET-CT scan images will be obtained according to local site imaging requirements. Submission instructions for the IRC review will be provided in a separate manual.

All response assessments should be conducted throughout the trial until disease progression or withdrawal of consent from trial participation. Response assessments will be performed by the investigators at the site to make decisions for continuation of treatment. Imaging findings suggestive of progressive disease despite evidence of clinical benefit have been described with immunomodulatory agents, eg, tumor flare or pseudoprogression (Cheson et al., 2016). Currently, the potential for similar effect of GEN3017 is unknown, but should be taken into consideration when evaluating imaging during the trial. Accordingly, an increase in the size of previously involved lymph nodes, especially at the beginning of GEN3017 treatment, may represent pseudoprogression and may not be designated as progressive disease, unless there is continued increase in size on subsequent imaging studies or confirmed with biopsies. Hence, in order to avoid premature termination, subjects can continue receiving GEN3017 at investigator and subject discretion until the response or lack thereof is confirmed on subsequent imaging.

In expansion, sites will also be required to submit electronic copies of all scans on an ongoing basis to a centralized imaging vendor. An independent review of all scans will be conducted retrospectively by the IRC. Information regarding prior interventions (eg, radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline or screening, and on-trial

interventions should be transmitted to the imaging CRO via the baseline clinical form along with the baseline images for review by IRC members. Sites must ensure that the data entered on the form are the same as the data entered into the clinical database.

8.3 Safety Assessments

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 examination (according to SOC) should be performed during the screening period, on Day 1 of each cycle, at EOT, and at the post-treatment follow-up visit, as specified in the Schedule of Activities (Section 1.3). For C1D1, physical examination may be performed within 1 day prior to GEN3017 dosing. In addition, a symptom-directed/clinically indicated (brief) physical examination is recommended prior to the rest of trial visits prior to GEN3017 administration. After the first dose of GEN3017 treatment, new or worsening findings since the last assessment should be documented as AEs.

Complete (full) physical examinations should at a minimum evaluate possible presence of palpable lymph nodes, tumor masses, enlargement of liver and spleen, and include inspection and description of the treatment injection site. Complete physical examinations will include evaluation of additional organ systems as per site SOC.

8.3.2 Body Measurements

Height (without shoes) must be measured at screening 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.

For subjects with weight-based dosage, trial drug doses should be adjusted based on the subject's actual weight in kilograms measured within 3 days prior to the beginning (ie, Day 1) of each cycle. If the subjects' weight on dosing days has changed by >10% of the value for that cycle, then the dose should be recalculated for the cycle. This weight will be used for calculation of the dose and should be documented.

8.3.3 Vital Signs

Vital signs including temperature (°C or °F), respiratory rate, oxygen saturation, blood pressure (mm Hg), and heart rate (beats/min) will be measured in a supine or reclined position as indicated in the Schedule of Activities (Section 1.3). Vital signs should also be assessed and reported at all unscheduled visits, including any visit that occurs as a result of an AE.

The subjects should be resting and in a horizontal or half laid position for at least 10 minutes before vital signs are measured.

Temperature should be measured as an oral, axillary, rectal, or ear temperature. The temperature should be documented as a value corrected according to local standards.

Within each visit, preferably the same equipment shall be used for vital sign measurements. On GEN3017 administration days, vital sign assessments are conducted relative to GEN3017 administration.

8.3.4 Electrocardiograms

The ECGs will be recorded at the sites by using the standard 12-leads as indicated in the Schedule of Activities (Section 1.3).

For the ECG recordings, the subject must be resting and in a supine or reclined position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (eg, vomiting, cough) should either induce a repeat of the ECG or be annotated with the description and time of the occurrence.

ECGs will be performed in accordance with the ECG manual issued by the vendor. ECGs will be transmitted from the sites to a central laboratory for a treatment-blinded measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

The corrected QT interval (QTc) will be calculated using Fridericia's formula:

$$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator should interpret ECG using the paper ECG reading from the ECG machine, and sign and date the printout. The central reading will be used for trial analysis purposes.

8.3.5 Echocardiograms or MUGA Scans

An ECHO or MUGA scan is mandatory at screening. Assessments performed/obtained as routine SOC may be submitted as screening assessment, if the SOC assessment was performed within 42 days of Cycle 1 Day 1.

The ECHO or MUGA scan will be repeated as detailed in the Schedule of Activities (Section 1.3). When the examination is repeated, the same modality should be used.

8.3.6 Performance Status

The performance status (PS) will be assessed as indicated in the Schedule of Activities (Section 1.3). The ECOG PS will be assessed for adult subjects (18 years and older) in both dose escalation and expansion and scored using the ECOG PS scale index (Section 10.5). Karnofsky PS will be assessed for cHL subjects ≥16 and <18 years old (dose escalation and expansion, US and Australia only) (Sections 10.6, 10.18.3, and 10.18.4). Lansky PS will be assessed for cHL subjects ≥12 and <16 years of age) (expansion, US and Australia only) (Sections 10.6, 10.18.3, and 10.18.4).

The PS status should meet the eligibility criteria (Section 5.1) during screening and prior to GEN3017 administration on C1D1 to ensure that the subject is still eligible for the study treatment.

8.3.7 Clinical Laboratory Assessments

Samples will be collected as indicated in the Schedule of Activities (Section 1.3). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the trial.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

Laboratory test results should be assessed for abnormalities (see Section 10.2 for additional information on reporting of laboratory abnormalities that are considered AEs). When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

NOTE: A CTCAE grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

The tests detailed in Table 8-1 will be performed locally. The laboratory reports must be filed with the source documents.

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 subject is still eligible. For subsequent doses, these laboratory values must be obtained within 1 day, preferably on the day, prior to each trial drug administration and reviewed by the investigator prior to each trial drug administration to ensure the subject can be dosed according to the dosing instructions defined in the protocol.

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

Table 8-1 Protocol-Required Safety Local Laboratory Assessments

Laboratory Assessments	Test Name			
Hematology	Hematocrit Hemoglobin Platelet count RBC count	RBC indices: • MCH • MCHC • MCV • % reticulocytes	White blood cell (WBC) count with differential: a) Neutrophils b) Lymphocytes c) Monocytes d) Eosinophils e) Basophils	
Biochemistry	Albumin	Calcium	Gamma-glutamyl transferase	Potassium
	Alkaline phosphatase	Chloride	Glucose (non-fasting)	Sodium
	ALT	C-reactive protein[b]	LDH	Total and direct bilirubin
	Amylase	Creatinine and CrCl[a]	Lipase	Total protein
	AST	Ferritin[b]	Magnesium	Triglycerides[b]
	Blood urea nitrogen	Fibrinogen[b]	Inorganic phosphorus (phosphate)	Uric acid
Tumor lysis sample	Uric acid	Potassium	Inorganic phosphorus (phosphate)	Calcium
	Creatinine			
Coagulation factors[b]	PT	INR	aPTT	
Urinalysis	Leukocyte esterase/leukocytes	Protein		
Serology/ molecular testing[c]	HBsAg and HBcAb. If positive serology, PCR for HBV DNA to be performed. HCV antibody. If positive serology, PCR for HCV RNA to be performed. CMV serology (IgG and IgM) at screening. If positive serology, CMV PCR to be performed. Epstein-Barr virus PCR. HIV testing at screening only if required per local regulations or institutional standards. HTLV-1 and HTLV-2 serology. If positive serology, PCR for HTLV-1 and/or HTLV-2 to be performed accordingly.			
Pregnancy tests[d]	Serum β-hCG	Urine pregnancy test		
Additional tests	Beta2-microglobulin Immunoglobulins: IgA, IgE, IgG, and IgM Tuberculosis test (if clinical suspicion is high)			

ALT=alanine transaminase; aPTT=activated partial thromboplastin time; AST=aspartate transaminase; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; CMV=cytomegalovirus; CrCl=creatinine clearance; CRS=cytokine release syndrome; GFR=glomerular filtration rate; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HTLV-1=human T-cell leukemia virus type 1; HTLV-2=human T-cell leukemia virus type 2; Ig=immunoglobulin; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PCR=polymerase chain reaction; PT=prothrombin time; RBC=red blood cell; T3=total triiodothyronine; T4=free thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

a. Estimate creatinine clearance using Cockcroft-Gault (Section 10.7).
b. As indicated in Section 1.3 and if indicated during CRS (PT is optional).
c. Only performed if required by local regulations.

d. For female subjects with childbearing potential, a serum pregnancy test is required to be performed during the screening period. Additionally, a urine or serum test should be performed within 24 hours of dosing at the start of each cycle and at other visits as indicated in Section 1.3. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm. An additional pregnancy test is required 4 months after the last dose of GEN3017.

8.3.8 Other Safety Assessments

8.3.8.1 Neurological Evaluation

Assessment for neurotoxicity with a neurologic assessment must be performed during therapy with GEN3017 by trained trial-site staff. An assessment according to ICANS evaluation (Lee et al., 2019) should be performed as indicated in Section 1.3. ICANS assessments must be performed at least daily during CRS events, and once daily during hospitalization if subject was hospitalized. Finally, additional ICANS assessment should always be performed when clinically indicated.

ICANS is a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused immune effector cells, including T cells. ICANS may occur concurrently with CRS or shortly after CRS symptoms subside (but rarely before). Symptoms can be progressive and may include aphasia, altered level of consciousness, delirium, dizziness, encephalopathy, headache, impairment of cognitive skills, motor weakness, tremor, seizures, and cerebral edema (Lee et al., 2019).

The grading of ICANS requires assessment of the 10-point immune effector cell-associated encephalopathy (ICE) score as well as evaluation of 4 other neurologic domains: level of consciousness, seizures, motor symptoms, and signs of raised intracranial pressure/cerebral edema, which may occur with or without encephalopathy. See Section 10.14 for additional details for grading and management of ICANS.

Overall ICANS grade is determined by the most severe event of the neurotoxicity domains (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause. For example: subject with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS.

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

A subject with an abnormal ICE score must be assessed to determine if it is due to ICANS or an alternate cause. If not due to ICANS, the relevant condition will be reported as an AE.

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

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

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

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (eg, confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (eg, opioids), and other medical conditions. Other causes for such symptoms should be considered.

8.3.8.2 Constitutional Symptoms

Constitutional symptoms (B symptoms) will be evaluated for all subjects 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.

8.4 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 subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established 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, adverse events of special interest (AESIs), as well as attribution definitions; severity criteria; special reporting situations; and procedures, are provided in Section 10.2.

8.4.1.1 Adverse Events of Special Interest

The protocol-defined AESIs are:

1. CRS, graded according to ASTCT criteria ((Lee et al., 2019); Section 10.12 and Section 10.13)

2. ICANS, graded as ASTCT Criteria ((Lee et al., 2019); Section 10.14)

3. CTLS graded according to Cairo-Bishop ((Coiffier et al., 2008); Section 10.15)

Additional AESIs may be defined on the basis of an ongoing review of the safety data.

8.4.2 Adverse Event Reporting

Trial Period	Reporting Requirements
Signing of ICF through prior to first dose	AEs, if assessed by the investigator to be caused by a protocol-mandated procedure (eg, CT scan), including washout or discontinuation of prior medications.
First dose through safety follow-up visit	All AEs and SAEs (see definitions in Section 10.2), regardless of casualty, will be documented.

Safety follow-up visit through end of trial/after end of trial	There is no requirement to monitor subjects for SAEs following the protocol-required reporting period (ie, after the safety follow-up visit) or after end of trial. However, if the investigator becomes aware of an event, SAEs should be reported if judged by the investigator as related to trial drug(s).

NOTE: Any secondary primary malignancy(ies) (not a new lesion, recurrence, or transformation to a more aggressive histology of the disease under trial)] regardless of relatedness to trial drug(s), should be reported at any time during or after the trial if the investigator becomes aware of such an event.

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

8.4.3.1 Secondary Primary Malignancy

Secondary primary malignancy(ies) (not a new lesion, recurrence, or transformation to a more aggressive histology of the disease under trial), regardless of relatedness to trial drug(s), must be reported to the sponsor within 24 hours of knowledge of the event (at any time during or after the trial).

8.4.3.2 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:

- The subject visit at which the AE was reported, noted, or recognized.
- The principal investigator's or any investigator personnel's receipt of the test results.
- Other information from which the AE was reported, noted, or recognized.

8.4.3.3 Overdose/Medication Errors

An overdose is defined as a subject receiving a dose of GEN3017 in excess of 10% of that specified in this protocol. All cases of overdose with GEN3017, 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 6.8).

Overdose of concomitant medication should only be reported if associated with adverse events whether serious or not.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, whether associated with an AE or not, should be reported within 24 hours of knowledge of the event.

8.4.3.4 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported.

All reports of pregnancy in female subjects or partners of male subjects 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 subject, 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 outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to GEN3017 must be promptly reported to the sponsor or designee.

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

8.4.3.5 Adverse Events of Special Interest or Other Events of Interest

AESIs that have been defined in Section 8.4.1.1 must be reported within 24 hours of their knowledge of the event if they meet seriousness criteria, or reported within 72 hours if not serious.

8.4.4 Regulatory Reporting Requirements for SUSARs

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met (see Section 8.4.3.2).

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 competent regulatory authorities and/or to the ethics committee/IRBs according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods and according to local regulations.

The investigator should be aware of local reporting regulations to the 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. For SUSARs aggregated in a line listing distributed quarterly, or every 6 months, or in periods as warranted by the nature of the IMP and the trial, 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 subject 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 progression of the underlying disease should not be recorded as AEs or SAEs.
    - That is, the terms "Disease Progression," "Progression of Disease," or "Malignant Disease Progression" and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
        - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
        - Clinical symptoms of progression 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(s) or the start of new anticancer treatment, whichever comes first.

All SAEs and GEN3017-related AESIs qualifying for immediate reporting that are ongoing at the safety 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 safety information collected between IB updates will be communicated in the form of investigator notifications. This information will be included in the ICF and should be discussed with the subject during the trial as needed.

For approved products used in combination with GEN3017, reference the current prescribing information (eg, USPI, SmPC) for additional safety information.

8.5 Pharmacokinetics

Blood samples will be collected to evaluate the PK of GEN3017 at the time points specified in the Schedule of Activities (Section 1.3). The actual date and time of each sample must be recorded.

Samples will be analyzed to determine concentrations of GEN3017 using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

Samples collected for analyses of GEN3017 serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Additional samples may be collected during the trial if warranted and agreed upon between investigator and sponsor, eg, for safety monitoring.

Additional information about the collection, handling, and shipment of samples is included in the Laboratory Manual.

8.6 Pharmacodynamics

Pharmacodynamic assessments/samples will be performed/collected as per the time points specified in the Schedule of Activities (Section 1.3) to identify potential PD markers for GEN3017 treatment.

8.7 Biomarkers

Biomarker Sample Collection

Samples for biomarker analyses will be collected at the time points specified in the Schedule of Activities (Section 1.3). Subjects must consent to biomarker sample collection and assessment in order to participate in this trial. 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, Laboratory Manual and lab flowchart).

8.7.1 Biomarker Assessments in Tumor Samples

A fresh biopsy must be collected before administration of trial drug(s) (ie, during the screening period) for all subjects 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 GEN3017) representative of the histology under which the subject will be enrolled in the trial.

An on-treatment tumor biopsy is recommended at C3D1 and at time of disease relapse, if clinically safe and feasible. All biopsies can be a whole lymph node or core biopsy. A fine needle aspirate will not be sufficient. All tumor biopsies should be FFPE. During the trial, if any additional tumor biopsies are collected that are part of normal clinical practice, these will be examined as described below.

Biomarker analyses in tumor samples at baseline and during treatment with trial drug(s) may help confirm trial GEN3017's mode of action and enable the identification of biomarkers predictive of response to trial drug(s). Tumor biopsies will be evaluated for target expression (protein or RNA), as well as molecular profiling to identify potential mechanisms of tumor response and/or treatment-induced changes in the immune and tumoral microenvironment.

8.7.2 Protein Expression Analyses

Expression of CCI [redacted], and other molecular markers related to R/R cHL or TCL disease biology or the trial drugs' mode of action may be evaluated in tumor biopsies by immunohistochemistry on an automated staining platform. Tumor sections will be scored by a certified pathologist, and digital images will be made from stained tumor sections in order to be used for exploratory digital pathology analyses.

8.7.3 RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine tumoral gene expression signature levels, as well as to evaluate other potential genes associated with CD30 biology, with immune effector cell activation, or with cancer biology in general. FFPE biopsy samples may be used to collect genomic information from defined tumoral regions of interest, using digital profiling transcriptomic platforms.

8.7.4 DNA Analyses

Tumor biopsies may also be analyzed using next-generation sequencing (NGS) for analyses of CCI [redacted]. In addition, to assess minimal residual disease (MRD) status NGS may be used to detect expression of malignant clone immunoglobulin gene rearrangements CCI [redacted] in peripheral blood/plasma.

8.7.5 DNA/RNA Analyses

DNA/RNA samples extracted from whole blood or PBMCs may be analyzed if it is hypothesized that this may help resolve issues with the clinical data. CCI [redacted]
Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

A whole blood sample may also be evaluated to confirm the tumor specificity of any genomic alterations that are identified. Where required by local or county specific regulations, each

subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).

If DNA/RNA research evaluations are performed, the results may be reported in a separate report.

8.7.6 Biomarker Assessments in Blood Samples

CCI

Assessments will be performed at baseline (before infusion at Cycle 1 Day 1) and at later cycles during treatment in order to enable correlation analyses with response to treatment or disease biology. CCI

8.7.7 Immunophenotyping Analyses

CCI

8.7.8 Cytokine (Soluble Factors) Analyses

CCI

8.7.9 CCI

CCI

CCI

8.8 Immunogenicity

Venous blood samples will be drawn for analysis of anti-drug antibodies (ADAs) as per the time points specified in the Schedule of Activities (Section 1.3).

Serum samples will be screened for ADAs binding to GEN3017 and the titer of confirmed positive samples will be reported. Serum concentrations of GEN3017 will be analyzed (see Section 8.5) and those data will be used to for interpretation of the ADA data. The ADA samples may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity.

Neutralization characterization of ADAs may also be performed using appropriate methods.

Further details are included in the Laboratory Manual.

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.

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)	Subjects enrolled and treated with at least 1 dose of GEN3017. Subjects are analyzed according to DL.
Safety Set	Subjects enrolled and treated with at least 1 dose of GEN3017. Subjects are analyzed according to DL.
Dose-Determining Set (Dose Escalation Part only)	The Dose-Determining Set is relevant for the dose escalation part only and consists of all subjects from the Safety Set who meet the minimum exposure criteria for Cycle 1 and have either completed the DLT observation period or have experienced a DLT during Cycle 1. CCI [redacted] Subjects without any DLT must have completed the DLT observation period defined in Section 6.7.1. The Dose-Determining Set does not include backfilling subjects (see Section 4.1.1.6).
Response Evaluable Set (RES)	Subjects who receive CCI [redacted], have measurable disease at baseline, and have at least 1 post-baseline disease evaluation.

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 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 the incidence of DLTs. For analysis of AEs see Section 9.3.4.

The incidence of DLTs will be presented for the Dose-Determining Set using descriptive statistics.

9.3.2.2 Secondary Endpoints Analyses

For the dose escalation part of the trial the following secondary endpoints are presented:

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.

Immunogenicity

Immunogenicity will be presented as described in Section 9.3.8

Efficacy

Objective response rate

The ORR, as assessed by the investigator, will be classified according to Lugano criteria (Cheson et al., 2014), and will be summarized as described in Section 9.3.3.1.

Duration of 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 in Section 9.3.3.2.

Time to response

Time to response (TTR) is defined as the time from C1D1 to first documentation of objective response (CR or PR) in subjects achieving PR or CR. Time to response will be analyzed as described for PFS in Section 9.3.3.2.

9.3.2.3 Exploratory Endpoint Analyses

Exploratory endpoints will be presented descriptively.

9.3.3 Analysis of the Expansion Part

9.3.3.1 Primary Endpoint Analysis

The primary endpoint for the expansion part of the trial is ORR based on Lugano criteria (Cheson et al., 2014) as assessed by IRC.

The ORR is defined as the proportion of subjects 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.

The FAS will be used. The RES may also be used for sensitivity analysis.

9.3.3.2 Secondary Endpoints Analyses

Efficacy

All secondary efficacy analysis will be based on the FAS.

Objective response rate

ORR as assessed by investigator by Lugano criteria (Cheson et al., 2014) will be summarized as described in Section 9.3.3.1.

Complete response rate

The number of patients with CR will be summarized. CR as assessed by investigator and IRC by Lugano criteria (Cheson et al., 2014) will be presented.

Duration of response

DOR will be presented as described for the dose escalation part of the trial (Section 9.3.2.2) as assessed by investigator and IRC by Lugano criteria (Cheson et al., 2014).

Time to response

TTR will be presented as described for the dose escalation part of the trial (Section 9.3.2.2) as assessed by investigator and IRC by Lugano criteria (Cheson et al., 2014).

Progression-free survival

PFS is defined as the time from C1D1 to first documented progressive disease or death due to any cause, whichever occurs earlier. PFS will be censored similar to table C1 in Appendix C in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-small Cell Lung Cancer Drugs and Biologics (FDA Guidance for Industry, 2015). Further details will be provided in the statistical analysis plan.

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

PFS will be assessed by investigator and IRC by Lugano criteria.

Overall survival

OS is defined as the time from C1D1 to the date of death due to any cause. Subjects who withdrew consent to the trial or are lost to follow-up will be censored at the latest date the subject was known to be alive (on or before the cutoff date).

OS is presented as described for PFS.

Immunogenicity

Immunogenicity will be presented as described in Section 9.3.8.

Incidence of AE

For reporting of AEs see Section 9.3.4.

Pharmacokinetics

For reporting of PK concentrations and parameters see Section 9.3.7.

9.3.3.3 Exploratory Endpoint Analyses

Exploratory endpoints will be presented descriptively.

9.3.4 Safety Analyses

Safety analysis will be done for both escalation and expansion part of the trial. The Safety Set will be used.

Adverse Events

The on-treatment period is defined as the time from C1D1 until the end of safety follow-up.

TEAEs are events that occur during the on-treatment period or AEs starting before C1D1 and worsening during the on-treatment period.

Adverse events will be graded according to the NCI-CTCAE as described in Section 10.2.3.1.

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

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

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 subjects with at least 1 grade 3 or higher on-treatment laboratory test will be summarized.

ICE Score

ICE score will be presented descriptively.

Constitutional Symptoms

Constitutional symptoms will be presented descriptively.

ECOG

ECOG will be presented descriptively.

ECG

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

ECG measurements (ie, QTc) will be presented by visit and time point. Abnormal values as read by central reader will be presented.

Vital Signs

Number of patients with at least 1 clinically notable abnormal value will be presented.

9.3.5 Other Analyses

Subgroup analysis for the primary endpoint in the expansion part of the trial may be explored to investigate whether the treatment effect is consistent across various subgroups.

9.3.6 Planned Analyses

9.3.6.1 Interim Analysis

An interim analysis is not planned for this trial.

9.3.6.2 Primary Analysis

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

9.3.7 Pharmacokinetic Analyses

Dose Escalation Part

Individual curves of concentrations of GEN3017, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. PK endpoints will be calculated based on non-compartment methods and presented separately CCI [redacted]. 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 FAS will be used.

Expansion Part

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

9.3.8 Immunogenicity Analyses

Dose Escalation and Expansion Parts

The results from the analysis of immunogenicity samples 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 subjects having at least 1 confirmed ADA during treatment will be presented and the largest titer value will be presented for subjects having at least 1 confirmed ADA sample. The Safety Set will be used for immunogenicity analyses.

9.4 Sample Size Determination

No formal sample size calculations will be done for the dose escalation part. Sample size is given per the mBOIN algorithm as described in Section 4.1. With 10 expected DLs, and an average of 6 subjects per DL, 60 subjects are expected to be enrolled in each disease cohort.

No formal sample size calculations will be done for the expansion part. A sample of 20 subjects per cohort per DL is deemed enough to provide a preliminary assessment of efficacy and in line with recommendations in the FDA's Guidance on expansion cohorts (FDA Guidance for Industry, 2022).

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 CFR and European regulation 536/2014 for clinical trials, article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices," Japanese Ministerial Ordinance on Good Clinical Practice for Drugs [J-GCP]) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an 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 subjects.

10.1.2 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6(R2), 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 subjects. The investigator shall notify the sponsor immediately of any serious breach of ICH GCP E6(R2), the protocol, or any regulation where required.

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, subject 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 subjects, 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 subjects 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 subjects 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 Subject Identification, Enrollment, and Screening Logs

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

The subject 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 subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by their unique subject identifier.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the trial.

10.1.6 Informed Consent Process

The ICF(s) and assent form that is/are used must be approved by the reviewing IEC/IRB and be in a language that the subject can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, ICH GCP E6(R2), applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects (or their legally acceptable representative [not applicable in EU/EEA]) the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Subjects 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 subject 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 subject, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF the subject (or legally acceptable representative [not applicable in EU/EEA]) is authorizing such access, including permission to obtain information about survival status, and agrees to allow their trial physician to re-contact the subject 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 subject (or his/her legally acceptable representative [not applicable in EU/EEA]) 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 either the subject's or their legally acceptable representative's (not applicable in EU/EEA) personally dated signature.

Subjects (or his/her legally acceptable representative [not applicable in EU/EEA]) 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, HIPAA, and EU 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 subject.

If the subject (or legally acceptable representative [not applicable in EU/EEA]) 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 subject (or legally acceptable representative [not applicable in EU/EEA]) is obtained.

The sponsor will, on an ongoing basis, assess whether reconsent of subjects is needed.

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

10.1.7 Data Protection

The investigator will ensure that the confidentiality of all subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor/sponsor's representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed 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 subjects have been assessed and adequate technical and organizational measures are implemented to ensure a level of security appropriate to the risk.

The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data are only stored on 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 subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data 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 subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial and as specifically defined in the protocol.

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

The informed consent obtained from the subject (or their legally acceptable representative [not applicable in EU/EEA]) 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 subject has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including any other relevant agreement, and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

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

Dose Escalation Committee

The DEC will be chaired by the sponsor’s medical officer (or delegate) and membership will include investigator(s), a sponsor clinical scientist, a safety physician, a statistician, a clinical pharmacologist, and other sponsor staff, as appropriate. The DEC will meet at regular frequency throughout the dose escalation part.

The schedule of DEC meetings will depend on the completion of DLT(s) evaluation period(s) (period is defined for each trial).

All available data, including but not limited to safety, pharmacokinetic, and pharmacodynamic data, covering the DLT evaluation period will be reviewed by the DEC. Cumulative data from treatment doses after the DLT period may also be monitored. Recommendations on dose escalation (or de-escalation) will be made by the DEC to the Safety Committee.

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 subjects who participate in Genmab sponsored clinical trials or patients treated with marketed Genmab drugs. For FIH dose escalation Phase, the Safety Committee will consider the recommendation made by the DEC and make the final decision regarding dose escalation (or de-escalation). The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in subject benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

Decisions will be communicated to investigators and decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory 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, CTIS, and/or other national registries/Health Authority websites). In addition, after trial completion (defined as last subject 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/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(R2), the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH GCP Guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Medical Records (subjects' hospital record) is 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 subject 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. Subject 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 subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial, described in the monitoring guidelines (or equivalent), and captured in a source data verification log at site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial, to enable verification of eligibility. Signed and dated ICFs will be stored 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 subject:

- subject's name and date of birth
- screening/subject/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 subject at the end of trial
- reason for treatment discontinuation/trial withdrawal, if applicable

Any worksheets used to capture data to facilitate completion of the eCRF will become part of the subject's source documentation. In some cases, eg, demographic data (race, ethnicity, sex at birth), the eCRF may be considered the subject's source documentation.

In addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, PROs). Such data are considered source data and are accessible by both the investigator and sponsor.

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

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

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 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 subject 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(R2), and applicable regulatory requirements.
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further GEN3017 development.

The sponsor may, based on available data, discontinue further development of GEN3017.

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 subject(s) and should ensure appropriate subject therapy and/or follow-up.

10.1.13 Publication Policy

All information, including but not limited to information regarding GEN3017 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 GEN3017, 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 subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 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 patient or clinical trial subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

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

10.2.1.2 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 subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the subject 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 subject’s general condition
        - Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

10.2.1.3 Definition of Adverse Events of Special Interest

AESIs are defined as events (serious or nonserious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Additional AESIs can also be defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 8.4.1.1 and the IB.

10.2.2 Procedures for Recording and Reporting

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.

10.2.3 Evaluation of Adverse Events

10.2.3.1 Severity

Toxicities will be graded for severity according to the NCI-CTCAE, v5.0. CRS and ICANS will be evaluated according to the ASTCT criteria (Lee et al., 2019). 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 GEN3017 IB.

10.2.4 Annual Safety Reporting by Sponsor

Within the EU, the sponsor will submit independent Annual Safety Reports for all trial drugs in this clinical trial.

10.3 Appendix 3: Definition of Reproductive Potential and Contraception

Female subjects of reproductive potential must agree to use adequate contraception during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017. Based on preliminary data, recommendation for the period of contraception and prohibition of egg donation after the last dose of GEN3017 may be extended. Adequate contraception is defined as highly effective methods of contraception (see Table 10-1). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly. For the definitions of reproductive potential and contraception in Japan, see Section 10.18.2.

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

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

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during GEN3017 treatment and for 4 months after receiving the last dose of GEN3017.

Table 10-1 Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - 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 subject of reproductive potential (ie, the trial subject) 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 drug(s). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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 subjects. 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 cHL and R/R TCL, the dose response and/or prediction of response to GEN3017, 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 subject directly or to alter the treatment course, the results of any exploratory biomarker research are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required trial and subject 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 subject 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 subject 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 subject 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: Karnofsky and Lansky Performance Status

Condition	Percentage	Lansky level of performance (<16 years)	Karnofsky level of performance (≥16 to <18 years)
Able to carry on normal activity and to work; no special care needed.	100	Fully active; normal	Normal no complaints; no evidence of disease.
	90	Minor restrictions in physically strenuous activities	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Restriction in and less time spent in active play	Cares for self; unable to carry on normal activity or to do active work.
	60	Up and around; minimal active play; keeps busy with quieter activities	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance.
	30	In bed; needs assistance even with quiet play	Severely disabled; hospital admission is indicated although death not imminent.
	20	In bed, often sleeping; play limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Does not get out of bed; does not play	Moribund; fatal processes progressing rapidly.
	0	Unresponsive; dead	Dead

Source: (Karnofsky and Burchenal, 1949; Lansky et al., 1987)

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: 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.

10.9 Appendix 9: Corticosteroid Dose Equivalents

Steroid	Approximate Equivalent Dose	Duration
Dexamethasone	20 mg	Long-acting
Betamethasone	20 mg	Long-acting
Methylprednisolone	100 mg	Intermediate-acting
Triamcinolone	100 mg	Intermediate-acting
Prednisone	125 mg	Intermediate-acting
Prednisolone	125 mg	Intermediate-acting

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

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

Five-Point Scale (5-PS)

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

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

Notes:

- "X" will represent any area of uptake identified by the radiologist or equivalent as not likely to be related to lymphoma. At screening, these areas could be due to prior radiation therapy, surgery, or evidence of a benign radiographic abnormality. These will have no impact on the response.

- At the end of treatment assessment time point and at follow up (if applicable), X will represent any new areas of FDG-uptake unlikely due to lymphoma. These will have no impact on the response.

Diffusely increased bone marrow, even if greater than liver uptake, is likely not due to lymphoma and rather, due to cytokine effect.

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 subject's overall disease burden, including mediastinal and retroperitoneal disease, where applicable. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the 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, 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
	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

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

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 subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
   - Measured dominant (target) lesions: Up to 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: Grading and Management of Cytokine Release Syndrome

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

Grading of Cytokine Release Syndrome

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

BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE= Common Terminology Criteria for Adverse Events.
Note: organ toxicities or constitutional symptoms associated with CRS may be graded according to CTCAE but they do not influence CRS grading.

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

Source: (Lee et al., 2019)

10.13 Appendix 13: CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT)[a] Guidelines

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
Grade 1	Hold GEN3017 until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Supportive care per institutional standard of care (antipyretics and IV hydration) Closely monitor neurologic status	Consider anticytokine therapy[e] in certain cases, eg, advanced age, high tumor burden, circulating tumor cells, fever refractory to antipyretics. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Dexamethasone 10-20 mg per day (or equivalent) may be initiated. Note: In case of concurrent ICANS, initiation of corticosteroids are highly recommended (see ICANS guidelines in Section 10.12).
Grade 2	Hold GEN3017 until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Continuous cardiac telemetry and pulse oximetry as indicated IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids Supplemental oxygen as indicated	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Consider dexamethasone 10-20 mg per day (or equivalent). Note: In case of concurrent ICANS, initiation of corticosteroids is highly recommended (see ICANS guidelines in Section 10.12).
Grade 3	Hold GEN3017 until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy.	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Vasopressor support and/or supplemental oxygen. Consider cardiac echocardiogram. IV fluids as indicated.	Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	
Grade 4	Permanently discontinue GEN3017. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Mechanical ventilation and/or renal replacement therapy may be required Vasopressor support as indicated IV fluids as indicated. Consider and assess for development of macrophage activation syndrome/ hemophagocytic lymphohistiocytosis (MAS/HLH)[d], including monitoring of fibrinogen and triglyceride levels	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.
MAS/HLH	If MAS/HLH is combined with CRS, permanently discontinue GEN3017. Intensive supportive care is essential because of frequent life-	First-line treatment: Includes IL-6R-blockade with tocilizumab, unless tocilizumab was already administered for the management of CRS. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed).	

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	threatening, severe manifestations at presentation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation.	Second-line treatment: Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg SC. In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100-200 mg SC twice daily (every 12 hours), or higher doses (up to 8 mg/kg/day) in severe cases, should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment. In case of rapidly progressing clinical course with ongoing CRS, anakinra should be administered as first-line treatment.	

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

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

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

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

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

10.14 Appendix 14: ASTCT ICANS Consensus Grading and Management

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

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
Grade 1 • ICE score[a] 7-9 and/or depressed level of consciousness[b] but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema • Confusion: mild disorientation • Encephalopathy: mild limiting of ADLs • Dysphasia: not impairing ability to communicate	• Hold GEN3017 until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS • Aspiration precautions • Recommend brain imaging and EEG per institutional guidelines	No concurrent CRS: Anticytokine therapy not indicated Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Section 10.13.) • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone, 10 mg IV every 12 hours
• **Grade 2** • ICE score[a] 3-6 and/or depressed level of consciousness[b] but awakens to voice • No seizures, motor weakness, or raised ICP/cerebral edema • Somnolence-moderate, limiting instrumental ADLs • Confusion: moderate disorientation	• Hold GEN3017 until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy	Dexamethasone at 10-20 mg IV every 12 hours

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
• Encephalopathy: limiting instrumental ADLs • Dysphasia: moderate impairing ability to communicate spontaneously	• Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication	(ASTCT) Guidelines table in Section 10.13.) • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
• **Grade 3** • ICE score[a] 0-2 and/or depressed level of consciousness[b] but awakens to tactile stimulus • And clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention • No motor weakness • Focal/local edema on neuroimaging • Somnolence-obtundation or stupor • Confusion: severe disorientation • Encephalopathy: limiting self-care ADLs • Dysphasia: severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Hold GEN3017 until resolution of ICANS. • Management in monitored care or intensive care unit. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Section 10.13.) • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day.

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
	medication • Levetiracetam/non-sedating antiepileptics if subject has seizures	benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
• **Grade 4** • ICE score[a] 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness[c] such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging[d]; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation	• Permanently discontinue GEN3017. • Management in monitored care or intensive care unit. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication • Levetiracetam/non-sedating antiepileptics if subject has seizures • Mechanical ventilation may be required • Consider imaging of spine for focal motor weakness • Lower intracranial pressure (ICP) by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the American Society for Transplantation and Cellular Therapy (ASTCT) Guidelines table in Section 10.13.) • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
	ventriculoperitoneal shunt in patients with cerebral edema • Aggressive management of ICP with institutional standard of care		
Grade 5 (Fatal) Death due to ICANS in which another cause is not the principal factor leading to this outcome.			

ADLs=activities of daily living; ASBMT=American Society for Bone Marrow Transplant; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; IV=intravenous; MRI=magnetic resonance imaging; SC=subcutaneous.
Note: ICANS grade is determined by the most severe domain event not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

a. A subject with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Sources: (Lee et al., 2019)

ICANS Assessment and Grading

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

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; eg, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. Grade 5 is considered to be fatal.

CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable.

a. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0.

Source: (Lee et al., 2019)

The Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool

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

ICANS= immune effector cell-associated neurotoxicity syndrome; ICE= immune effector cell-associated encephalopathy.
Source: (Lee et al., 2019)

10.15 Appendix 15: Tumor Flare Reaction Management Guidance and Grading

Subjects in this study should be monitored for tumor flare reaction (TFR). TFR is defined as a sudden and tender increase in the size of the disease-bearing sites, including the lymph nodes, spleen, and/or the liver often accompanied by low-grade fever, diffuse rash, and in some cases increase in the peripheral blood lymphocyte counts. TFR will be assessed according to the following CTCAE v5 criteria:

- Grade 1: Mild pain
- Grade 2: Moderate pain; limiting instrumental activity of daily life (ADL)
- Grade 3: Severe pain; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

TFR Management Guidelines

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that TFR be treated with corticosteroids at the investigator's discretion. NSAIDs (ie, ibuprofen 400 to 600 mg orally every 4 to 6 hours as needed) and/or narcotic analgesics for pain management may also be administered as needed. In mild to moderate cases, it is suggested that GEN3017 is continued along with symptomatic treatment as indicated above. Table 6-4 includes dose modification guidance as it relates to TFR.

10.16 Appendix 16: Classification and Management of Laboratory and Clinical Tumor Lysis Syndrome

Subjects who are considered to have an increased risk for tumor lysis syndrome (TLS), eg, due to the type of lymphoma, the tumor burden (bulky disease and/or elevated LDH), renal impairment and/or elevated uric acid should be considered for hydration and prophylactic treatment with a uric acid lowering agent as well as frequent monitoring, according to local standards or available guidelines (Coiffier et al., 2008).

In addition, close monitoring of laboratory parameters to allow for early diagnosis of possible TLS is recommended at the investigator's discretion. For details, refer to Table 1-1 and Table 1-2 for the minimum sampling time points for tumor lysis. If signs of TLS occur, supportive therapy, including rasburicase, may be used as clinically indicated at the investigator's discretion.

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.

Definitions of Laboratory and Clinical Tumor Lysis Syndrome

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

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

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

Source: (Howard et al., 2011)

Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

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

ADL=activities of daily living; CHF=congestive heart failure; ULN=upper limit of normal.
a. If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.

Source: (Coiffier et al., 2008)

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

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise re-check in 1 hour. Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis syndrome. At the discretion of the investigator, consider re-checking tumor lysis syndrome (TLS) laboratory values prior to hospitalization. If stable or decreased, and still within normal limits (WNL), hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be re-checked within 24 hours.
Potassium > upper limit of normal	Perform STAT electrocardiogram (ECG) and commence telemetry. Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg intravenously (IV) × 1. Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis syndrome.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 – 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Re-check potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Notify nephrology (or other acute dialysis service). Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. Telemetry. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis syndrome.
Creatinine	
Increase ≥25% from baseline	Start or increase rate of IV fluids. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 – 2 hours STAT.

ECG=electrocardiogram; IV=intravenous; TLS=tumor lysis syndrome.

10.17 Appendix 17: Statistical Methodologies

An mBOIN design will be utilized to guide optimal recommendation for dose escalation at the end of each dose level. Compared to a classical 3+3 design, the mBOIN design allows reescalation to an already investigated dose level and it also ensures that a dose level is terminated due to toxicity as a dose level can no longer be investigated if an additional DLT-free DL would lead to de-escalation. Thus, with the mBOIN design the number of subjects on a toxic dose level is limited.

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For cohorts with 3 DLT-evaluable subjects, the decision during escalation will be consistent with the '3+3' design (ie, escalate if no DLT, remain on same dose level if 1 DLT, de-escalate if 2 DLTs and terminate dose level if 3 DLTs).

Operational characteristics in terms of subjects treated for the mBOIN design are given below. These are based on 4 different toxicity scenarios, when assuming 10 dose levels, and 100000 simulations.

		DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8	DL9	DL10	Total subjects
1	Prob (DLT)	0	1%	1%	2%	3%	4%	5%	10%	20%	30%	
	Subjects treated	1	1.1	1.1	3.2	3.3	3.4	3.8	5.2	6.1	4.7	32.9
2	Prob (DLT)	1%	2%	4%	8%	16%	24%	32%	35%	40%	45%	
	Subjects treated	1.1	1.2	1.6	4.8	5.8	5.2	3.1	1.4	0.5	0.2	24.8
3	Prob (DLT)	1%	2%	10%	15%	20%	25%	30%	35%	40%	45%	
	Subjects treated	1.1	1.4	2.9	5.5	5.0	3.8	2.3	1.1	0.4	0.1	23.5
4	Prob (DLT)	1%	2%	10%	15%	20%	25%	30%	40%	50%	60%	
	Subjects treated	1.1	1.4	2.9	5.5	5.0	3.8	2.4	1.1	0.3	0	23.4

DL=dose level; DLT=dose-limiting toxicity.

10.18 Appendix 18: Country-Specific Considerations

10.18.1 IMP/AMP EU Authorisation Status

Drug Name	IMP or AMP[a]	EU Authorisation Status	AMPs only: if unauthorised, justification for use
GEN3017	IMP	Unauthorised	
Tocilizumab	AMP	Authorised	To be administered in cases of CRS per Section 10.13.
Siltuximab	AMP	Authorised	To be administered in cases of ICANS as well as cases of CRS with concurrent ICANS per Section 10.13 and Section 10.14.
Anakinra	AMP	Authorised	To be administered in cases of ICANS as well as cases of CRS with concurrent ICANS per Section 10.13 and Section 10.14.
Diphenhydramine (or equivalent)	AMP	Authorised	
Paracetamol/acetaminophen (or equivalent)	AMP	Authorised	
Dexamethasone or methylprednisolone (or equivalent)	AMP	Authorised	

AMP=auxiliary medicinal product; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; IMP=investigational medicinal product.
a. For unauthorised AMPs, refer to Section 6.3.2 for details regarding drug accountability and destruction.

10.18.2 Japan-Specific Requirements

Section	Country-Specific Language
4.3.2.5 Siltuximab	Siltuximab is not approved in Japan
4.3.2.6 Anakinra	Anakinra is not approved in Japan
Section 10.3 Definition of Reproductive Potential and Contraception	**Definition of Reproductive Potential and Contraception** In this trial, a female is considered of childbearing potential, UNLESS they are postmenopausal or permanently sterile. A postmenopausal state is defined as no menses, in subjects >45 years of age, for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Female subjects of reproductive potential must agree to use adequate contraception during GEN3017 treatment and for 4 months after the last dose of GEN3017. Adequate contraception is defined as highly effective methods of contraception (Table 10-2). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

Table 10-2 Highly Effective Methods of Contraception – Trials Conducted in Japan

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
- 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 of childbearing potential trial subject, 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 drug(s). The reliability of 'not engaging in sexual intercourse' needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10.18.3 United States-Specific Requirements

Section	Country-Specific Language
4.1.1	In the US, subjects 16-17 years old will be eligible to participate in the R/R CD30+ cHL dose escalation cohort.
4.1.2	In the US, subjects ≥12 and <18 years old will be eligible to participate in the R/R CD30+ cHL expansion cohort
5.1, 1US	R/R cHL escalation cohort: Subjects with cHL must be at least 16 years of age.
5.1, 5US	For subjects ≥16 and <18 years of age (US), Karnofsky score of >60% per Karnofsky performance scale.
5.1, 7	Subjects ≥ 18 years of age enrolled in the US CCI [redacted] For subjects ≥16 and <18 years old, CCI [redacted]
5.1.2, 1US	For subjects in the R/R CD30+ cHL cohort in the US, age ≥12 and <18 years; assent is required of children capable of understanding the nature of the trial as described in the ICF
5.1.2, 5US1	For subjects ≥16 and <18 years old (US), Karnofsky score of >60% per Karnofsky performance scale.
5.1.2, 5US2	For subjects ≥12 and <16 years of age) (US), Lansky score of CCI per Lansky play-performance scale.
5.1.2, 7	Subjects ≥18 years of age enrolled in the US CCI [redacted]
5.1.2.1, A.2US	CCI [redacted] CCI [redacted]

	CCI CCI

cHL=classical Hodgkin lymphoma; CCI ; ICF=informed consent form; R/R=relapsed/refractory; ULN= upper limit of normal.

10.18.4 Australia-Specific Requirements

Section	Country-Specific Language
4.1.1	In Australia, subjects 16-17 years old will be eligible to participate in the R/R CD30+ cHL dose escalation cohort.
4.1.2	In Australia, subjects ≥12 and <18 years old will be eligible to participate in the R/R CD30+ cHL expansion cohort
5.1, 1AU	R/R cHL escalation cohort: Subjects with cHL must be at least 16 years of age.
5.1, 5AU	For subjects ≥16 and <18 years of age (Australia), Karnofsky score of >60% per Karnofsky performance scale.
5.1, 7	For subjects ≥16 and <18 years old CCI
5.1.2, 1AU	For subjects in the R/R CD30+ cHL cohort in Australia, age ≥12 and <18 years; assent is required of children capable of understanding the nature of the trial as described in the ICF
5.1.2, 5AU1	For subjects ≥16 and <18 years old (Australia), Karnofsky score of >60% per Karnofsky performance scale.
5.1.2, 5AU2	For subjects ≥12 and <16 years of age) (Australia), Lansky score of CCI per Lansky play-performance scale
5.1.2.1, A.2AU	CCI CCI CCI

cHL=classical Hodgkin lymphoma; ICF=informed consent form; R/R=relapsed/refractory; ULN= upper limit of normal.

11 LAY PROTOCOL SYNOPSIS

Protocol Title	A Phase 1/2a, Open-Label, Dose Escalation Trial of GEN3017 With Expansion Cohorts in Relapsed or Refractory CD30+ Classical Hodgkin Lymphoma and CD30+ Non-Hodgkin Lymphoma	
Brief Title	A first-in-human trial of safety and efficacy of GEN3017 in subjects with Hodgkin lymphoma or non-Hodgkin lymphoma	
Protocol Number	GCT3017-01	
Regulatory Agency Identifier Number(s)	**EU CT No.**	2023-503348-15-00
	NCT No.	NCT06018129

Brief Summary:

The purpose of this trial is to measure the following in patients with R/R cHL or TCL who receive GEN3017

- The side effects seen with GEN3017
- What the body does with GEN3017 once it is administered
- What GEN3017 does to the body once it is administered
- How well GEN3017 works against cHL and TCL

The trial's estimated duration will be approximately 2 years, consisting of a 21-day screening period, an estimated 1-year treatment period (the duration of treatment may vary for each subject), a 60-day safety follow-up period, a post-treatment follow-up if you stop GEN3017 prior to your disease worsening, and a survival follow-up period (the duration of follow-up may vary for each subject).

Participation in the study will require visits to the sites. CCI [redacted]

All participants will receive active drug; no one will be given placebo.

Rationale:

GEN3017 is a combination of two antibodies. It was designed to stimulate part of the immune system called T cells. GEN3017 belongs to a group of drugs known as immunotherapy. It works by using the immune system to fight cancer. Some tumors are able to hide from the immune system by inactivating the T cells. GEN3017 works by attaching T cells to part of your tumor cells (called CD30). It also attaches to part of the immune cells (called CD3). This helps the immune system attack the tumor.

This trial is being run to find out if GEN3017 is safe in patients with cHL or TCL. GEN3017 has not yet been approved to treat cHL and TCL. In this trial, GEN3017 will be tested in humans for the first time.

Genmab wants to find out if this trial drug is safe in subjects with cHL or TCL and to find the best dose. The results of this trial may be used for further development and future approval of GEN3017. The trial has 2 parts: Part 1 (dose escalation) is the beginning of the trial, where the safest and efficacious dose to continue with is to be found, and Part 2 (expansion), is where to expand the trial and give many more subjects the same dose(s). Up to 240 subjects may be treated in this trial; 120 in the dose escalation part and 120 in the expansion part.

Objectives (Purpose)/Endpoints (Assessments):

Dose Escalation

Primary Objective(s)	***Primary Endpoint(s)***
Determine the dose of GEN3017 to be studied in the expansion part	The main study endpoint in dose escalation is "dose-limiting toxicities (DLTs)," which are a specific category of side effects that guide the investigators about what doses to investigate next.
Secondary Objective(s)	***Secondary Endpoints(s)***
Evaluate what the body does with GEN3017	How long does it take for GEN3017 to be taken from the injection site and transported around the body. Then, how long it takes the body to remove GEN3017 from the body.
Evaluate immunogenicity	Does the body create antibodies that target GEN3017

Evaluate the ability of GEN3017 to reduce tumor size	The investigator will determine the following based on scans done throughout the study: • Objective response rate (a measurement of how the tumor has reacted [shrinkage or growth] to treatment) • Duration of response (the time period with tumor shrinkage before the growth starts again) • Time to response (the time period before the tumor stops growing and/or tumor shrinkage can be measured)
Expansion	
Primary Objective(s)	***Primary Endpoint(s)***
Evaluate the ability of GEN3017 to reduce tumor size	The following will be determined based on scans done throughout the study: • Objective response rate (as determined by an independent committee)
Secondary Objective(s)	***Secondary Endpoints(s)***
Evaluate the ability of GEN3017 to reduce tumor size	The investigator will determine the following based on scans done throughout the study: • Objective response rate (as determined by the investigator) • Complete response (a substantial decrease in tumor size) • Duration of response • Time to response • Progression free survival (how long it takes for patients with tumor shrinkage before their tumor starts to grow again) Overall survival (how long a patient lives for after the first dose of GEN3017)
Evaluate safety and immunogenicity of GEN3017	• What side effects are after GEN3017 treatment • Does the body create antibodies that target GEN3017
Characterize the PK of GEN3017	How long does it take for GEN3017 to be taken from the injection site and transported around the body. Then, how long it takes the body to remove GEN3017 from the body.

Trial Population

Patients with cHL or TCL that is not responding to treatment or that has returned, 18 years of age and older (with the exception of some younger subjects permitted in the US and Australia in select trial groups [≥16 years in dose escalation with cHL and ≥12 years of age in expansion with cHL). Patient must have archival or fresh biopsy confirm that the tumor is CD-30 positive.

Intervention

GEN3017 will be injected [redacted]

Before any injection of GEN3017, medications such as antihistamines, antipyretics, and/or steroids will be administered before receiving GEN3017 to help prevent or reduce any possible side effects.

Additional medications (tocilizumab, anakinra, and siltuximab) may be used to treat side effects of GEN3017, if they occur.

Ethical Considerations

Research in cells and animals suggests that GEN3017 may be effective in treating cHL and TCL in humans. However, there is limited information about GEN3017 in humans. Side effects, including but not limited to inflammation, cytokine release syndrome, a transient neurological disorder called ICANS, and tumor lysis syndrome, may be experienced. They are based on information from other similar drugs used in humans and data from studies in animals with GEN3017. All tests and procedures performed throughout the study are done to find out if GEN3017 is safe in subjects with cHL or TCL.

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Protocol Amendment Summary of Changes

Protocol Amendment 1 (18 Oct 2023)

This amendment is considered to be a substantial modification based on the criteria set forth in Article 2(13) of the EU Clinical Trial Regulation and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment was prepared in response to comments from Health Authorities in EU regarding Amendment 1 (v2.0) dated 28 June 2023. As applicable, changes included in the Summary of Changes table are incorporated in the Trial Synopsis.

Description of Changes:

Section	Description of Change	Brief Rationale
Global	Updated safety follow-up from 30 days to 60 days after the last dose of GEN3017	As requested by Health Authorities in EU
Global	Updated the phrase "legally acceptable representative(s)" or "legally authorized representative(s)" to "legally acceptable representative (not applicable in EU/EEA)"	As requested by Health Authorities in EU
Global	Updated hospitalization requirements post-GEN3017 administration in Cycle 1 of dose escalation	As requested by Health Authorities in EU
Title pages	Updated title page information to include study NCT number and updated Sponsor address for countries is the EEA, Switzerland, and the United Kingdom	Administrative update
Section 5.1.1., Inclusion Criteria – Dose Escalation (All Disease Cohorts) Section 5.1.2, Inclusion Criteria - Expansion	CCI [redacted]	As requested by Health Authorities in EU

Section	Description of Change	Brief Rationale
Section 1.1, Trial Synopsis, Key Exclusion Criteria for Dose Escalation and Expansion Section 5.2.1, Exclusion Criteria – Dose Escalation Section 5.2.2, Exclusion Criteria – Expansion	Clarified exclusion criterion 3b disease eligibility requirements based on inclusion of cHL patients who have CCI Modified exclusion criterion 5b to include specific QTcF requirements for men and women	For consistency based on requested change by Health Authority in EU above As requested by Health Authorities in EU
Section 1.1, Trial Synopsis, Other Trial Treatment Section 1.3, Schedule of Activities, Table 1-1, Table 1-2 Section 6.1.2, Premedication and Post-GEN3017 Monitoring, Table 6-3 Section 11, Lay Protocol Synopsis	Clarified antipyretic and antihistamine premedication throughout the study prior to GEN3017 administration	As requested by Health Authorities in EU
Section 6.7.1, Dose-Limiting Toxicity (Dose Escalation of GEN3017)	Update to include a DLT exception for grade 3 amylase or lipase that is not associated with symptoms, clinical manifestations, or radiological imaging of pancreatitis	As requested by Health Authorities in EU

Section	Description of Change	Brief Rationale
Section 6.7.2.1, Dose Escalation Part (GEN3017 Monotherapy) Table 6-4	Correct typographical errors in hemoglobin laboratory parameters to be consistent with CTCAE grading	Administrative update
Section 9.4, Sample Size Determination	Correcting typographical error in sample subject number to be consistent with protocol	Administrative update
Section 10.1.7, Data Protection	Added description of risk mitigation in the event of data security breach	As requested by Health Authorities in EU
Section 10.3, Appendix 3: Definition of Reproductive Potential and Contraception	Added the possibility of an eventual extension of contraception and prohibition of egg donation after the last dose of GEN3017	As requested by Health Authorities in EU
Section 10.18.1, IMP/AMP EU Authorisation Status	Updated drug name to be consistent with Table 6-2 in global protocol	Administrative update