CLINICAL TRIAL PROTOCOL

Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-cell Non-Hodgkin Lymphoma – A First-in-Human, Open-label, Phase I/IIa Dose Escalation Trial with Dose Expansion Cohorts

Protocol no.:	GCT3009-01
Sponsor Name:	Genmab*
Clinical Research Organization:	PPD
EudraCT No.:	2019-002752-16
IND No.:	145264
IMP Name:	GEN3009 (DuoHexaBody®-CD37); GEN3013 (DuoBody®-CD3xCD20, Epcoritamab)
Development Phase:	1/2a
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STATEMENT OF COMPLIANCE

GCP Compliance

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

Confidentiality Statement

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ABBREVIATIONS AND DEFINITIONS OF TERMS

5-PS	5-point scale for evaluation of PET positivity
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBMT	American Society for Blood and Marrow Transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
B-cell NHL	B-cell non-Hodgkin lymphoma
BCR	B-cell receptor
BR	bendamustine plus rituximab
CAR	chimeric antigen receptor
CDC	complement-dependent toxicity
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTR	clinical trial report
C_{trough}	predose trough concentration
DEC	dose escalation committee
DL	dose level
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
FCR	fludarabine, cyclophosphamide, plus rituximab
FcRn	neonatal Fc receptor
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
FIH	first-in-human

FL	follicular lymphoma
FSH	follicle-stimulating factor
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GDS&PV	Global Drug Safety & Pharmacovigilance
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
HDT	high-dose chemotherapy
HGBCL	high-grade B-cell lymphoma
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HSCT	hematopoietic stem cell transplantation
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
IEC	independent ethics committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IRB	institutional review board
IRR	infusion-related reaction
IV	Intravenous(ly)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LDT	lymphocyte doubling time
MABEL	minimum anticipated biological effect level
mBOIN	Modified Bayesian Optimal Interval
MCL	mantle cell lymphoma
MDRD	modification of diet in renal disease
MoA	mechanism of action
MRD	minimal residual disease
MRD–	minimal residual disease negative
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
ND	newly diagnosed
NGS	next generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal large B-cell lymphoma

PR	partial response
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	safety committee
s.c.	subcutaneous(ly)
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TEAEs	treatment-emergent adverse events
TFR	tumor flare reaction
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TTR	time to response
ULN	upper limit of normal

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5, v 7.0 (TMF 29340)	09 Jul 2021
Amendment 4/GB-1, v1.0	22 Jan 2021
Amendment 4, v 6.0 (TMF 29340)	23 Jul 2020
Amendment 3, v.5.0 (TMF 29340)	30 Apr 2020
Amendment 2, v 4.0 (TMF 29340)	16 Dec 2019
Amendment 1, v3.0 (TMF 29340)	09 Dec 2019
Original Protocol, v2.0 (TMF 29340)	22 Oct 2019
Protocol v1.0 (not submitted) (TMF 29340)	15 Oct 2019

Amendment 5 (09 Jul 2021)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Table 1 Summary of Changes

Section and Name	Description of Change	Brief Rationale
Section 1 Visit Assessment Schedules - Tables 2-9	Assessments, section references, and timepoints updated for Dose Escalation and Dose Expansion GEN3009 monotherapy.	To reflect current assessment practice and clarity
Section 1 Visit Assessment Schedules - Tables 10-16	Schedules of Assessments added for Dose Expansion GEN3009 + GEN3013 combination therapy.	To detail assessments planned for combination therapy.
2.1.2.1 GEN3009	Repetitive language removed. Language standardized. Reference to Investigator's Brochure added	For clarity.
2.1.2.2 GEN3013	Method of action described and DuoBody technology explained.	To introduce product to be used in combination with GEN3009.
2.1.3 Summary of Nonclinical Studies	Language simplified. Information about combination added. Adverse reactions described.	For clarity and to support changes in trial design.
2.1.4. Summary of Clinical Trials	Clinical trial information for 3009 added including dose, TEAEs, preliminary results, and progress on trial. Dose Escalation phase described. GCT3013-01 Expansion described. Effect on circulating lymphocytes described. Preliminary anti-tumor therapy described.	To provide up to date safety and efficacy information for GEN3009 and GEN3013.
2.2 Rationale	Language revised and supplemented.	To explain and support changes in trial design.
2.3 Benefit-Risk Assessment (including Table 17)	Language updated for GEN3009. Benefit-risk assessment for GEN3009 + GEN3013 combination therapy added.	To support changes in trial design.
3 Objectives and Endpoints	Updated to reflect the objectives and endpoints.	To clarify the way results will be interpreted.
4 Description of Trial Design	Revised to include details of new trial design including the rationale behind the design, dose and schedule rationale for GEN3009 monotherapy and GEN3009 + GEN3013 combination, and end of trial and end of treatment definitions.	To explain revised trial design and clarify key definitions for trial execution, discontinuation, and termination.

Section and Name	Description of Change	Brief Rationale
5. Trial Population	Inclusion and exclusion criteria delineated for Dose Esclation and Dose Expansion parts of trial.	To ensure appropriate trial population is enrolled and to meet comitments to health authorities.
6.1.2. Treatment Assignment or Randomization	Added statements that subjects will be assigned based on slot availability.	To describe method of assigning subjects to dose cohorts.
6.2.1 Premedication in GEN3009 Administration Monotherapy Cohorts	Premedication 1-4 added and information regarding steroids/IRR/antipyretics and antihistamines are added.	To provide clarity on premedications and procedures to be used in the GEN3009 monotheraphy cohorts.
6.2.2 Premedication and CRS Prophylaxis in GEN3009 + GEN3013 Combination Cohort	Premedications for combination therapy discussed.	To provide information on premedications and procedures to be used in GEN3009 + GEN3013 combination cohort.
6.3 Management of Infusion-Related Reactions	Section added.	To provide information on how to handle IRRs (known to occur with GEN3009 administration).
6.4 Dosage(s) and Administration	Section regarding GEN3009 + GEN3013 combination cohort added.	To provide details on the dose levels, routes, and schedules for GEN3009 and GEN3013 in the combination cohort.
6.6 Concomitant Medications and Therapies	Section revised.	To indicate that medical monitor should be contacted for questions about concomitant medications and to describe in detail any medications or therapies that are/are not permitted for subjects receiving GEN3009 monotherapy or GEN3009 + GEN3013 combination therapy.
6.7 Investigational Medicinal Product Information	Section revised and expanded.	To clarify information about GEN3009 product and provide information about GEN3013.
7.3 Safety Run-in for Expansion: Dose-limiting Toxicity	Section revised.	To reflect Dose Expansion including combination therapy of GEN3009 + GEN3013. Grade 5 heme and non-heme toxicities are listed. Frequent lab blood monitoring discussed for tracking resolution of hematological AEs.
7.4 Dose Modification Guidance and Safety Stopping Rules	Section revised.	To detail dose modification rules for safety run-in, GEN3013, and toxicity management.
7.5 Management of Specific Adverse Events	Section added.	To describe what to do in the event that subjects experience neutropenia and other cytopenias, CRS, neurotoxicity syndrome, TLS, and tumor flare reaction.
8 Discontinuation, Follow-up and Completion	Section revised.	To provide clarity for patient follow-up timeframes after discontinuation of treatment.
9 Trial Assessments	Section revised.	To reflect updated descriptions of assessments and timepoints.
10 Safety Monitory and Adverse Event Reporting	Section revised.	To reflect addition of combination therapy of GEN3009 + GEN3013 combination therapy and template language, as appropriate.
11 Statistics	Section revised.	To clarify analyses that will be performed based on new trial design, objectives, and endpoints.
13 Ethics	Section revised.	To reflect new trial design as applicable.
15. References	Section revised.	To reflect references currently cited in revised protocol.

Section and Name	Description of Change	Brief Rationale
Appendix 4 Tumor Lysis Syndrome	Section revised.	To include updated cross references.
Appendix 12 Definition of Reproductive Potential and Contraception	Section replaced.	To include information from latest version of CTFG recommendations.

Note: Commitments to health authorities have been met and incorporated into this global protocol amendment.

Overall Rationale for the Amendment: Overall, the trial was amended to allow for higher doses (ie, ≥CCI mg) of GEN3009 monotherapy in the Dose Escalation part and a combination of GEN3009 + GEN3013 in the Dose Expansion part. The bases for these changes are discussed in detail in Sections 4.3.1 and 4.3.2, respectively.

TRIAL SYNOPSIS

Title	Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-cell Non-Hodgkin Lymphoma – A First-in-Human, Open-label, Phase I/IIa Dose Escalation Trial with Dose Expansion Cohorts
Brief Title	First-in-Human (FIH) Trial of GEN3009 in Subjects with Relapsed or Refractory B-cell non-Hodgkin Lymphoma
Clinical Phase	Phase 1/2a
Purpose and Rationale	Over the last 2 decades, the clinical course of B-cell non-Hodgkin lymphoma (B-cell NHL) has been changed dramatically by anti-CD20 antibody (eg, rituximab, ofatumumab, obinutuzumab)-containing chemotherapies with substantially improved outcomes. However, for most relapsed or refractory (R/R) lymphomas and chronic lymphocytic leukemia (CLL), there is still no treatment that can lead to a cure. This unmet medical need warrants developing new efficacious therapies for patients with advanced B-cell NHL whose disease no longer responds to standard therapies. Identification of a target other than CD20, such as CD37, may represent an attractive alternative strategy. Furthermore, a chemo-free regimen by combining an anti-CD37 therapy with a T- cell-engaging therapy such as a CD3xCD20 bispecific antibody may present an efficacious treatment option for patients who have exhausted standard- of- care. GEN3009 (DuoHexaBody®-CD37) is a bispecific antibody with a hexamerization-enhancing mutation that targets 2 different epitopes of the CD37 antigen. GEN3009 induced tumor cell killing via enhanced complement-dependent cytotoxicity (CDC) and by FcγR-mediated effector functions including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody antibody-dependent cell-mediated phagocytosis (ADCP). Nonclinically, CD37-targeting GEN3009 has demonstrated more potent tumor-cell killing than clinically validated CD20-targeting antibodies across a variety of B-cell NHL subtypes, regardless of the relapse status (ie, similar anti-tumor effect observed in newly diagnosed samples and R/R samples). GEN3009 also showed potent CDC activity in a limited set of primary samples from ibrutinib-treated NHL patients. In addition to these findings, therapeutic activity of GEN3009 was observed in tumor cell line-derived xenografts (ie., diffuse large B-cell lymphoma [DLBCL], Burkitt's lymphoma, and CLL) and patient patient-derived xenografts (ie., DLBCL). GEN3013 (DuoBody®-CD3xCD20, epcoritamab) is a fully human IgG1 bispecific antibody that induces potent T- cell-mediated cytotoxicity of CD20-expressing cells. Clinical data from an ongoing Phase 1/2 trial (GCT3013-01) demonstrated that GEN3013 as a single agent induced high objective response rate (ORR) with a manageable safety profile in heavily pre-treated B-cell NHL including DLBCL and follicular lymphoma (FL) (Hutchings, et al., 2020). As of 31 Jan 2021, a total of 178 subjects with aggressive and indolent NHL have been treated with GEN3013 across 5 ongoing trials. In the Dose Escalation (N=68) part of GCT3013-01 (NCT03625037), the most advanced study, GEN3013 was well tolerated at doses up to 60 mg. Recommended Phase 2 dose (RP2D) was declared as 48 mg for further development in the Expansion. Among 10 subjects treated at 48 mg, the ORR was 70.0% (3 complete response [CR], 4 partial response [PR]); among 9 DLBCL subjects, ORR was 77.8% (3 CR, 4 PR). The 4 most common treatment-emergent adverse events (TEAEs) were pyrexia (69.1%), cytokine release syndrome (CRS) (58.8%), injection site reaction (47.1%), and fatigue (44.1%). Adverse events of special interest (AESIs) occurred in approximately two-thirds of subjects; of these, 40 subjects (58.8%) experienced CRS, 4 subjects (5.9%) experienced neurological symptoms, and 1 subject (1.5%) experienced clinical tumor lysis syndrome. Due to the non-overlapping mechanisms of action (MoAs) for GEN3009 and GEN3013, it is hypothesized that the combination of GEN3009 with GEN3013 may induce deeper and durable remissions in R/R B-cell NHL. The aim of this first-in-human (FIH) trial is to characterize the safety and tolerability, pharmacokinetic (PK), and pharmacodynamic characteristics of GEN3009 as a single agent and in combination with GEN3013 in subjects with R/R B-cell NHL. In the Dose Escalation part, dose-limiting toxicity will be monitored to determine the maximum tolerated dose (MTD) and/or RP2D for GEN3009. In the Expansion part, clinical activity of GEN3009 monotherapy at the RP2D

<table>
<tr><td></td><td>in DLBCL, FL, and CLL will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers. In addition, the safety and preliminary efficacy of the combination regimen of GEN3009 and GEN3013 in R/R DLBCL will be evaluated.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
Dose Escalation: GEN3009 for R/R B-cell NHL Including CLL/Small Lymphocytic Lymphoma (SLL)
<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• Determine the MTD with and/or determine the RP2D of GEN3009</td><td>• Rate of dose-limiting toxicities (DLTs)</td></tr>
<tr><td>• Evaluate safety and tolerability of GEN3009</td><td>• Frequency and severity of adverse events (AEs)/AESIs/SAEs
• Changes in laboratory parameters
• Changes in vital signs
• Frequency of dose interruptions, dose delays, and dose intensity</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• Establish PK profile of GEN3009</td><td>• PK parameters</td></tr>
<tr><td>• Evaluate immunogenicity of GEN3009</td><td>• Incidence of neutralizing anti-GEN3009 antibodies (ie, anti-drug antibodies [ADAs])</td></tr>
<tr><td>• Evaluate preliminary anti-tumor efficacy of GEN3009</td><td>• ORR
• CR rate
• Duration of response (DoR)
• Time to response (TTR)</td></tr>
<tr><td>• Evaluate preliminary clinical efficacy of GEN3009</td><td>• Progression-free survival (PFS)
• Overall survival (OS)</td></tr>
<tr><td colspan="2">Exploratory</td></tr>
<tr><td>• Assess potential biomarkers predictive of clinical response to GEN3009 and evaluate potential surrogacy with PFS and OS</td><td>• CD37 expression
• Minimal residual disease (MRD) status</td></tr>
<tr><td>• Assess pharmacodynamic markers related to MoA of GEN3009</td><td>• Pharmacodynamic markers in blood samples</td></tr>
</table>
Expansion: GEN3009 for R/R DLBCL, FL, and CLL Cohorts
<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• Evaluate (preliminary) anti-tumor efficacy of GEN3009</td><td>• ORR</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• Establish PK profile of GEN3009</td><td>• PK parameters</td></tr>
<tr><td>• Evaluate safety and tolerability of GEN3009</td><td>• Frequency and severity of AEs/AESIs/SAEs
• Changes in laboratory parameters
• Changes in vital signs
• Frequency of dose interruptions, dose delays, and dose intensity</td></tr>
<tr><td>• Evaluate clinical efficacy of GEN3009</td><td>• CR rate
• DoR
• TTR
• PFS
• OS</td></tr>
<tr><td>• Evaluate immunogenicity of GEN3009</td><td>• Incidence of neutralizing anti-GEN3009 antibodies (ie, ADAs)</td></tr>
</table>
</td></tr>
</table>

Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 and evaluate potential surrogacy with PFS and OS	• Expression of CD37 and CD59 in tumor biopsies before and during treatment • Abundance of immune effector cells in tumor microenvironment • Circulating tumor DNA (ctDNA) as response biomarker • MRD status as response biomarker in DLBCL, FL, and CLL and evaluate potential surrogacy with PFS/OS • DNA mutational status and gene expression profiling (RNA-seq) in blood and malignant cells
• Assess pharmacodynamic markers related to MoA of GEN3009	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy) (leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Expansion: GEN3009 + GEN3013 Safety Run-in for R/R B-cell NHL

OBJECTIVES	ENDPOINTS
Primary	
• Identify the RP2D of GEN3009 + GEN3013 combination	• Rate of DLTs
• Evaluate safety and tolerability of GEN3009 + GEN3013 combination	• Frequency and severity of AEs/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
Secondary	
• Establish the pharmacokinetic (PK) properties of GEN3009 and GEN3013	• PK parameters
• Evaluate immunogenicity	• Incidence of neutralizing anti-drug antibodies (ADAs) to GEN3009 • Incidence of neutralizing anti-drug antibodies (ADAs) to GEN3013
• Assess the preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• CR rate • ORR • DoR • TTR • PFS • OS
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 + GEN3013 combination	• Expression of CD3, CD20, CD37, and molecular markers before and during treatment • MRD status
• Assess pharmacodynamic markers related to MoA of GEN3009 and GEN3013	• Pharmacodynamic markers in blood samples (leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory

	protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Expansion: GEN3009 + GEN3013 for R/R DLBCL

OBJECTIVES	ENDPOINTS
Primary	
• Assess preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• CR rate
Secondary	
• Further assess the preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• ORR • DoR • TTR • PFS • OS • Rate and duration of MRD negativity
• Evaluate the safety and tolerability of GEN3009 + GEN3013	• Frequency and severity of AEs/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
• Establish the PK properties of GEN3009 and GEN3013	• PK parameters
• Evaluate immunogenicity	• Incidence of neutralizing ADAs to GEN3009 • Incidence of neutralizing ADAs to GEN3013
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 + GEN3013 combination	• Expression of CD37, CD20, CD3 and other markers in tumor biopsies before and during treatment • DNA mutation status and gene expression profiling (RNA-seq) in blood and malignant cells • ctDNA as response biomarker • Evaluation of immune populations, phenotype and function in tumors and blood
• To evaluate pharmacodynamic markers linked to efficacy and mechanism of action of GEN3009 and GEN3013	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy) ((leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Trial Design

This trial is a FIH, open-label, multicenter trial to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3009 as a single agent and in combination with GEN3013 in subjects with R/R B-cell NHL.

The trial will be conducted in 2 parts, Dose Escalation and Expansion. In the Dose Escalation, GEN3009 will be administered by intravenous (IV) infusions at 10 dose levels (DLs) ranging from [redacted] mg to [redacted] mg in 28-day cycles. DLTs will be assessed during the first treatment cycle and the MTD may be identified. The totality of the data including safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated to guide further development for Expansion, with additional subjects treated at the RP2D.

In the Dose Expansion, there are 4 cohorts:

- GEN3009 monotherapy cohorts: R/R DLBCL (N =20), R/R FL (N =20), and R/R CLL (N =20)

<table>
<tr><td></td><td>
GEN3009 + GEN3013: safety run-in phase in R/R DLBCL or FL (N=6-12) followed by R/R DLBCL (N =20)
GEN3009 will be administered as IV infusions at CCI mg and RP2D and GEN3013 as subcutaneous injections with a step-up dosing method (ie, priming dose followed by intermediate dose and full dose) in 28-day treatment cycles.

Dosing schedule for Cohort 4 GEN3009 + GEN3013 in R/R DLBCL

(Each treatment cycle is 28 days)
<table>
<tr><th>GEN3009 IV as assigned

DL1: CCI mg

DL2: RP2D</th><th>GEN3013 s.c.

DL1: 48 mg</th></tr>
<tr><td>Cycles 1-3: Days 1, 8, 15, 22
Cycles 4-12: Day 1</td><td>Cycle 1:
0.16 mg (priming dose) on Day 8
0.8 mg (intermediate dose) on Day 15
48 mg (full dose) on Day 22
Cycles 2 and 3: 48 mg on Days 1, 8, 15, and 22
Cycles 4-12: 48 mg on Day 1
After completion of Cycle 12:
Subjects who are in SD, PR or CR:
Every 4 weeks (Cycles 13, 14, 15+): 48 m</td></tr>
</table>
A safety run-in phase including 6-12 subjects with either R/R DLBCL or FL followed by 1 expansion cohort in R/R DLBCL. DLTs will be evaluated during the first treatment cycle (28 days). Subjects in the safety run-in will continue on treatment and subsequently in safety and survival follow-up.

Subjects must be hospitalized for CRS monitoring for at least 24 hours after the third dose (first full dose) of GEN3013 (ie, 48 mg) at Cycle 1 Day 22. Additional or longer hospitalization is allowed at the investigator's discretion.

After completion of Cycle 12, subjects who have stable disease or better will have the option to continue receiving GEN3013 every 4 weeks until any discontinuation criterion is met.

A data monitoring committee (DMC) will assess the totality of safety information of the safety run-in part and identify additional safety signal according to a DMC charter.

Positron emission tomography computed tomography scan will be conducted at screening, at Cycle 2 (Week 6), Cycle 3 (Week 12), Cycle 5 (Week 18), Cycle 6 (Week 24), Cycle 9 (Week 36), Cycle 12 (Week 48), then every 24 weeks thereafter until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first.
</td></tr>
<tr><td>Population</td><td>For GEN3009 monotherapy, approximately 90 subjects with R/R B-cell NHL (including CLL/SLL, will be enrolled in the Dose Escalation). Approximately 92 subjects will be enrolled in the Dose Expansion.</td></tr>
<tr><td>Key Inclusion Criteria</td><td>Each potential subject must fulfill all of the following criteria to be enrolled in the trial (applicable to both Dose Escalation and Dose Expansion unless otherwise indicated).

Be at least 18 years of age.
Must sign an informed consent form (ICF) prior to any screening procedures.
Has histologically or cytologically confirmed relapsed or refractory B-cell NHL with no available standard therapy or is not a candidate for available standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN3009 or GEN3009 + GEN3013 may be beneficial. All subjects must have received at least 2 prior lines of systemic therapy, and,

A. For all indolent NHL (FL, marginal zone lymphoma [MZL], and SLL) as well as aggressive NHL (DLBCL, high-grade B-cell lymphoma [HGBCL], and primary mediastinal large B-
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</table>

	cell lymphoma [PMBCL]), at least 1 of the 2 prior lines of treatment must have been a CD20-containing systemic regimen; B. For mantle cell lymphoma (MCL), subjects must have had or are otherwise ineligible for treatment with a BTK inhibitor, and; C. For CLL, subjects must have received at least 1 prior line of BTK inhibitor or BCL-2 inhibitor. Note: See Section 11.8.1.3 for definitions of "relapsed" disease. • Has 1 of the following B-cell NHL subtypes: • DLBCL, de novo or histologically transformed • HGBCL (Dose Escalation only) • PMBCL (Dose Escalation only) • FL, with advanced symptomatic disease and with a need for treatment (Dose Escalation only) Or FL Grade 1, 2 and 3a, with advanced symptomatic disease and with a need for treatment initiation (Expansion only) • MCL, without leukemic manifestation (Dose Escalation only) • MZL, either nodal, extranodal, or mucosa associated, with a need for treatment initiation based on symptoms and/or disease burden (Dose Escalation only) • SLL, with a need for treatment based on symptoms and/or disease burden (Dose Escalation only) • CLL, with B-cell count $<100 \times 10^9$/L (100,000/µL) in the peripheral blood and presence of measurable lymphadenopathy and/or organomegaly (Dose Escalation only) Or CLL, must have active disease that needs treatment with at least 1 of the following criteria being met (Expansion only): • Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia • Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly • Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy • Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time <6 months • Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids • Symptomatic or functional extra-nodal involvement (eg, skin, kidney, lung, spine) • Disease-related symptoms as defined by any of the following: • Unintentional weight loss ≥10% within the previous 6 months • Significant fatigue • Fevers ≥38.0°C (100.5°F) for 2 or more weeks without evidence of infection • Night sweats for ≥1 month without evidence of infection

	• Documented CD20+ DLBCL or FL based on representative pathology report (GEN3009 + GEN3013 combination Expansion cohort only) • Has measurable disease for B-cell NHL or active disease for CLL. • Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • Has acceptable laboratory parameters. • Before the first dose of GEN3009, during the trial, and for 12 months after the last dose of GEN3009 and/or GEN3013, a woman must be either not of childbearing potential or of childbearing potential and practicing a highly effective method of birth control, and must have a negative serum beta-human chorionic gonadotropin (beta-hCG) at screening. • A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control. • Documented CD20+ DLBCL or FL based on representative pathology report (GEN3009 + GEN3013 combination Expansion cohort only). • Subjects must have a life expectancy of at least 3 months.
Key Exclusion Criteria	Any potential subject who meets any of the following criteria will be excluded from participating in the trial (applicable to both Dose Escalation and Expansion unless otherwise indicated).. • Prior treatment with a CD37-targeting agent. • Prior allogeneic hematopoietic stem cell transplantation (HSCT). • Prior treatment with a CD3xCD20 bispecific antibody (GEN3009 + GEN3013 combination Expansion cohort only). • Autologous HSCT within 3 months before the first dose of GEN3009. • Lymphomas leukemic phase: high absolute lymphocyte count or the presence of abnormal cells in the peripheral blood indicating circulating lymphoma cells. • Treatment with an anti-cancer biologic including anti-CD20 therapy, radio-conjugated or toxin-conjugated antibody or chimeric antigen receptor T cell therapy within 4 weeks or 5 half-lives, whichever is shorter, before the first dose of GEN3009. Treatment with small molecules such as BTK inhibitors, BCL2 inhibitors, or PI3K inhibitors within 5 half-lives prior to the first dose of GEN3009. • Chemotherapy or radiation therapy within 2 weeks of the first dose of GEN3009. • Treatment with an investigational drug or an invasive investigational medical device within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3009, and at any time during the study treatment period. • Autoimmune disease or other diseases that require permanent or high-dose immunosuppressive therapy. • Received a cumulative dose of corticosteroids more than the equivalent of 250 mg of prednisone within the 2–week period before the first dose of GEN3009. • Has uncontrolled intercurrent illness, including but not limited to: a. Ongoing or active infection requiring intravenous antibiotics treatment at the time of enrollment or within the previous 2 weeks prior to the first dose of GEN3009 or GEN3013. b. Symptomatic congestive heart failure (grade III or IV as classified by the New York Heart Association ([NYHA]), unstable angina pectoris or cardiac arrhythmia (refer to Appendix 2) and/or known decrease ejection fraction of <45% c. Myocardial infarction, intracranial bleed, or stroke within the past 6 months.

	d. Screening 12-lead electrocardiogram showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec.
	• Seizure disorder requiring therapy (such as steroids or anti-epileptics) (GEN3009 + GEN3013 combination Expansion cohort only).
	• History of severe allergic or anaphylactic reactions to monoclonal antibody therapy
	• Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
	• Primary central nervous system (CNS) lymphoma or known CNS involvement at screening.
	• Has known past or current malignancy other than inclusion diagnosis, except for:
	  • Cervical carcinoma of Stage 1B or less
	  • Non-invasive basal cell or squamous cell skin carcinoma
	  • Non-invasive, superficial bladder cancer
	  • Prostate cancer with a current PSA level <0.1 ng/mL
	  • Any curable cancer with a CR of >2 years duration
	• Had allergic reactions to anti-CD20 or anti-CD37 monoclonal antibody treatment or intolerant to GEN3009 excipients (refer to the GEN3009 Investigator's Brochure (IB) for more information)
	• Intolerant to GEN3013 excipients (refer to the GEN3013 IB for more information) (GEN3009 + GEN3013 combination Expansion cohort only).
	• Has had major surgery within 4 weeks before screening or will not have fully recovered from surgery, or has major surgery planned during the time the subject is expected to participate in the trial (or within 4 weeks after the last dose of GEN3009 and/or GEN3013).
	• Has known history/positive serology for hepatitis B.
	• Known medical history or ongoing hepatitis C infection that has not been cured.
	• Known history of seropositivity for HIV infection. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
	• Is a woman who is pregnant or breast-feeding, or who is planning to become pregnant while enrolled in this trial or within 12 months after the last dose of GEN3009 and/or GEN3013.
	• Is a man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3009 and/or GEN3013.
	• 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.
	• Exposed to live/live attenuated vaccine within 4 weeks prior to initiation of GEN3009 treatment.

IMP	GEN3009 will be administered intravenously in 4-week cycles (ie., 28 days). In the Dose Escalation, the starting dose is [redacted] mg. Ten DLs may be tested. Additional/intermediate DLs may also be explored based upon emerging data. In the Expansion, CCI mg and the RP2D of GEN3009 will be investigated together with GEN3013 at 48 mg. GEN3013 will be administered s.c. in 4-week cycles (ie., 28 days).

	In the Expansion, 48 mg of GEN3013 will be investigated together with GEN3009 at CCI mg and the RP2D.
Statistics	In the Dose Escalation, MTD and/or RP2D will be determined using a modified Bayesian Optimal Interval (mBOIN) design. Expansion of GEN3009 monotherapy will be conducted in 3 indications with a maximum sample size of 20 per indication. Expansion of GEN3009 in combination with GEN3013 will be conducted in 1 indication following a safety run-in phase with a maximum sample size of 32 for the cohort. No formal statistical hypothesis testing will be performed. AEs will be described using summary statistics. Individual curves of plasma concentration for GEN3009 or GEN3013 will be presented for all subjects. PK parameters will be calculated based on non-compartmental methods and calculated separately. The revised response criteria (Cheson et al., 2014) will be used to assess the response for B-cell NHL and the International Workshop on Chronic Lymphocytic Leukemia (Hallek et al., 2018) for CLL.

1 VISIT ASSESSMENT SCHEDULES

The following visit assessments are provided in this section:

The assessment schedules list all the assessments and indicates with an “X” the visits when they are performed. In addition to the fixed visits, it may be necessary to perform some of the assessments at unscheduled time points if deemed clinically necessary by the investigator. All data obtained from these assessments must be supported in the subject’s source documentation.

Table 2 Visit Assessment Schedule for Screening and Cycle 1 - Dose Escalation

Treatment Cycle: 28-day cycle	**Section**	**Screening**	**Cycle 1**											
Day		**≤ 21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8d[a]**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
Informed Consent	13.2.3	X (before any trial-specific procedures)												
Eligibility Criteria	5.1, 5.2	X												
Demographics	9.1.1	X												
Disease Status: Includes diagnosis and staging criteria	9.1.2	X												
Medical History[b]	9.1.3	X	X											
Prior Anti-neoplastic Therapy	9.1.5	X												
DLBCL or CLL Cytogenetics and Molecular Status	9.4.1	X												
FDG-PET CT/CT/MRI[c]	9.2.2.1	X												
Lymphoma with Bone Marrow Involvement and CLL: Unilateral bone marrow biopsy and aspirate[d]	9.2.2.2	X												
Height	9.3.1	X												
Body Weight	9.3.1	X	X			X			X			X		
Physical Examination (including lymph node assessment)[e]	9.3.1	X	X			X			X			X		
Vital Signs	9.3.2	X	X[f]	X[f]	X	X[f]	X	X	X[f]	X		X[f]	X	
ECG (in triplicate)	9.3.3	X	X[g]	X[g]	X	X[g]	X	X	X[g]			X[g]		
ECOG Performance Status	9.3.4	X	X											
Constitutional Symptoms	9.3.5	X	X			X			X			X		
Adverse Events[h]	10	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X
Premedication prior to GEN3009 Administration	6.2		X	X[i]		X			X			X		
GEN3009 Administration	6.4.1		X	X[i]		X			X			X		

Treatment Cycle: 28-day cycle	Section	Screening	Cycle 1											
Day		**≤ 21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8d[a]**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
LABORATORY ASSESSMENTS														
Hematology: Complete blood count and differential count[e]	9.4.1	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative Lymphocyte Subsets	9.4.1	X												
Biochemistry[e]	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Coagulation[e]	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Immunoglobulins (IgA, IgE, IgG, IgM)	9.4.1	X												
Urinalysis[e]	9.4.1	X	X			X								
Serum β_2-microglobulin	9.4.1	X												
Pregnancy Test (serum)	9.4.1	X												
Pregnancy Test (either urine or serum)[e]	9.4.1		X											
HIV Serology[i]	9.4.1	X												
Hepatitis B and C Serology	9.4.1	X												
Cytomegalovirus (CMV) Serology	9.4.1	X												

a. Subjects must remain at the clinic for at least 4 hours for observation following GEN3009 administration. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions occur following discharge from the 4-hour observation period. Observation of up to 24 hours postdose during Cycle 1 is permissible at the discretion of the investigator.
b. Any medical condition (ie, signs, symptoms and diagnosis) occurring prior to the first GEN3009 dose should be recorded as medical history.
c. Refer to Section 9.2.2.1 for imaging requirements. Imaging assessments performed as SOC prior to the subject signing of informed consent may be submitted as screening assessment, if imaging is performed within 21 days of the first dose of GEN3009, and all other requirements for imaging are met.
d. CLL/SLL subjects and lymphoma subjects with bone marrow involvement: fresh bone marrow biopsy and aspirate are required. Prior bone marrow biopsy samples done within 4 weeks before Cycle 1 Day 1 are acceptable. Fresh bone marrow aspirate is mandatory at screening.
e. Physical examination or clinical laboratory tests may be performed within 1 day prior to GEN3009 dosing
f. On GEN3009 administration days in Cycle 1, vital signs are to be obtained: 1) Before administration, 2) 15 minutes (± 5 minutes) after administration and 3) every 30 minutes (± 5 minutes) during the 4-hour postdose observation period.
g. In triplicate, 5 minutes apart (± 5 minutes), before GEN3009 administration and 1-2 hours (± 15 minutes) after administration.
h. All AEs must be reported from the first GEN3009 dose until 30 days after the last dose (refer to Table 3 for details on the safety follow-up visit). Medical conditions that occur after the ICF is signed and prior to first GEN3009 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
i. HIV testing is required at screening only if required per local health authorities or institutional standards.

j. At dose levels ≥CCI mg, the first dose of GEN3009 can be split into 2 consecutive days (ie, CCI mg at C1D1 and remaining amount at C1D2) after approval of the sponsor's medical monitor.

Table 3 Visit Assessment Schedule from Cycle 2 and Beyond – Dose Escalation

Treatment Cycle: 28-day cycle	**Section**	**Cycle 2-3**						**Cycle 4-9**		**Cycle 10 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit[a]**	**Safety Follow-up Visit[a]**	**Survival Follow-up[b]**
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**15d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**30 days after last dose**	**Every 12 weeks after last dose**
Visit Window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**±2d**	**±2d**		**+7d**	**+14d**	**±14d**
Body Weight	9.3.1	X		X		X	X	X	X	X	X	X		
Physical Examination (including lymph node assessment)[c]	9.3.1	X						X		X	X	X		
Vital Signs	9.3.2	X[d]		X[d]		X[d]	X[d]	X[d]	X[d]	X[d]	X	X		
ECG (in triplicate)	9.3.3	X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X	X		
ECOG Performance Status	9.3.4	X						X		X	X	X		
Constitutional Symptoms	9.3.5	X						X		X	X	X		
Adverse Events[f]	10	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	
Premedication prior to GEN3009 Administration	6.2	X		X		X	X	X	X	X				
GEN3009 Administration	6.4.1	X		X		X	X	X	X	X				
New Anti-cancer Treatment												X	X	X
Survival Status	9.3.6												X	X
EFFICACY ASSESSMENTS														
FDG-PET CT/CT/MRI	9.2.2.1	X[g]												

Treatment Cycle: 28-day cycle	**Section**	**Cycle 2-3**						**Cycle 4-9**		**Cycle 10 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit[a]**	**Safety Follow-up Visit[a]**	**Survival Follow-up[b]**
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**15d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**30 days after last dose**	**Every 12 weeks after last dose**
Visit Window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**±2d**	**±2d**		**+7d**	**+14d**	**±14d**
Lymphoma with Bone Marrow Involvement and CLL: Unilateral bone marrow biopsy and aspirate	9.2.2.2	X (at time of CR and clinically indicated)												
LABORATORY ASSESSMENTS														
Hematology: Complete blood count and differential count[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Biochemistry[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Coagulation[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Immunoglobulins (IgA, IgE, IgG, IgM)	9.4.1	X						X		X		X		
Urinalysis[c]	9.4.1	X						X		X	X	X		
Pregnancy Test (either urine or serum)	9.4.1	X						X		X	X	X	X	
Hepatitis B and C Serology	9.4.1											X[h]		

a. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days after the last dose of GEN3009. If the subject initiates new anti-lymphoma therapy within 4 weeks of the last dose of GEN3009, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.

b. Subjects will enter the survival follow-up after completion of the safety follow-up or if new anti-cancer treatment has been started. Survival follow-up contact may be performed as a telephone call, email, or on-site visit.

c. Physical examination and clinical laboratory tests may be performed within 1 day prior to GEN3009 dosing.

d. On dosing days, vital signs are performed predose and postdose, and more frequently at the discretion of the investigator. If the subject has stable vital signs and no other issues, the subject may be discharged from the clinic after all assessments are completed as required by protocol. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions occur following discharge from the clinic.

e. In triplicate, 5 minutes apart (± 5 minutes), before GEN3009 administration and 1-2 hours (± 15 minutes) after administration.

f. All AEs must be reported from the first GEN3009 dose until 30 days after the last dose. If the subject initiates new anti-lymphoma therapy within 30 days of the last dose of GEN3009, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
g. Refer to Section 9.2.2.1 for imaging requirements.
h. Only for subjects with positive serology.

Table 4 Visit Assessment Schedule for PK, Immunogenicity, Biomarkers/Pharmacodynamics, and Tumor Lysis Syndrome Surveillance Sampling – Dose Escalation

Treatment Cycle: 28-day cycle	**Screening**	**Cycle 1 and 2**								
Day	**≤ D21 prior to C1D1**	**1d**	**2d**	**4d**	**8d**	**9d**	**15d**	**16d**	**22d**	**23d**
Visit window										
Predose (-30 minutes)	Fresh tumor biopsy or archival samples for IHC	PK/ADA[a]/Cy/Co/I/TLS	PK[g]		PK/I/TLS		PK/ADA[b]/Cy/Co/I		PK/ADA[b]/I	
End of infusion[c] (+5 minutes)		PK/Cy[f]/TLS	PK[g]/Cy[g]		PK/TLS		PK/Cy[b]		PK	
End of infusion +2 hours (±15 minutes)		PK[f]/Cy[f]/TLS	PK[g]/Cy[g]		TLS		Cy[b]			
End of infusion +4 hours (±30 minutes)		PK[f]/Cy[f]/Co[f]/I[f]/TLS	PK[g]/Cy[g]/Co[g]/I[g]		I[b]/TLS		Cy[b]/Co[b]/I[b]		I[b]	
End of infusion +24 hours (±2 hours)			PK[f]/Cy[f]/I[f]/TLS			I[b]/TLS		I[b]		I[b]
End of infusion +72 hours (±24 hours)[h]				PK/I/TLS						

Treatment Cycle: 28-day cycle	**Cycle 3**				**Cycle 4-9**		**Cycle 10 And Beyond**	**Unscheduled**	**Treatment Discontinuation Visit**
Day	**1d**	**8d**	**15d**	**22d**	**1d**	**15d**	**1d**		
Visit window		**+2d**	**+2d**	**+2d**	**+3d**	**±3d**	**±4d**		
Predose (-30 minutes)	PK/I/Co	PK/I/Co	PK/I/Co	PK/I/Co	PK/ADA[d]/I[d]/Co[d]	PK/I[d]/Co[d]	PK/ADA[d]/I[d]/Co[d]		
End of infusion[c] (+5 minutes)	PK	PK	PK	PK	PK	PK	PK		
Unscheduled Visit								PK/ADA/I/Co/Cy/TB[e]	PK/ADA

Note: Sample collection timing may be modified during the trial based on emerging data.
PK=Pharmacokinetics (Section 9.5); ADA=anti-drug antibody (Section 9.6); Cy=cytokine (Section 9.8.3.2); Co=complement (Section 9.8.3.3); I=immunophenotyping on peripheral blood (Section 9.8.3.1); TLS=tumor lysis syndrome (Table 31); TB=tumor biopsy (Section 9.7/9.8.2)

a. Day 1 ADA in Cycle 2 only.
b. Cycle 1 only.
c. After flush.
d. ADA and biomarker samples in even cycles only.
e. Refer to Section 9.7.

f. Only in case of full dose on Day 1
g. Only in case of split dose between Day 1 and Day 2.
h. In case of split dose between Day 1 and Day 2, the Day 4 sample will be 48 hours after the complete infusion.

Table 5 Visit Assessment Schedule for Screening and Cycle 1 – Expansion GEN3009 Monotherapy

Treatment Cycle: 28-day cycle	**Section**	**Screening**	**Cycle 1**											
Day		**≤21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8d[a]**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
Informed Consent	13.2.3	X (before any trial-specific procedures)												
Eligibility Criteria	5.1, 5.2	X												
Demographics	9.1.1	X												
Disease Status: Includes diagnosis and staging criteria	9.1.2	X												
Medical History[b]	9.1.3	X	X											
Prior Anti-neoplastic Therapy	9.1.5	X												
DLBCL or CLL Molecular Status	9.4.1	X												
FDG-PET CT/CT/MRI[c]	9.2.2.1	X												
Lymphoma with Bone Marrow Involvement and CLL: Unilateral bone marrow biopsy and aspirate[d]	9.2.2.2	X												
Height	9.3.1	X												
Body Weight	9.3.1	X	X			X			X			X		
Physical Examination (including lymph node assessment)[e]	9.3.1	X	X			X			X			X		
Vital Signs	9.3.2	X	X[f]	X[f]	X	X[f]	X	X	X[f]	X		X[f]	X	
ECG (in triplicate)	9.3.3	X	X[g]	X[g]	X	X[g]	X	X	X[g]			X[g]		
ECOG Performance Status	9.3.4	X	X											
Constitutional Symptoms	9.3.5	X	X			X			X			X		
Adverse Events[h]	10	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X
Premedication prior to GEN3009 Administration	6.2		X	X		X			X			X		
GEN3009 Administration	6.4.1		X	X		X			X			X		
LABORATORY ASSESSMENTS														

Treatment Cycle: 28-day cycle	Section	Screening	Cycle 1											
Day		**≤21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8d[a]**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
Hematology: Complete blood count and differential count[e]	9.4.1	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative Lymphocyte Subsets	9.4.1	X												
Biochemistry[e]	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Coagulation[e]	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Tumor Lysis Syndrome Panel	9.4.1		X	X	X	X	X	X	X	X		X	X	
Immunoglobulins (IgA, IgE, IgG, IgM)	9.4.1	X												
Urinalysis[e]	9.4.1	X	X			X								
Serum β_2-microglobulin	9.4.1	X												
Pregnancy Test (serum)	9.4.1	X												
Pregnancy Test (either urine or serum)[e]	9.4.1		X											
HIV Serology[i]	9.4.1	X												
Hepatitis B and C Serology	9.4.1	X												
Cytomegalovirus (CMV) Serology	9.4.1	X												

a. Subjects must remain at the clinic for at least 2 hours for observation following GEN3009 administration. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions occur following discharge from the 2-hour observation period.
b. Any medical condition (ie, signs, symptoms and diagnosis) occurring prior to the first GEN3009 dose should be recorded as medical history.
c. Refer to Section 9.2.2.1 for imaging requirements. Imaging assessments performed as SOC prior to the subject signing of informed consent may be submitted as screening assessment, if imaging is performed within 21 days of the first dose of GEN3009, and all other requirements for imaging are met.
d. CLL/SLL subjects and lymphoma subjects with bone marrow involvement: fresh bone marrow biopsy and aspirate are required. Prior bone marrow biopsy samples done within 4 weeks) before Cycle 1 Day 1 are acceptable. Fresh bone marrow aspirate is mandatory at screening.
e. Physical examination and clinical laboratory tests may be performed within 1 day prior to GEN3009 dosing.
f. On GEN3009 administration days in Cycle 1, vital signs are to be obtained: 1) Before administration, 2) 15 minutes (± 5 minutes) after administration and 3) every 30 minutes (±5 minutes) during the 2-hour postdose observation period.
g. In triplicate, 5 minutes (± 5 minutes) apart, before GEN3009 administration and 1-2 hours (± 15 minutes) after administration.
h. All AEs must be reported from the first GEN3009 dose until 30 days after the last dose. Medical conditions that occur after the ICF is signed and prior to first GEN3009 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
i. HIV testing is required at screening only if required per local health authotites or institutional standards.
j. At dose levels ≥CCI mg, the first dose of GEN3009 can be split into 2 consecutive days (ie, CCI mg at C1D1 and remaining amount at C1D2) after approval of the sponsor's medical monitor.

Table 6 Visit Assessment Schedule from Cycle 2 and Beyond – Expansion GEN3009 Monotherapy

Treatment Cycle: 28-day cycle	**Section**	**Cycle 2-3**						**Cycle 4-9**		**Cycle 10 And Beyond**	**Unscheduled**	**Treatment Discontinuation Visit[a]**	**Safety Follow-up Visit[a]**	**Survival Follow-up Visit[b]**
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**15d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**30 days after last dose**	**Every 12 weeks after last dose**
Visit window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**±2d**	**±2d**		**+7d**	**+14d**	**±14d**
Body Weight	9.3.1	X		X		X	X	X	X	X	X	X		
Physical Examination (including lymph node assessment)[c]	9.3.1	X						X		X	X	X		
Vital Signs	9.3.2	X[d]		X[d]		X[d]	X[d]	X[d]	X[d]	X[d]	X	X		
ECG (in triplicate)	9.3.3	X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X		
ECOG Performance Status	9.3.4	X						X		X	X	X		
Constitutional Symptoms	9.3.5	X						X		X	X	X		
Adverse Events[f]	10	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	
Premedication prior to GEN3009 administration	6.2	X		X		X	X	X	X	X				
GEN3009 Administration	6.4.1	X		X		X	X	X	X	X				
New Anti-Cancer Treatment													X	X
Survival Status	9.3.6												X	X
EFFICACY ASSESSMENTS														
FDG-PET/CT/MRI	9.2.2.1	X[g]												

Treatment Cycle: 28-day cycle	**Section**	**Cycle 2-3**						**Cycle 4-9**		**Cycle 10 And Beyond**	**Unscheduled**	**Treatment Discontinuation Visit[a]**	**Safety Follow-up Visit[a]**	**Survival Follow-up Visit[b]**
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**15d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**30 days after last dose**	**Every 12 weeks after last dose**
Visit window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**±2d**	**±2d**		**+7d**	**+14d**	**±14d**
Lymphoma with bone marrow involvement and CLL: Unilateral bone marrow biopsy and aspirate	9.2.2.2	X (at time of CR and clinically indicated)												
LABORATORY ASSESSMENTS														
Hematology: complete blood count with differential[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Biochemistry[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Coagulation[c]	9.4.1	X	X	X	X	X	X	X	X	X	X	X		
Immunoglobulins (IgA, IgG, IgM)	9.4.1	X						X		X		X		
Urinalysis[c]	9.4.1	X						X		X	X	X		
Pregnancy Test (either urine or serum)	9.4.1	X						X		X	X	X	X	
Hepatitis B and C Serology	9.4.1											X[h]		

a. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days after the last dose of GEN3009. If the subject initiates new anti-lymphoma therapy within 4 weeks of the last dose of GEN3009, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
b. Subjects will enter the survival follow-up after completion of the safety follow-up or if new anti-cancer treatment has been started. Survival follow-up contact may be performed as a telephone call, email, or on-site visit.
c. Physical examination and clinical laboratory tests may be performed within 1 day prior to GEN3009 dosing.
d. On dosing days, vital signs are performed predose and postdose, and more frequently at the discretion of the investigator. If the subject has stable vital signs and no other issues, the subject may be discharged from the clinic after all assessments are completed as required by protocol. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions occur following discharge from the clinic.
e. In triplicate, 5 minutes apart (± 5 minutes), before GEN3009 administration and 1-2 hours (± 15 minutes) after administration. During Cycle 4 and for all subsequent cycles, ECGs are required at predose only. During an unscheduled visit, ECG is performed only if clinically indicated.
f. All AEs must be reported from the first GEN3009 dose until 30 days after the last dose. If the subject initiates new anti-lymphoma therapy within 30 days of the last dose of GEN3009, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.

g. Refer to Section 9.2.2.1 for imaging requirements.
h. Only for subjects with positive serology.

Table 7 Visit Assessment Schedule for PK and ADA– Expansion GEN3009 Monotherapy

Treatment Cycle: 28-day cycle	**Section**	**Cycle 1**								
Day		**1d**	**2d**	**4d**	**8d**	**9d**	**15d**	**16d**	**22d**	**23d**
Visit window										
Predose (-30 minutes)	9.5, 9.6	ADA/PK	PK[c]		PK		PK		PK	
End of infusion[a] (+5 minutes)		PK	PK[c]		PK		PK		PK	
End of infusion +2 hours (+1 hour)		PK[b]	PK[c]							
End of infusion +24 hours (±2 hours)			PK[b]							
End of infusion +72 hours (±24 hours)[d]				PK						

Treatment Cycle: 28-day cycle	**Section**	**Cycles 2 and 3**				**Cycles 4-9**		**Cycle 10 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit**
Day		**1d**	**8d**	**15d**	**22d**	**1d**	**15d**	**1d**		
Visit Window			**+2d**	**+2d**	**+2d**	**+3d**	**±3d**	**±4d**		
Predose (-30 min)	9.5, 9.6	ADA[e]/ PK	PK	PK	PK	ADA[e]/ PK	PK	ADA[e]/ PK		
End of infusion[a] (+5 min)		PK								
Unscheduled Visit									ADA/ PK	ADA/ PK

Note: Sample collection timing may be modified during the trial based on emerging data.
a. After flush.
b. Only in case of full infusion on Day 1.
c. Only in case of split dose between Day 1 and Day 2.
d. In case of split dose between Day 1 and Day 2, the Day 4 sample will be 48 hours after the complete infusion.
e. Even cycles only.

Table 8 Visit Assessment Schedule for Biomarkers – Expansion GEN3009 Monotherapy

Treatment Cycle: 28-day cycle	**Section**	**Cycles 1 and 2**								
Day		**Screening**	**1d**	**2d**	**2d+2h**	**4d**	**8d**	**15d**	**16d**	**22d**
Visit window										
Tumor biopsy	9.7/9.8.2	X[a]						X[b,f]		
Cytokines	9.8.3.2		X[c]					X[c]		
Complement	9.8.3.3		X[c]	X[d,h]	X[d,i]			X[c]	X[d]	
Immunophenotyping	9.8.3.1		X[c]	X[d,h]		X[d,i]		X[c]	X[d]	
PBMC	9.8.3.1		X[c]				X[c,d]	X[c,d]		X[c,d]
Saliva DNA	9.8.3.4	X								
ctDNA/MRD plasma	9.8.3.4/9.2.2.3		X[c]					X[c,f]		

Treatment Cycle: 28-day cycle	**Section**	**Cycle 3**		**Cycle 4-9**		**Cycle 10 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit**
Day		**1d**	**15d**	**1d**	**15d**	**1d**		
Visit window			**+2d**	**+3d**	**±3d**	**±4d**		
Tumor biopsy	9.7/9.8.2							X[b]
Cytokine	9.8.3.2						X	
Complement	9.8.3.3			X[e]	X[e]	X[e]	X	X
Immunophenotyping	9.8.3.1	X[c]	X[c]	X[c,e]	X[c,e]	X[c,e]	X	
PBMC	9.8.3.1			X[c,e]			X	X
Saliva DNA	9.8.3.4							
ctDNA/MRD plasma	9.8.3.4/9.2.2.3	X[c]		X[c,g]		X[c,g]	X	

a. Fresh lymph node biopsy (to be taken from patients with easily accessible lesions) or an archival lymph node biopsy (formalin-fixed paraffin-embedded [FFPE], which is taken after most recent therapy prior to enrollment and taken within 6 months of Cycle 1 Day 1) is mandatory for lymphoma, SLL and CLL. Baseline biopsy samples are requested to be submitted by C1D1.

b. Unless otherwise agreed with sponsor's medical monitor or delegate, a fresh core biopsy is to be taken from patients with easily accessible lesions in Cycle 2 (Week 6) and at the End of Treatment visit.
c. If the visit occurs on an infusion day, the sample must be taken before IMP treatment (-30 minutes).
d. Cycle 1 only.
e. Samples in even cycles only, starting Cycle 4.
f. Cycle 2 only.
g. Samples to be taken C5, C7, C10 and C13 only. After C13 a sample will be obtained every 6 months (±1 month) for up to 3 years.
h. Only in case of full infusion on Day 1
i. Only in case of split dose between Day 1 and Day 2

Table 9 Visit Assessment Schedule for MRD – Dose Escalation and Expansion GEN3009 Monotherapy

	Cycles 1, 2, 3, 5, 7, and 10	Cycle 13 and onward
Day or Time post dose (window)	Day 1 (+2 days)	Day 1 (+2 days)
Whole blood MRD[a]	X	A whole blood sample will be obtained every 6 months (±1 month) for up to 3 years
Bone marrow aspirate MRD	• For CLL, SLL and B-cell NHL subjects with bone marrow involvement at baseline: If a subject is in CR by imaging, a portion of the aspirate collected to confirm CR will be used to assess MRD. • For B-cell NHL subjects with no bone marrow involvement at baseline, no bone marrow examination for MRD is required. • If a subject is MRD-positive in the bone marrow but maintains CR, an additional bone marrow aspirate will be collected after 3 months, if clinically feasible.	

a. Upon reaching CR on PET-CT scan, an additional blood sample will be collected if not within 2 weeks of another collection to evaluate MRD.

Table 10 Visit Assessment Schedule for Screening and Cycle 1 Expansion GEN3009 + GEN3013 (including Safety Run-in)

Treatment Cycle: 28-day cycle	**Section**	**Screening**	**Cycle 1**											
Day		**≤ 21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8da**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
Informed Consent	13.2.3	X (before any trial-specific procedures)												
Eligibility Criteria	5.1, 5.2	X												
Demographics	9.1.1	X												
Disease Status: Includes diagnosis and staging criteria	9.1.2	X												
Medical History[b]	9.1.3	X	X											
Prior Anti-neoplastic Therapy	9.1.5	X												
DLBCL Molecular Status	9.4.1	X												
FDG-PET CT/CT/MRI[c]	9.2.2.1	X												
Lymphoma with Bone Marrow Involvement: Unilateral bone marrow biopsy and aspirate[d]	9.2.2.2	X												
MRI/CT Scan and Lumbar Puncture (brain)[i]	9.2.2.1	X												
Height	9.3.1	X												
Body Weight	9.3.1	X	X			X			X			X		
Physical Examination (including lymph node assessment)[e]	9.3.1	X	X			X			X			X		
Neurotoxicity Syndrome Assessment	9.3.1.1	X	X			X	X	X	X	X	X	X	X	X
Vital Signs	9.3.2	X	X[f]	X[f]	X	X[f]	X	X	X[f]	X		X[f]	X	
ECG (in triplicate)	9.3.3	X	X[g]	X[g]		X[g]			X[g]			X[g]		
ECOG Performance Status	9.3.4	X	X											
Constitutional Symptoms	9.3.5	X	X			X			X			X		

Treatment Cycle: 28-day cycle	**Section**	**Screening**	**Cycle 1**											
Day		**≤ 21 days prior to C1D1**	**1d[a]**	**2d**	**4d**	**8da**	**9d**	**11d**	**15d[a]**	**16d**	**18d**	**22d[a]**	**23d**	**25d**
Visit Window					**±1d**	**±1d**		**±1d**	**±1d**			**±1d**		
Adverse Events[h]	10	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X
Premedication & CRS Prophylaxis	6.2		X	X[k]		X			X			X		
GEN3009 Administration	6.4.2		X	X[k]		X			X			X		
GEN3013 Administration	6.4.2					X			X			X		
Hospitalization												X		
LABORATORY ASSESSMENTS														
Hematology: Complete blood count and differential count[e]	9.4.1	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative Lymphocyte Subsets	9.4.1	X												
Biochemistry	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Tumor Lysis Syndrome Panel			X	X	X	X	X	X	X	X		X	X	X
Coagulation	9.4.1	X	X	X	X	X	X	X	X	X		X	X	
Immunoglobulins (IgA, IgE, IgG, IgM)	9.4.1	X												
Urinalysis	9.4.1	X	X			X								
Serum β2-microglobulin	9.4.1	X												
Pregnancy Test (serum)	9.4.1	X												
Pregnancy Test (either urine or serum)	9.4.1		X											
HIV Serology[j]		X												
Hepatitis B and C Serology	9.4.1	X												
Cytomegalovirus (CMV) Serology	9.4.1	X												

a. Subjects must remain at the clinic for at least 2 hours for observation following GEN3009 administration. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions and/or CRS (eg, fever, lightheadedness, shortness of breath, etc) occur following discharge from the 2-hour observation period. Observation of up to 24 hours postdose during Cycle 1 is permissible at the discretion of the investigator. All subjects must be hospitalized for CRS monitoring for at least 24 hours after the third dose (first full dose) of GEN3013 (ie, 48 mg) at C1D22.
b. Any medical condition (ie, signs, symptoms and diagnosis) occurring prior to the first GEN3009 dose should be recorded as medical history.
c. Refer to Section 9.2.2.1 for imaging requirements. Imaging assessments performed as SOC prior to the subject signing of informed consent may be submitted as screening assessment, if imaging is performed within 21 days of the first dose of GEN3009, and all other requirements for imaging are met.
d. Lymphoma subjects with bone marrow involvement: fresh bone marrow biopsy and aspirate are required. Prior bone marrow biopsy samples done within 4 weeks before Cycle 1 Day 1 are acceptable. Fresh bone marrow aspirate is mandatory at screening.
e. Physical examination may be performed within 1 day prior to GEN3009 dosing. Refer to Section 9.4.1 for timing of laboratory assessments.
f. On GEN3009 administration days in Cycle 1, vital signs are to be obtained: 1) Before administration, 2) 15 minutes (± 5 minutes) after administration and 3) every 30 minutes (± 5 minutes) during the 2-hour postdose observation period.
g. In triplicate, 5 minutes (± 5 minutes) apart, before GEN3009 administration and 1-2 hours (± 15 minutes) after administration.
h. All AEs must be reported from the first GEN3009 dose until 30 days after the last dose (refer to Table 6 for details on the safety follow-up visit). Medical conditions that occur after the ICF is signed and prior to first GEN3009 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
i. MRI/CT scan of the brain is mandatory during screening within 21 days of C1D1. Lumbar puncture is required only if clinically indicated and required within 21 days of C1D1.
j. HIV testing is required at screening only if required per local health authorities or institutional standards
k. At dose levels >=CCI mg, the first dose of GEN3009 can be split into 2 consecutive days (ie, CCI mg at C1D1 and remaining amount at C1D2) after approval of the sponsor's medical monitor.

Table 11 Visit Assessment Schedule from Cycle 2 and Beyond – Expansion GEN3009 + GEN3013 (including Safety Run-in)

Treatment Cycle 28-day cycle	**Section**	**Cycle 2-3**						**Cycle 4 -12**	**Cycle 13 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit[a]**	**Safety Follow-up Visit[a]**	**Survival Follow-up Visit[b]**
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**60 days after last dose**	**Every 12 weeks after last dose**
Visit Window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**+7d**		**+7d**	**+14d**	**±14d**
Body Weight	9.3.1	X		X		X	X	X	X	X	X		
Physical Examination (including lymph node assessment)[c]	9.3.1	X						X	X	X	X		
Neurotoxicity Syndrome Assessment	9.3.1.1	X		X		X	X	X	X	X	X		
Vital Signs	9.3.2	X[d]		X[d]		X[d]	X[d]	X[d]	X	X	X		
ECG (in triplicate)	9.3.3	X[e]		X[e]		X[e]	X[e]	X[e]		X[e]	X		
ECOG Performance Status	9.3.4	X						X	X	X	X		
Constitutional Symptoms	9.3.5	X						X	X	X	X		
Adverse Events[f]	10	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication and Procedures	9.1.4	X	X	X	X	X	X	X	X	X	X	X	
Premedication & CRS Prophylaxis	6.2	X		X		X	X	X	X				
GEN3009 Administration	6.4.2	X		X		X	X	X					
GEN3013 Administration	6.4.2	X		X		X	X	X	X[g]				
New Anti-cancer Treatment												X	X
Survival Status	9.3.6											X	X
EFFICACY ASSESSMENTS													

Treatment Cycle 28-day cycle	Section	Cycle 2-3						Cycle 4 -12	Cycle 13 and Beyond	Unscheduled	Treatment Discontinuation Visit[a]	Safety Follow-up Visit[a]	Survival Follow-up Visit[b]
Day		**1d**	**4d**	**8d**	**11d**	**15d**	**22d**	**1d**	**1d**	**--**	**As soon as possible after withdrawn from treatment**	**60 days after last dose**	**Every 12 weeks after last dose**
Visit Window		**±2d**		**±2d**		**±2d**	**±2d**	**±2d**	**+7d**		**+7d**	**+14d**	**±14d**
FDG-PET/CT/MRI	9.2.2.1	X[h]											
Lymphoma with Bone Marrow Involvement: Unilateral bone marrow biopsy and aspirate	9.2.2.2	X (at time of CR and clinically indicated)											
LABORATORY ASSESSMENTS													
Hematology: Complete blood count with differential[c]	9.4.1	X	X	X	X	X	X	X	X	X	X		
biochemistry	9.4.1	X	X	X	X	X	X	X	X	X	X		
Coagulation	9.4.1	X	X	X	X	X	X	X	X	X	X		
Immunoglobulins (IgA, IgE, IgG, IgM)	9.4.1	X						X	X		X		
Urinalysis	9.4.1	X						X	X	X	X		
Pregnancy Test (either urine or serum)	9.4.1	X						X	X	X	X	X	
Hepatitis B and C Serology	9.4.1										X[i]		

a. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 60 days after the last dose of GEN3009 and/or GEN3013. If the subject initiates new anti-lymphoma therapy within 60 days of the last dose of GEN3009 and/or GEN3013, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
b. Subjects will enter the survival follow-up after completion of the safety follow-up or if new anti-cancer treatment has been started. Survival follow-up contact may be performed as a telephone call, email, or on-site visit.
c. Physical examination may be performed within 1 day prior to GEN3009 dosing. Refer to Section 9.4.1 for timing of laboratory assessments.
d. On dosing days, vital signs are performed predose and postdose, and more frequently at the discretion of the investigator. If the subject has stable vital signs and no other issues, the subject may be discharged from the clinic after all assessments are completed as required by protocol. Subjects must be instructed to contact the investigator should signs or symptoms of infusion-related reactions and/or CRS (eg, fever, lightheadedness, shortness of breath, etc.) occur following discharge from the clinic.

e. In triplicate, 5 minutes apart (± 5 minutes), before GEN3009 administration and 1-2 hours (± 15 minutes) after administration. During Cycle 4 and for all subsequent cycles, ECGs are required at predose only. During an unscheduled visit, ECG is performed only if clinically indicated.
f. All AEs must be reported from the first GEN3009 dose until 60 days after the last dose. If the subject initiates new anti-lymphoma therapy within 60 days of the last dose of GEN3009 and/or GEN3013, the safety follow-up visit should be performed prior to starting new anti-cancer therapy.
g. After completion of Cycle 12, subjects who are in SD or better will have the option to continue receiving GEN3013 every 4 weeks until any discontinuation criteria is met.
h. Refer to Section 9.2.2.1 for imaging requirements.
i. Only for subjects with positive serology.
j. Even cycles only.

Table 12 Visit Assessment Schedule for PK and ADA – Expansion GEN3009 + GEN3013 (including Safety Run-in)

Treatment Cycle: 28-day cycle	**Section**	**Cycle 1**									
Day		**1d**	**2d**	**4d**	**8d**	**9d**	**15d**	**16d**	**18d**	**22d**	**23d**
Visit Window											
Predose (-30 min)	9.5, 9.6	ADA: 09 and 013 / PK: 09 only	PK: 09 only[c]		PK: 09 and 13		PK: 09 and 13			PK: 09 and 13	
Start of GEN3013 Injection +1 hour (+15 min)							PK: 13 only			PK: 13 only	
End of GEN3009 infusion[a] (+5 min)		PK: 09 only	PK: 09 only[c]		PK: 09 only		PK: 09 and 13			PK: 09 and 13	
End of GEN3009 infusion +2 hours (+1 hour)		PK: 09 only[b]	PK: 09 only[c]								
End of GEN3009 Infusion +24 hours (±2 hours)			PK: 09 only[b]					PK: 13 only			PK: 13 only
End of GEN3009 Infusion +72 hours (±24 hours)[d]				PK: 09 only					PK: 13 only		

Treatment Cycle: 28-day cycle	**Section**	**Cycle 2**								
Day		**1d**	**2d**	**4d**	**8d**	**9d**	**15d**	**16d**	**22d**	**23d**
Visit Window										
Predose (-30 min)	9.5, 9.6	ADA/PK: 09 and 13			PK: 09 and 13		PK: 09 and 13		PK: 09 and 13	
Start of GEN3013 injection +1 hour (+15 min)		PK: 13 only								
End of GEN3009 infusion +5 min[a] (+5 min)		PK: 09 and 13								
End of GEN3009 infusion +2 hours (+1 hour)		PK: 09 only								
End of GEN3009 Infusion +24 hours (±6 hours)			PK: 09 and 13							
End of GEN3009 Infusion +72 hours (±24 hours)				PK: 09 and 13						

Treatment Cycle: 28-day cycle	**Section**	**Cycle 3**	**Cycle 4-12**	**Cycle 13 and Beyond**	**Unscheduled**	**Treatment Discontinuation Visit**

Day		**1d**	**8d**	**15d**	**22d**	**1d**	**1d**		
Visit Window			**+2d**	**+2d**	**+2d**	**±4d**	**+7d**		
Predose (-30 min)	9.5, 9.6	ADA/PK: 09 and 13	PK: 09 and 13	PK: 09 and 13	PK: 09 and 13	ADA[c]/PK: 09 and 13	ADA[c]		
Start of GEN3013 injection +1 hour (+15 min)									
End of GEN3009 Infusion +5 min[a] (+5 min)		PK: 09 only							
Unscheduled Visit								PK: 09 and 13	PK: 09 and 13

Note: Sample collection timing may be modified during the trial based on emerging data.
09=GEN3009; 13=GEN3013.

a. After flush.
b. Only in case of full infusion on Day 1.
c. Only in case of split dose between Day 1 and Day 2.
d. In case of split dose between Day 1 and Day 2, the Day 4 sample will be 48 hours after the complete infusion.
e. Even cycles only.

Table 13 Visit Assessment Schedule for Biomarkers – Expansion GEN3009 + GEN3013 (including Safety Run-in)

Treatment Cycle: 28-day cycle	**Section**	**Cycles 1 and 2**										
Day		**Screening**	**1d**	**2d**	**2d+2h**	**4d**	**8d**	**15d**	**16d**	**22d**	**22d+6h**	**23d**
Visit Window							**+2d**	**+2d**		**+2d**	**+8h**	
Tumor Biopsy	9.7/ 9.8.2	X[a]	X[b,f]									
Cytokines	9.8.3.2		X[c]				X[c,d]	X[d,h]		X[c,d]	X[d]	X[d]
Complement	9.8.3.3		X[c]	X[d,i]	X[d,j]			X[c, d]	X[d]			
Immunophenotyping	9.8.3.1		X[c]	X[d,i]		X[d,j]	X[c,d]	X[c]		X[c,d]		X[d]
PBMC	9.8.3.1		X[c]				X[c,d]	X[c,d]		X[c]		
Saliva DNA	9.8.3.4	X										
ctDNA/MRD Plasma	9.8.3.4/ 9.2.2.3		X[c]									

Treatment Cycle	**Section**	**Cycle 3**		**Cycles 4-12**	**Unscheduled**	**Treatment DiscontinuationVisit**
Day		**1d**	**15d**	**1d**		
Visit Window			**+2d**	**±4d**		
Tumor Biopsy	9.7 /9.8.2					X[b]
Cytokine	9.8.3.2	X[c]			X	
Complement	9.8.3.3			X[c,e]	X	X
Immunophenotyping	9.8.3.1	X[c]	X[c]	X[c,e]	X	
PBMC	9.8.3.1			X[c,e]	X	X
Saliva DNA	9.8.3.4					

ctDNA/MRD Plasma	9.8.3.4/ 9.2.2.3	X[c]		X[c,g]	X	

a. Fresh lymph node biopsy (to be taken from patients with easily accessible lesions) or an archival lymph node biopsy (formalin-fixed paraffin-embedded, which is taken after most recent therapy prior to enrollment and taken within 6 months of Cycle 1 Day 1) is mandatory for lymphoma.
b. Unless otherwise agreed with sponsor's medical monitor or delegate, a fresh core biopsy is to be taken from patients with easily accessible lesions in Cycle 2 and at the End of Treatment visit.
c. If the visit occurs on an infusion day, the sample must be taken before IMP treatment(s) (-30 minutes).
d. Cycle 1 only.
e. Samples in even cycles only, starting Cycle 4.
f. Cycle 2 only.
g. Samples to be taken C5, C7, C10 and C13 only. After C13 a sample will be obtained every 6 months (±1 month) for up to 3 years.
h. Sample to be taken during Safety Run-in only.
i. Only in case of full infusion of GEN3009 on Day 1
j. Only in case of GEN3009 split dose between Day 1 and Day 2

Table 14 Visit Assessment Schedule for MRD – Expansion GEN3009 + GEN3013

Cycle	**Cycles 1, 2, 3, 5, 7, and 10**	**Cycle 13 and onward**
Day or Time post dose (window)	Day 1 (+2 days)	Day 1 (+2 days)
Whole blood MRD[a]	X	A whole blood sample will be obtained every 6 months (±1 month) for up to 3 years
Bone marrow aspirate MRD	• For B-cell NHL subjects with bone marrow involvement at baseline: If a subject is in CR by FDG-PET, a portion of the aspirate collected to confirm CR will be used to assess MRD. • For B-cell NHL subjects with no bone marrow involvement at baseline, no bone marrow examination for MRD is required. • If a subject is MRD-positive in the bone marrow but maintains CR, an additional bone marrow aspirate will be collected after 3 months, if clinically feasible.	

a. Upon reaching CR on PET-CT scan, an additional blood sample will be collected if not within 2 weeks of another collection to evaluate MRD.

Table 15 GEN3013 Repriming Cycle – Expansion GEN3009 + GEN3013 (including Safety Run-in)

	Day 1	Day 8	Day 15	Day 22
Body Weight	X		X	
Complete physical examination	X			
Lymph node examination	X			
Neurological Evaluation (ICANS)[b]	X	X	X	X
Vital signs[c]	X	X	X	X
12-Lead ECG (triplicate)	X			
ECOG Performance Status	X			
Constitutional Symptoms (ie, B Symptoms)	X		X	
Adverse Events	X	X	X	X
Previous and concomitant medications	X	X	X	X
Concomitant procedures	X	X	X	X
STUDY TREATMENT ADMINISTRATION				
Hospitalization[d]			X	
Premedications[e]	X	X	X	X
CRS prophylaxis[f]	X	X	X	X
GEN3013 administration	X	X	X	X
LOCAL LABORATORY ASSESSMENTS				
Hematology	X		X	
Biochemistry	X		X	
Coagulation	X		X	
Immunoglobulins (IgA, IgE, IgG, gM)	X			
Urinalysis	X			
Pregnancy Test (urine or serum)[g]	X			
TLS Monitoring	X			
CENTRAL LABORATORY ASSESSMENTS				
Immunophenotyping (by flow cytometry)	X[h]	X[h]	X[h]	X
Pharmacokinetics (GEN3009 and GEN3013)	X[h]	X[h,i]	X[h,i]	X[h,i]
Anti-drug antibodies	X[h]			

a. Once the full repriming cycle is completed, the subject should resume treatment with Day 1 of the next planned cycle (subsequent to the cycle during which the dosing was delayed); see Section 7.4.2.2.
b. ICANS evaluation, based on (Lee et al., 2019), must also be performed in the presence of CRS-type symptoms or any neurological signs/symptoms.
c. Vital sign assessment must be conducted before dosing and 1 hr (±30 min) following each dose

d. Subjects are to be hospitalized for at least 24 hours after the third (full dose) administration of GEN3013 in a repriming cycle. Additional or longer hospitalization should be per the investigator's discretion.
e. Premedication should be administered 30 min to 2 hours before administration of GEN3013.
f. CRS prophylaxis consists of prednisolone 100 mg (or alternative steroid equivalent) daily for Days 1-4, 8-11, 15-18, and 22-25 of a repriming cycle. On GEN3013 dosing days, corticosteroid should be given 30 min to 2 hrs prior to GEN3013 injection. See also Section 6.2.2.
g. Results must be available before dosing.
h. Predose only.
i. PK sample for GEN3009 only if dosed weekly.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Disease

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of lymphoid malignancies that originate from B-cell lymphocytes, T-cell lymphocytes, and natural killer (NK) cells. In the US, an estimated 74,200 new cases of NHL will be diagnosed in 2019 with 19,970 deaths expected (SEER, 2019). Approximately 85-90% of NHLs are derived from B cells (B-cell NHL). According to the World Health Organization 2016 classification of lymphoid neoplasm (Swerdlow et al., 2016), B-cell NHL subtypes including diffuse large B cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), mantle cell lymphoma (MCL), primary mediastinal large B-cell lymphoma (PMBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), etc, are categorized as mature B-cell neoplasms.

2.1.1.1 Therapy for DLBCL

DLBCL is the most common aggressive lymphoma representing 30-35% of all NHL cases (Ghielmini et al., 2013). Although the majority of DLBCL patients can be cured with combinational immuno-chemotherapy (ie, rituximab plus doxorubicin-based combination chemotherapy, R-CHOP), approximately one-third of patients will develop relapsed or refractory (R/R) disease. It is known DLBCL patients with high-risk features (eg, double-hit lymphoma, transformed lymphomas, or early relapse) will become refractory to standard therapies and will have limited alternatives for cure.

For patients with R/R DLBCL, approximately 60% remain sensitive to conventional second-line immunochemotherapy; and these patients can undergo subsequent high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplantation (HSCT) and achieve long-term survival (Gisselbrecht et al., 2010; Sehn et al., 2012). On the contrary, R/R DLBCL patients who do not respond to second-line immunochemotherapy only have a life expectancy of 3 to 4 months (Elstrom et al., 2010; Friedberg, 2011). Due to advanced age and/or comorbidities only half of R/R DLBCL patients are eligible for HDT-HSCT. For transplant-eligible candidates who have failed second-line therapy or whose disease has relapsed post-transplantation, the prognosis is dismal. Recently, CD19-directed chimeric antigen receptor (CAR) T cell therapies (ie, KYMRIAH®, YESCARTA®) have revolutionized the treatment of refractory B-cell lymphoid malignancies and demonstrated durable remissions in R/R large B-cell lymphomas including DLBCL, HGBCL, and PMBCL (Locke et al., 2019; Schuster et al., 2019). However, potentially life-threatening toxicities including cytokine release syndrome (CRS) and neurotoxicity, extended production time precluding patients with rapidly progressing disease, and high-treatment expense have limited the access. Taken together, most patients with R/R DLBCL cannot expect to be cured with secondary therapies and a new investigational therapy with manageable toxicities is needed.

2.1.1.2 Therapy for FL

FL is the most common subtype of indolent NHL and accounts for 22-25% of all new diagnoses. Although indolent in nature and often responding to the initial treatment, FL of advanced stage is

incurable with frequent relapses. In advanced, symptomatic FL, first-line treatment is anti-CD20 monoclonal antibodies (ie, rituximab or obinutuzumab) in combination with multi-agent chemotherapy. HSCT is typically reserved for patients with relapsed disease (Cheson et al., 2014; NCCN, 2019). Although the current treatments are initially effective in inducing responses in most patients, they are not curative and show decreasing efficacy with increasing lines of therapy.

In relapsed FL, treatment in patients with late relapse (>2 years; 80%) is reinduction by salvage treatment with rituximab-containing chemotherapy followed by rituximab maintenance therapy for 2 years. Irrespective of first-line treatment choice, early relapse occurs in 20% within 24 months and is a robust predictor of poorer overall survival (OS), with only 34-50% of patients being alive at 5 years. Second-line treatments include lenalidomide with rituximab (Andorsky et al., 2016; Leonard et al., 2019), polatuzumab vedotin with rituximab (Morschhauser et al., 2019), idelalisib for double-refractory cases (Gopal et al., 2014a; Gopal et al., 2017), and allogeneic HSCT in selected fit patients. Finally, bispecific antibodies targeting CD3 and CD20 may represent an attractive treatment as preliminary data have shown high response rates in R/R FL with acceptable toxicity profiles (Dickinson et al., 2019; Topp et al., 2019). In summary, early relapsed FL represents a particular unmet medical need; treatment options are limited for patients who have failed several lines of therapy.

2.1.1.3 Therapy for CLL

CLL is the most common leukemia in adults in Western countries, accounting for approximately 25% to 30% of all leukemias in the US with estimated 20,720 new cases and 3,930 deaths (Siegel et al., 2019). Worldwide, there are approximately 105,000 cases per year, of which 35,000 are deaths (Global Burden of Disease Cancer et al., 2018).

Most patients with newly diagnosed CLL present with asymptomatic disease and can be monitored without therapy until disease progression. For symptomatic or high-risk disease, standard of care includes cytotoxic chemotherapy (fludarabine, cyclophosphamide, bendamustine, and chlorambucil) in combination with anti-CD20 monoclonal antibodies (ie, rituximab or obinutuzumab) (Hallek et al., 2010); (Goede et al., 2014). Although bendamustine plus rituximab (BR) had shorter median progression-free survival (PFS) as compared to fludarabine, cyclophosphamide, plus rituximab (FCR) (Eichhorst et al., 2016), BR regimen can be an alternative first-line treatment for physically fit older patients (>65 years) due to decreased toxicity. Recently, kinase inhibitors ibrutinib and idelalisib have gained considerable momentum as first-line treatment for high-risk CLL with TP53 aberrations (O'Brien et al., 2016; Sharman et al., 2014). Ibrutinib demonstrated improved objective response rate (ORR) (86% vs 35%), 2-year PFS (89% vs. 34%) and 2-year OS (98% vs. 85%) as compared to chlorambucil (Burger et al., 2015). Subsequently, 2 large Phase 3 studies comparing ibrutinib alone or with rituximab to BR (older patients ≥65 years) or FCR (younger patients <65 years) in the front-line setting were conducted. Although both studies showed the ibrutinib rituximab combination was superior to BR and FCR with longer PFS, a notable lack in the ability of ibrutinib to induce complete response (CR) and minimal residual disease (MRD)-negative remissions were observed: 30% CR, with MRD-negative in 59% on FCR and 8% on BR; whereas ibrutinib-containing regimens on these trials, the CR rates were <20% with <10% of patients achieved MRD negativity in the peripheral blood (Woyach et al., 2018). Most recently, in an international Phase 3 CLL14 study, the combination of venetoclax and obinutuzumab was compared to chlorambucil and obinutuzumab in patients with untreated CLL with medical comorbidities; a superior 2-year PFS rate of 88% over 64% was observed (Fischer et al., 2019).

In R/R CLL, a Phase 3 study comparing the combination of venetoclax and rituximab to BR has shown very encouraging activity: 2-year PFS 85% vs. 36% with BR. This PFS improvement was observed across all high-risk groups including patients with del(17p) karyotype. There was also an impressive ORR of 92% with 84% achieving MRD-negative status in the peripheral blood (Seymour et al., 2018). Preliminary data from a Phase 1 study showed the doublet of venetoclax and obinutuzumab appeared to be highly effective in R/R CLL irrespective of cytogenetic risk factors with an overall best response rate of 95% (CR/CRi, 37%) (Flinn et al., 2019). Overall, in CLL, a new agent that can potentially induce deeper remission with higher percentage of MRD negativity is warranted for further investigations.

2.1.2 Introduction to Investigational Medicinal Products

2.1.2.1 GEN3009

GEN3009 (DuoHexaBody®-CD37) is a bispecific antibody with a hexamerization-enhancing mutation that targets 2 different epitopes of the CD37 antigen (biparatopic binding). GEN3009 was designed to induce highly potent cytotoxicity towards B cells in a variety of B-cell malignancies through enhanced complement-dependent cytotoxicity (CDC) and by FcγR-mediated effector functions including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP).

The bispecific antibody is generated by controlled Fab arm exchange (DuoBody® technology (de Jong et al., 2016; Labrijn et al., 2014) of 2 humanized CD37-specific immunoglobulin G (IgG) molecules that were originally obtained by immunization of rabbits with human and cynomolgus monkey CD37. Introduction of an E430G mutation results in enhanced Fc-Fc–mediated antibody hexamerization on the cell surface (HexaBody® technology) upon CD37 binding, while retaining monomeric properties in solution (de Jong et al., 2016). Moreover, GEN3009 has CMC properties comparable to regular human IgG1 and the HexaBody mutation was shown to have no meaningful impact on nonclinical pharmacokinetic (PK) behavior in absence of target.

Please refer to the GEN3009 Investigator's Brochure (IB) for more detailed information.

2.1.2.2 GEN3013

GEN3013 is a bispecific antibody recognizing the T-cell antigen CD3 and the B-cell antigen CD20. GEN3013 triggers potent T-cell-mediated killing of CD20-expressing cells.

The mechanism of action (MoA) of GEN3013 is engagement of T-cells as effector cells to induce killing of CD20-expressing B-cells and tumor cells. This is a different MoA compared to that of chemotherapy or conventional CD20-targeting monoclonal antibodies that can induce cytotoxicity through Fc-mediated effector functions such as ADCC, ADCP and CDC and in some cases programmed cell death.

GEN3013 is generated using Genmab's DuoBody technology (Labrijn et al., 2013; Labrijn et al., 2014). DuoBody molecules are bispecific antibodies with a regular IgG1 structure and biochemical characteristics typical of human IgG1. Accordingly, DuoBody molecules show normal binding to the neonatal Fc receptor (FcRn), resulting in the relatively long plasma half-life that is typical for IgG1 molecules. The Fc domain of GEN3013 has been modified to silence Fc-mediated effector functions, ensuring that GEN3013 does not activate T cells through Fcγ-mediated CD3 crosslinking. FcRn binding was preserved.

Please refer to the epcoritamab (GEN3013) IB for more detailed information.

2.1.3 Summary of Nonclinical Studies

GEN3009 showed dose-dependent binding to both malignant B cells and normal B cells from healthy donors with minimal binding to other leukocyte populations.

GEN3009 induced potent CDC of malignant B cells in primary samples obtained from patients with DLBCL, FL, and CLL, including patients who had been previously treated with anti-CD20 monoclonal antibodies. GEN3009 CDC activity was superior to that of rituximab, ofatumumab and obinituzumab. The nonclinical anti-tumor activity of GEN3009 was confirmed in vivo in multiple mouse xenograft lymphoma models.

GEN3009 combined with GEN3013 showed increased cytotoxicity in DLBCL derived cell lines in the presence of T cells and normal human serum (CCI). GEN3009 did not affect GEN3013-mediated T-cell activation.

Nonclinical safety assessment of GEN3009 included in vitro studies using human cells and tissues (cytokine release assay, tissue cross-reactivity, hemolytic potential and plasma compatibility assays), which identified no significant safety concerns.

A Good Laboratory Practice (GLP) toxicity study was conducted in cynomolgus monkeys, with 5 weekly intravenous (IV) doses of 3, 10, or 30 mg/kg. Pharmacology was observed at all doses including complement activation/consumption and decreases in CD20+ total B-cells. Adverse observations at ≥10 mg/kg included petechial bleeding after the third dose, and microscopic adrenal findings of cortical hemorrhage, vacuolation and/or degeneration and medullary congestion, which were reversible during a 4-week postdose recovery period. At 30 mg/kg, severe but transient decreases in systolic, diastolic, and mean arterial blood pressure were observed after the fourth dose. Consequently, the highest non-severely toxic dose (HNSTD) following 5 weekly IV administrations was 10 mg/kg.

An integrated evaluation of the data from nonclinical pharmacology, PK, and toxicology studies led to the first-in-human (FIH) starting dose of mg (refer to Section 4.3).

Refer to the IB for more detailed information on GEN3009 nonclinical studies.

2.1.4 Summary of Clinical Trials

2.1.4.1 Clinical Trials for GEN3009

This is the first time GEN3009 is being tested in humans; no prior clinical experience of GEN3009 is available. In this FIH trial of GEN3009 in R/R B-cell NHL, as of the data cut: 11 Jun 11 2021, there were 18 subjects evaluated for dose-limiting toxicities for GEN3009 at doses ranging from mg to CCI mg: mg (N=1), CCI mg (N=1), CCI mg (N=1), CCI mg (N=4), CCI mg (N=4), CCI mg (N=4), and CCI mg (N=3). No dose-limiting toxicity (DLT) was observed. Based on the preliminary safety, PK, biomarker, and efficacy data accumulated, the dose escalation committee (DEC) and safety committee (SC) approved to add additional dose levels (ie, CCI mg and CCI mg) to further assess the safety, tolerability, PK, and biomar of GEN3009 in R/R B-cell NHL.

Among the 18 subjects treated with GEN3009, the most common treatment-emergent adverse events (TEAEs) in ≥ 20% of subjects treated across all dose levels include infusion-related reactions (IRRs) (61.1%); heamatlogical adverse events such as neutropenia (94.4%), leukopenia

(50.0%), lymphopenia (38.9%), thrombocytopenia (38.9%), and anemia (27.8%); and fatigue and fatigue (22.2%) and headache (22.2%). IRR is an adverse event of special interest (AESI) for GEN3009 and mostly occurred during the first infusion and was of Grade 1 or 2 in severity. IRRs are manageable with interruption of the infusion, treatment, and lowering the infusion rate upon resuming the infusion. Neutropenia events were observed in majority of subjects post-GEN3009 infusions; neutrophil counts typically recovered by the next dose of GEN3009 without any clinical consequences.

Preliminary anti-tumor activity has been observed in R/R B-cell NHL subjects with GEN3009 monotherapy including 1 CR in DLBCL at CCI mg; 1 CR in SLL, 1 CR in MZL, and 1 PR in FL at CCI mg.

2.1.4.2 Clinical Trials for GEN3013

There are 5 ongoing trials investigating GEN3013 either as monotherapy or in combination with standard of care. As of 31-Jan-2021, GEN3013 has been tested in a total of 178 subjects with various subtypes of B-cell NHL. In the FIH Phase 1/2 trial (GCT3013-01; NCT03625037), among the 68 subjects with R/R B-cell NHL, no DLT was reported at doses up to 60 mg; the maximum tolerated dose (MTD) was not reached; and the recommended Phase 2 dose (RP2D) was declared to be a full dose of 48 mg. Major safety findings from the Dose Escalation and Expansion parts are summarized as below:

- All 68 subjects in the GCT3013-01 Dose Escalation part experienced at least 1 TEAE; 80.9% of subjects had at least one Grade 3 or higher TEAE. The 4 most common TEAEs were pyrexia (69.1%), CRS (58.8%), injection site reaction (47.1%), and fatigue (44.1%). AESIs occurred in approximately two-thirds of subjects; of these, 40 subjects (58.8%) experienced CRS, 4 subjects (5.9%) experienced neurological symptoms, and 1 subject (1.5%) experienced clinical tumor lysis syndrome (TLS).

  There were 13 subjects with TEAEs leading to death (11 subjects with malignant neoplasm progression, 1 with euthanasia [also in the context of progressive disease], and 1 with COVID-19 pneumonia). Serious adverse events (SAEs) were reported for 67.6% of subjects. The most common SAE considered related to trial drug was pyrexia, which was reported as a symptom of CRS. TEAEs leading to permanent treatment discontinuation were reported in 13.2% of subjects.

- A total of 76 subjects (89.4%) in the GCT3013-01 Dose Expansion part experienced at least 1 TEAE; 40.0% of subjects had at least one Grade 3 or higher TEAE. The most common TEAEs were CRS, fatigue, and pyrexia. There were 7 subjects with TEAEs leading to death (disease progression [1], general physical health deterioration [1], COVID-19 [2], hepatotoxicity [1], malignant neoplasm progression [1], and immune effector cell-associated neurotoxicity syndrome [1]). SAEs were reported for 55.3% of subjects. The most common SAE considered related to trial drug was CRS. TEAEs leading to permanent treatment discontinuation were reported in 5.9% of subjects. AESIs included the following: 40 subjects experienced CRS, 3 subjects experienced ICANS, and 1 subject experienced clinical TLS.

GEN3013 administration induced rapid and sustained depletion of circulating B cells (in the subset of subjects with detectable B cells, which are absent in most patients due to prior anti-CD20 therapy) and increases in peripheral T cells and circulating IFNγ.

No significant anti-drug antibody (ADA, titers >1) against GEN3013 has been observed.

Preliminary anti-tumor activity has been observed in R/R B-cell NHL subjects treated with GEN3013 monotherapy. In the GCT3013-01 Dose Escalation part, the ORR was 44.1% for all dose levels (DLs) combined and 66.7% for the RP2D level (48 mg). GEN3013 is currently being evaluated in multiple expansion cohorts in GCT3013-01 as well as in 4 other global studies.

2.2 Rationale

Over the last 2 decades, the clinical course of B-cell NHL has been changed dramatically by anti-CD20 antibody (eg, rituximab, ofatumumab, obinutuzumab)-containing immunochemotherapies with substantially improved outcome. However, for most R/R lymphomas and CLL, there is still no treatment that can lead to cure. This unmet medical need warrants developing new efficacious therapies for patients with advanced B-cell NHL whose disease no longer responds to standard therapies. Identification of a target other than CD20 such as CD37 may represent an attractive alternative strategy. Furthermore, a chemo-free regimen by combining an anti-CD37 therapy with a T cell- engaging therapy such as a CD3xCD20 bispecific antibody may present an efficacious treatment option for patients who have exhausted SOC.

2.2.1 GEN3009 Monotherapy

Nonclinically, CD37-targeting GEN3009 has demonstrated more potent tumor-cell killing than clinically validated CD20-targeting antibodies across a variety of B-cell NHL subtypes regardless of the relapse status (ie., similar anti-tumor effect observed in ND samples and R/R samples). GEN3009 also showed potent CDC activity in a limited set of primary samples from ibrutinib-treated NHL patients. In addition to these findings, therapeutic activity of GEN3009 was observed in tumor cell line-derived xenografts (ie, DLBCL, Burkitt's lymphoma, and CLL) and patient-derived xenografts (ie., DLBCL).

The aim of this FIH trial is to characterize the safety and tolerability, PK, and pharmacodynamic characteristics of GEN3009 in subjects with R/R B-cell NHL (eg, DLBCL, HGBCL, PMBCL, FL, MCL, MZL, CLL/SLL). In the Dose Escalation, DLTs will be monitored to determine the MTD and/or RP2D for GEN3009. The totality of the data including safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated to guide further development for Expansion. In the Expansion, clinical activity of GEN3009 at the RP2D in R/R DLBCL, R/R FL, and R/R CLL will be assessed together with safety, tolerability, PK, pharmacodynamic, and biomarkers.

2.2.2 GEN3009 + GEN3013 Combination

GEN3013 (DuoBody®-CD3xCD20, epcoritamab) is a fully human IgG1 bispecific antibody that induces potent T cell-mediated cytotoxicity of CD20-expressing cells. Clinical data from an ongoing Phase 1/2 trial (GCT3013-01; NCT03625037) demonstrated that GEN3013 as a single agent induced high ORR with manageable safety profile in heavily pre-treated B-cell NHL including DLBCL and FL (ASH 2020). In the Dose Escalation (N=68), GEN3013 was well tolerated at doses up to 60 mg. RP2D was declared as 48 mg for further development in the Expansion. At 48 mg, the ORR was 70.0% (N=10; 1 FL and 9 DLBCL); among 9 DLBCL subjects, the ORR was 77.8% (3 CR, 4 PR).

Due to the non-overlapping MoAs for GEN3009 and GEN3013, it is hypothesized that the combination of GEN3009 with GEN3013 may induce deeper and durable remissions in R/R B-cell NHL. Nonclinically, GEN3009 combined with GEN3013 showed increased cytotoxicity in DLBCL-derived cell lines in the presence of T-cells and normal human serum.

In the Expansion, the safety and preliminary efficacy of the combination regimen of GEN3009 and GEN3013 in R/R DLBCL will be evaluated.

2.3 Benefit-Risk Assessment

2.3.1 GEN3009 Monotherapy

GCT3009-01 is a FIH trial of GEN3009 in R/R B-cell NHL, and the safety profile for GEN3009 is still being established with limited data collected. However, the benefit-risk profile of GEN3009 appears to be favorable. The trial population is limited to subjects with R/R B-cell NHL who have exhausted standard therapies or are ineligible for standard therapies. The risks to subjects in this trial are being minimized by compliance with the eligibility criteria, trial procedures, with close monitoring, and proper/prompt management of TEAEs.

CD37 is exclusively expressed in hematopoietic lineage cells with a high expression in B cells and a much lower expression on T cells, monocytes, NK cells, and neutrophils. In recent years, several CD37-targeting biologics including otlertuzumab, BI836826, IMGN529, betalutin (^{177}Lu-conjugated lilotumab), and AGS-67E have been developed and evaluated in Phase 1/2a clinical trials in various B-cell NHL (Stathis et al., 2018); (Stilgenbauer et al., 2019); (Witkowska et al., 2018); (Blakkisrud et al., 2017); (Payandeh et al., 2018; Salles, 2019). Findings from these early phase studies indicate manageable safety profiles with majority of adverse reactions being hematological (eg, neutropenia, thrombocytopenia, anemia). IRRs and infections were common TEAEs. Of note, no CRS was reported. Preliminary data showed single-agent activity: betalutin in relapsed indolent B-cell NHL including FL, MCL, and MZL: ORR 69% with 28% being CR (Kolstad et al., 2017); IMGN529 in R/R B-cell NHL: ORR 13% with 4 responders in DLBCL (Stathis et al., 2018); BI836826 in R/R CLL: ORR 35% all being PR (Stilgenbauer et al., 2019). Promising clinical efficacy of otlertuzumab was observed in indolent B-cell NHL when combined with BR (Gopal et al., 2014b) and in relapsed CLL when combined with bendamustine (Robak et al., 2017). Collectively, these data warrant clinical development of CD37-targeting compounds for B-cell NHL.

The expected MoA for GEN3009 include: 1) enhanced CDC activity through Fc-Fc–mediated hexamerization upon binding to CD37 on the target cell surface, and 2) FcγR-mediated effector functions including ADCC activity and ADCP activity.

Toxicology studies in cynomolgus monkeys have shown that GEN3009 was tolerated when administered intravenously at doses 0.1, 1, 3, and 10 mg/kg. MTD was deemed as 3 mg/kg in a GLP study where monkeys received 5 weekly doses and the HNSTD was considered as 10 mg/kg. Major findings from this pivotal GLP repeated-dose toxicity study include:

- B-cell depletions in peripheral blood and lymph nodes at doses ranging from 3 to 30 mg/kg;
- Transient and reversible decrease in lymphocyte, T cell, NK cell and platelet counts at 3, 10, and 30 mg/kg;
- Minimal elevations in cytokines (eg, IL-6, IL-10, and/or MCP-1) occurring shortly after dosing and returning to baseline within 12 to 24 hours which is not indicative of a CRS;
- IRRs were observed after GEN3009 administrations;
- Clinically significant and reversible hypotension observed immediately after infusion at 30 mg/kg;

- Adverse microscopic findings in the adrenal gland at 10 or 30 mg/kg;
- All GEN3009-treated animals tested positive for ADA from Day 15.

TLS is a known risk in the treatment of hematological malignancies and prophylaxis guidelines are provided in Section 6.6.1. Premedication and management for IRRs are provided in Section 6.2. Scheduled blood collections for immunogenicity are provided in Section 9.6.

2.3.2 GEN3009 + GEN3013 Combination

The expected MoA of GEN3013 is activation of the T cells upon binding to CD3, simultaneously with CD20 binding, with release of perforin/granzymes and Fas ligand and lysis of the CD20-expressing target cell. CD20 is exclusively expressed on B-cells, so eradication of cells other than B cells is not expected.

The main risks identified for GEN3013 are CRS and ICANS. ICANS was not a frequent event with GEN3013 (see epcoritamab IB). It was reported that obinutuzumab (anti-CD20 mAb) pretreatment was effective in mitigating the risk of CRS of glofitamab (CD3 × CD20 bispecific antibody in R/R B-cell NHL (Dickinson et al., 2019; Hutchings, 2021). The incidence and severity of CRS caused by GEN3013 are expected to be decreased or downgraded as a result of pretreatment with GEN3009 1 week prior to the combination; 2 additional doses of GEN3009 in concomitant with step-up doses of GEN3013 (ie, priming dose, intermediate dose) followed by clinical active full doses of GEN3013 will further reduce the risk of CRS. Investigators and site staff will be trained for early detection, prophylaxis and management of CRS and ICANS to reduce the frequency or severity of these events. Immediate access to tocilizumab is mandated on site.

Identification of potential risks and the risk mitigation strategies are detailed for epcoritamab (with which GEN3009 will be combined) in Table 16.

Table 16 Potential Risks from Combination Treatment

Potential Risk	Risk Mitigation
IRR (including injection site reactions)	• Premedication prior to GEN3009 and/or GEN3013 is mandated in all cycles as described in Section 6.2.2. • Instructions are provided for appropriate management of IRRs in Section 6.3. • Subjects will be asked to stay in the clinic for at least 2 hours after completion of GEN3009 infusion for monitoring of signs and symptoms of IRRs until administration of GEN3009 in combination with the second full dose of GEN3013 (ie, C2D1), and instructed to contact the investigator should any reactions occur following discharge at any cycle.
CRS symptoms (not limited to chills, fever, hypotension, and hypoxia)	• The first dose of GEN3013 is a priming dose (ie, a lower dose than subsequent doses); the second dose is an intermediate dose (ie, higher than the priming dose but lower than the subsequent full-dose levels) (Section 6.4.2). • Premedication is mandatory prior to the first 4 administrations of GEN3013 and optional for later administrations (Section 6.2.2).

	• Prophylactic corticosteroids are mandatory for 2 days following each of the first 4 weekly administrations of GEN3013; for subsequent administrations, prophylactic steroids are only necessary if CRS ≥Grade 2 occurs following the fourth GEN3013 administration (Section 6.2.2). • Hospitalization for CRS monitoring is mandatory for at least 24 hours following the third dose (first full dose) of GEN3013 administration only. A lead-in dose of GEN3009 will be given a week before GEN3009 + GEN3013 combination to reduce the potential risk of CRS with GEN3013. See Section 7.5.2 and Appendix 13 for supportive care and management of CRS.
ICANS	Monitoring of the neurologic and cognitive status (including, but not limited to, confusion, expressive aphasia, headache, seizures and altered level of consciousness) of subjects to secure timely introduction of supportive care (Sections 7.5.3 and 9.3.1.1 and Appendix 14)
Clinical TLS	Laboratory monitoring; prophylaxis and management guidelines (Appendix 4).

The risks to subjects treated with the GEN3009 and GEN3013 combination will be minimized by a preceding safety run-in phase to inform the tolerability of the combination treatment before opening the Expansion phase, staggered dosing among subjects within a DL, requirement for hospitalization following the third dose (first full dose) of GEN3013 treatment, and established guidelines for the recognition and management of CRS and ICANS in addition to the compliance with the eligibility criteria, trial procedures, and close monitoring and management of TEAEs.

Furthermore, aggregate safety data will be reviewed by an independent data monitoring committee (DMC) on a regular basis to ensure the benefit to risk ratio remain acceptable for trial subjects.

In summary, this trial explores GEN3009 as a single agent and in combination with GEN3013 in subjects with R/R B-cell NHL who have limited treatment options. Based on nonclinical data and preliminary clinical data from GEN3009 and GEN3013 and clinical data from other CD37-targeting compounds, GEN3009 monotherapy and in combination with GEN3013 have the potential to address the highly unmet medical need in this patient population. With safety precautions and close monitoring plan in place, the described risks are outweighed by the potential benefit subjects might receive from GEN3009 alone or in combination with GEN3013.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described for the Dose Escalation in Table 17 and for the Expansion in Table 18, Table 19, and Table 20.

Table 17 Objectives and Endpoints for Dose Escalation (GEN3009 for R/R B-cell NHL Including CLL/SLL)

OBJECTIVES	ENDPOINTS
Primary	
• Determine the MTD with and/or determine the RP2D of GEN3009	• Rate of DLTs
• Evaluate safety and tolerability of GEN3009	• Frequency and severity of adverse events (AEs)/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
Secondary	
• Establish PK profile of GEN3009	• PK parameters: clearance, volume of distribution and area under the curve (AUC) at different time points (AUC_{7days}, AUC_{last} and AUC_{inf}), maximum concentration (C_{max}), time to C_{max} (T_{max}), predose trough concentrations (C_{trough}), and half-life ($T_{1/2}$)
• Evaluate immunogenicity of GEN3009	• Incidence of neutralizing anti-GEN3009 antibodies (ie, ADAs)
• Evaluate preliminary anti-tumor efficacy of GEN3009	• ORR • CR rate • DoR • TTR
• Evaluate preliminary clinical efficacy of GEN3009	• PFS • OS
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 and evaluate potential surrogacy with PFS and OS	• CD37 expression • Minimal residual disease (MRD) status
• Assess pharmacodynamic markers related to MoA of GEN3009	• Pharmacodynamic markers in blood samples (leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Table 18 Objectives and Endpoints for Expansion (GEN3009 for R/R, DLBCL, FL, and CLL Cohorts)

OBJECTIVES	ENDPOINTS
Primary	
• Evaluate (preliminary) anti-tumor efficacy of GEN3009	• ORR
Secondary	
• Establish PK profile of GEN3009	• PK parameters: CL, AUC_{7days}, AUC_{last}, C_{max}, T_{max}, C_{trough} and $T_{1/2}$
• Evaluate safety and tolerability of GEN3009	• Frequency and severity of AEs/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
• Evaluate clinical efficacy of GEN3009	• CR rate • DoR • TTR • PFS • OS
• Evaluate immunogenicity of GEN3009	• Incidence of neutralizing anti-GEN3009 antibodies (ie, ADAs)
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 and evaluate potential surrogacy with PFS and OS	• Expression of CD37 and CD59 in tumor biopsies before and during treatment • Abundance of immune effector cells in tumor microenvironment • Circulating tumor DNA (ctDNA) as response biomarker • MRD status as response biomarker in DLBCL, FL, and CLL and evaluate potential surrogacy with PFS/OS • DNA mutational status and gene expression profiling (RNA-seq) in blood and malignant cells
• Assess pharmacodynamic markers related to MoA of GEN3009	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy) (leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Table 19 Objectives and Endpoints for Expansion (GEN3009 + GEN3013 Safety Run-in for R/R B-NHL)

OBJECTIVES	ENDPOINTS
Primary	
• Identify the RP2D of GEN3009 + GEN3013 combination	• Rate of DLTs
• Evaluate safety and tolerability of GEN3009 + GEN3013 combination	• Frequency and severity of AEs/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
Secondary	
• Establish the PK properties of GEN3009 and GEN3013	• PK parameters: CL, AUC_{7days}, AUC_{last}, C_{max}, T_{max}, C_{trough}, and $T_{1/2}$
• Evaluate immunogenicity	• Incidence of neutralizing ADAs to GEN3009 • Incidence of neutralizing ADAs to GEN3013
• Assess the preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• CR rate • ORR • DoR • TTR • PFS • OS
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 + GEN3013 combination	• Expression of CD3, CD20, CD37, and molecular markers before and during treatment • MRD status
• Assess pharmacodynamic markers related to MoA of GEN3009 and GEN3013	• Pharmacodynamic markers in blood samples (leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation [CH50], and cytokine levels)

Table 20 Objectives and Endpoints for Expansion (GEN3009 + GEN3013 for R/R DLBCL)

OBJECTIVES	ENDPOINTS
Primary	
• Assess preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• CR rate
Secondary	
• Further assess the preliminary anti-tumor activity of GEN3009 + GEN3013 combination	• ORR • DOR • TTR • PFS • OS • Rate and duration of MRD negativity
• Evaluate the safety and tolerability of GEN3009 + GEN3013	• Frequency and severity of AEs/AESIs/SAEs • Changes in laboratory parameters • Changes in vital signs • Frequency of dose interruptions, dose delays, and dose intensity
• Establish the PK properties of GEN3009 and GEN3013	• PK parameters: CL, AUC_{7days}, AUC_{last}, C_{max}, T_{max}, C_{trough}, and $T_{1/2}$
• Evaluate immunogenicity	• Incidence of neutralizing ADAs to GEN3009 • Incidence of neutralizing ADAs to GEN3013
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3009 + GEN3013 combination	• Expression of CD3, CD20, CD37, and other markers in tumor biopsies before and during treatment • DNA mutation status and gene expression profiling (RNA-seq) in blood and malignant cells • ctDNA as response biomarker • Evaluation of immune populations, phenotype and function in tumors and blood
• Assess pharmacodynamic markers linked to efficacy and MoA of GEN3009 and GEN3013	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy) ((leukocyte subset frequencies and phenotype, target antigen expression, complement regulatory protein expression, plasma complement levels and activation (CH50), cytokine levels)

4 TRIAL DESIGN

4.1 Description of Trial Design

This trial is a FIH, open-label, multicenter trial to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3009 (DuoHexaBody®-CD37) as a single agent and in combination with GEN3013 (DuoBody®-CD3xCD20, epcoritamab) in subjects with R/R B-cell NHL.

The trial will be conducted in 2 parts, Dose Escalation and Expansion. Up to 90 subjects with R/R B-cell NHL will be enrolled in the Dose Escalation, and approximately 92 subjects will be enrolled in the Expansion as follows:

- GEN3009 monotherapy cohorts: R/R DLBCL (N=20), R/R FL (N=20), and R/R CLL (N=20)
- GEN3009 + GEN3013 combination cohorts: safety run-in phase in R/R DLBCL or R/R FL (N=6-12) followed by Expansion phase in R/R DLBCL(N = 20).

For GEN3009 monotherapy cohorts , GEN3009 will be administered IV in 4-week cycles (ie, 28 days), with a schedule of weekly dosing in Cycles 1 through 3, every second week in Cycles 4 through 9, and every 4 weeks in Cycle 10 until disease progression, unacceptable toxicity, death or end of trial.

For GEN3009 + GEN3013 combination cohorts, GEN3009 will be administered IV in 4-week cycles (ie, 28 days), with a schedule of weekly dosing in Cycles 1 through 3, and every 4 weeks in Cycles 4 through 12 until up to a maximum of 12 cycles or any discontinuation criteria met (see Section 8), whichever occurs earlier. GEN3013 will be administered subcutaneously (s.c.) in Cycles 1 (starting from C1D8) through 3 , and then every 4 weeks in Cycles 4 through 12 until up to a maximum of 12 cycles or any discontinuation criteria met, whichever occurs earlier (see Table 21). After completion of Cycle 12, subjects who are in SD or better will have the option to continue receiving GEN3013 every 4 weeks until any discontinuation criterion is met.

Table 21 Dose and Schedule

GEN3009 IV as assigned **DL1: CCI mg** **DL2: RP2D**	**GEN3013 s.c.** **DL1: 48 mg**

• Cycles 1-3: Days 1, 8, 15, 22
• Cycles 4-12: Day 1
	• Cycle 1:
	  ○ 0.16 mg (priming dose) on Day 8
	  ○ 0.8 mg (intermediate dose) on Day 15
	  ○ 48 mg (full dose) on Day 22
	• Cycles 2 and 3: 48 mg on Days 1, 8, 15, and 22
	• Cycles 4-12: 48 mg on Day 1
	After completion of Cycle 12:
	• Subjects who are in SD, PR or CR:
	  ○ Every 4 weeks (Cycles 13, 14, 15+): 48 mg on Day 1

In treatment Cycle 1 during the Dose Escalation, all subjects are required to remain at the clinic after the GEN3009 administration for at least 4 hours where they will be observed for AEs, have vital signs measured, and have blood samples taken for laboratory parameters such as cytokines,

PK, and pharmacodynamic measurements. Observation of up to 24 hours postdose during Cycle 1 is permissible at the discretion of the investigator.

In treatment Cycle 1 during the Expansion, all subjects (including those in the combination cohort) are required to remain at the clinic after the GEN3009 administration for at least 2 hours where they will be observed for AEs and other assessments.

In the GEN3009 + GEN3013 combination cohort, all subjects must be hospitalized for CRS monitoring for at least 24 hours after the third dose (first full dose) of GEN3013 (ie, 48 mg) at Cycle 1 Day 22. Additional or longer hospitalization is based per the investigator's discretion.

The design of the GCT3009-01 trial is shown in Figure 1.

Figure 1 GCT3009-01 Trial Design

4.1.1 Dose Escalation

The Dose Escalation will consist of 10 DLs (including one optional intermediate dose level) as shown in Figure 1.

The initial 3 DLs will be single-subject cohorts, which is the accelerated titration part of the Dose Escalation. The start of standard titration begins with the enrollment of the 3-subject cohorts at the fourth DL. Additional intermediate dose levels (eg, CCI mg) may also be explored based upon emerging data.

In the accelerated titration part of Dose Escalation, single-subject cohorts will be expanded to a 3-subject cohort if the subject experiences a grade ≥2 toxicity (ie, related AE), during the DLT evaluation period (ie, 28 days), or based on the decision of the sponsor's SC. When those subjects have completed their DLT evaluation period, the escalation model in Section 4.1.1.1 will be

initiated. If any single-subject cohort is expanded to a total of 3 subjects, all subsequent cohorts will initially have 3 subjects per cohort.

After all subjects within a DL cohort have completed the DLT evaluation period, the DEC will review the data and propose for initiation of the next DL cohort. The sponsor's SC will have to endorse the proposal before the next DL cohort can start dosing subjects. To supplement routine safety monitoring by the SC, as outlined in this protocol, a DMC will monitor safety data for the trial on a quarterly basis or more frequently as determined by the sponsor. Recommendations from the DEC, SC, and DMC will be based on evaluation of all available data including but not limited to clinical, safety, PK and pharmacodynamic data. Additional details regarding DEC, SC, and the DMC can be found in Sections 10.8 and 10.9.

The timeframe for dosing subjects in a DL cohort should proceed as follows:

- For an investigated, non-cleared DL, there should be at least 3 days between administration of the first dose to the first subject and the second subject within the same DL.
- Any additional subjects dosed in the investigated, non-cleared DL should receive their first dose at least 1 day apart.
- For a DL cleared for safety as recommended by the DEC/SC, there is no specific timeframe for subjects to receive their first dose (ie, additional subjects may be treated in parallel at the respective DLs that are considered safe).

4.1.1.1 Dose Escalation and De-escalation rules

A modified Bayesian Optimal Interval (mBOIN) design will be utilized to make optimal recommendations at the end of each observed cohort (Yuan et al., 2016). A property of the mBOIN design is that re-escalation is allowed when the previous DL is considered safe (based on data from additional subjects). However, re-escalation is not allowed to DLs that have been terminated. For this trial, a target toxicity level of ϕ=25% has been chosen.

For DLs with 3 DLT-evaluable subjects the decision regarding dose escalation and de-escalation will be consistent with the "3+3" design, ie, escalate if no DLT is observed, enroll 3 additional subjects if 1 DLT is observed and de-escalate if 2 DLTs are observed. If 3 DLTs are observed, the DL will be terminated.

For DLs with 4 or more DLT-evaluable subjects the decision regarding dose escalation and de-escalation will be based on the rules of the BOIN design. With the assumptions that ϕ_1=0.6ϕ is the highest sub-therapeutic DLT rate and ϕ_2=1.4ϕ is the lowest DLT rate that has excessive toxicity, the thresholds that minimizes the decision error at end of each cohort are λ_1=0.197 and λ_2=0.298 (Yuan et al., 2016). If an additional DLT-free cohort on the same DL would lead to de-escalation, the DL will be terminated.

After completion of the DLT period, based on cumulative safety data and the recommendation from the design rules presented in Table 22, the DEC will recommend the DL for the next cohort of subjects to the SC. The SC must endorse using the recommended or higher dose in the next cohort DL prior to implementation.

Table 22 Escalation Rules Based on Number of Subjects with DLTs

Decision, Based on the Number of Subjects with DLTs (N_{DLT})	Number of Subjects Evaluable for DLT at the Current DL						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Escalate	0	0	0	≤1	≤1	≤1	≤1
Remain on the same dose level	1	1	1	NA	2	2	2
De-escalate	2	2	2	2	3	3	3
Terminate a dose level	≥3	≥3	≥3	≥3	≥4	≥4	≥4

Parallel Cohort Enrollment

To better understand the safety, tolerability, PK, pharmacodynamic, or anti-tumor activity, approximately 7 additional subjects in total may be allocated in parallel to DLs (in the 3-subject cohorts only) that are considered safe for such allocation (DLs at or below the currently investigated one). In total, up to 49 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 DMC who will review the data in totality.

Cohort Size

During the standard titration part, it is allowed to execute the BOIN if 1 subject is non-DLT-evaluable and the remaining 2 subjects are deemed DLT-evaluable, provided neither of these 2 subjects experienced any grade ≥2 toxicity (ie, related AE) during the DLT evaluation period. If a DL has, in total, 2 subjects being DLT-evaluable and no DLTs are observed, the BOIN rule is to escalate. Also, over-recruitment by 1 subject is allowed in each cohort so that each cohort may consist of 2 to 4 subjects who are evaluable for DLT.

In case a DL is being revisited (eg, due to de-escalation) and less than 3 subjects have previously been evaluated on this DL, the next cohort on this DL may be enlarged to bring the number of DLT-evaluable subjects up to a multiple of 3.

Stopping Rules

The Dose Escalation stops, when either:

- 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, or
- the lowest dose is disallowed

Recommended Phase 2 Dose

The MTD is defined as the highest dose with DLT rate closest to 25%. By the end of the Dose Escalation, all available data, including but not limited to safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated and incorporated in a PK/pharmacodynamic modeling to guide RP2D selection and the RP2D would not exceed the MTD. A RP2D can be declared without exploring the highest dose level planned based on the totality of emerging clinical and PK/PD data.

4.1.2 Expansion

Following the determination of the MTD/RP2D, the Expansion will recruit approximately 92 subjects in 4 parallel expansion cohorts (GEN3009 in R/R DLBCL [n=20], GEN3009 in R/R FL [n=20], GEN3009 in R/R CLL [n=20], and GEN3009 + GEN3013 in R/R DLBCL [n=20] with

a preceding safety run-in [n = ~6-12; R/R DLBCL or FL]) to provide additional safety and initial efficacy information, as well as more detailed data related to the MoA. Expansion cohorts will start and enroll in parallel and independently unless otherwise decided by the sponsor.

4.1.2.1 Safety Run-in for the GEN3009 + GEN3013 Combination Cohort

The safety run-in will be conducted to assess the initial safety and tolerability of escalating GEN3009 DLs in combination with GEN3013 RP2D prior to the initiation of the GEN3009 + GEN3013 DLBCL expansion cohort.

GEN3013 will be administered as s.c. injections at RP2D with a step-up dosing method (ie, priming dose followed by intermediate and full dose while GEN3009 monotherapy will be administered as IV infusions at assigned DL (ie, CCI mg [DL1] and RP2D from Dose Escalation part [DL2]). Only cleared DLs of GEN3009 monotherapy at Dose Escalation can be studied in combination with GEN3013.

Decision regarding dose escalation and de-escalation will follow the dose escalation/de-escalation rules specified in Section 4.1.1.1. For DLs with 3 DLT-evaluable subjects, the decision will be consistent with the "3+3" design, ie, escalate if no DLT is observed, enroll 3 additional subjects if 1 DLT is observed and de-escalate if 2 DLTs are observed. If 3 DLTs are observed, the DL will be terminated. For DLs with 4 or more DLT-evaluable subjects the decision will be based on the rules of mBOIN design.

Dosing of subjects will be staggered following the same rules described in Section 4.1.1.

One combination treatment cycle will be 28 days. DLTs (see Section 7.3) will be evaluated during the first 28 days. After completion of the DLT period, based on cumulative safety data and the recommendation from the dose decision criteria described above, the DEC will provide a recommendation on the respective DL to the SC. The SC must endorse using the recommended or higher dose prior to implementation. Refer to Section 4.1.1.1 for further information including, but not limited to, mBOIN design and MTD/RP2D definitions.

4.2 Trial Design Rationale

This trial is being conducted to identify the MTD and/or RP2D of GEN3009, evaluate safety, and obtain preliminary efficacy of GEN3009 as a single agent and in combination with GEN3013 in subjects with R/R B-cell NHL, including CLL.

Escalation and de-escalation in the Dose Escalation and combination safety run-in cohorts will be guided by the mBOIN approach. To collect further data on the safety, tolerability, PK and anti-lymphoma activity, the selected RP2D of GEN3009 from the Dose Escalation will be studied in the Expansion. The Expansion will include 4 cohorts (ie, R/R DLBCL, R/R FL and R/R CLL in monotherapy cohorts, and R/R DLBCL in the GEN3009 + GEN3013 cohort with a preceding safety run-in) for further investigation. A safety run-in for the combination cohort, evaluating escalating DLs of GEN3009 with GEN3013 for DLTs, will ensure the safety and tolerability of the GEN3009 + GEN3013 combination prior to the initiation of the combination expansion.

4.3 Dose and Schedule Rationale

4.3.1 GEN3009 Monotherapy Cohorts

A starting dose of [redacted] mg of GEN3009 is proposed for this FIH clinical trial. This dose was derived by an integrated evaluation of preclinical pharmacology, PK, and toxicology studies.

A maximum recommended starting dose (MRSD) was defined using the HNSTD of 10 mg/kg in the pivotal GLP toxicity study as a starting point. A translational PK model based on cynomolgus monkey PK data was used to derive the human dose expected to give rise to 1-week average plasma exposure equivalent to one-sixth that in cynomolgus monkey at the HNSTD. The resulting dose of 2.34 mg/kg can be considered the MRSD.

GEN3009 was shown to have pharmacological activity at lower DLs. It showed significant effects on tumor size and inhibition of tumor outgrowth in various mouse xenograft models at 0.1 mg/kg. Furthermore, transient but substantial B-cell depletion was observed in cynomolgus monkey at 0.1 mg/kg. This pharmacological activity in vivo was compared to a minimum anticipated biological effect level (MABEL) approach based on CDC in vitro as an endpoint. CDC is expected to be the driving effector mechanism given that the DuoHexaBody format strongly enhances hexamer formation and C1q binding. The EC50 for CDC was established in a clinically relevant setting using ex vivo primary subject samples. The translational PK model was used to derive the dose expected to give rise to a 1-week average concentration equal to the CDC EC50 of 0.145 µg/mL, resulting in a dose of 0.25 mg/kg.

As a conservative approach, a FIH starting dose of CCI mg/kg was selected, which is expected to be at the lower end of the pharmacologically active range. The dose was converted to a flat dose equivalent of [redacted] mg.

A high degree of receptor occupancy (ie, target saturation) throughout the dosing interval is often correlated with optimal anti-tumor activity of therapeutic antibodies with similar MoAs (CDC, ADCC, ADCP [eg, daratumumab and ofatumumab], etc). Therefore, maintaining a high % of CD37 saturation would be critical for efficacy. IgG1 Fc-domain associated effector functions including CDC, ADCC, and ADCP are known to require a high degree of receptor occupancy throughout the dosing interval for optimal effect. In cynomolgus monkey, approximately linear PK was observed at 3 mg/kg and above, suggesting sustained saturation of target mediated clearance. A near complete depletion of B cells in circulation was observed at these dose levels. In patients, the additional CD37 on malignant cells is expected to increase the dose required for sustained target saturation compared to healthy cynomolgus monkeys. Target mediated clearance is expected to be reduced over the course of treatment at efficacious dose levels due to the depletion of malignant cells, so that target saturation can be maintained with less frequent dosing. The schedule therefore starts with weekly dosing for the first 3 cycles of 28 days before the dosing frequency is reduced to once every 2 weeks (six 28-day cycles; Cycle 4 through 9) and once every 4 weeks (Cycle 10 and onwards).

Preliminary results from the Dose Escalation part of GCT3009-01 among patients treated with GEN3009 at doses ranging from [redacted] mg to CCI mg at dose intervals of weekly in cycles 1-3, biweekly in cycles 4-9, and monthly from cycle 10 and beyond have shown the following:

- GEN3009 was well-tolerated with clinically manageable side effects at doses up to CCI mg. The most common TEAEs were IRRs and the most frequent laboratory

abnormalities were neutropenia. Both IRR and neutropenia are not dose-dependent; No dose-dependent toxicity has been observed so far.

- From the PK perspective, GEN3009 exhibited target-mediated drug disposition as expected, particularly at lower dose/concentration levels and resulting in rapid clearance of the drug-CD37 complex. High interindividual variability in target-mediated clearance was observed. For the majority of subjects doses up to CCI mg and for one out of three subjects at CCI mg were not sufficient to maintain saturating exposure throughout the dosing interval.

It is at present apparent that the highest dose initially planned of CCI mg is not sufficient to overcome target-mediated drug disposition in all subjects, and higher doses (eg, ≥CCI mg) are required to improve target saturation and minimize the impact of target-mediated clearance. Higher dose levels of GEN3009 (ie, CCI mg, CCI mg [optional intermediate dose], and CCI mg) are therefore added to the Dose Escalation to achieve target saturating exposure.

4.3.2 GEN3009 + GEN3013 Combination Cohort

The dosage of GEN3013 that will be tested in the combination regimens is the RP2D (ie, full dose of 48 mg) declared for R/R DLBCL and FL from the GCT3013-01 trial (NCT03625037). A step-up dosing schedule (ie, 0.16 mg on C1D8 [priming dose]; 0.80 mg on C1D15 [intermediate dose]; 48 mg on C1D22 [full dose]; and onward) for GEN3013 is selected to reduce the risk of CRS.

There will be 2 parts to test the GEN3009 + GEN3013 combination regimen:

- A safety run-in phase in R/R DLBCL and FL: to assess the safety, tolerability, PK, and immunogenicity of the GEN3009 + GEN3013 combination regimen. GEN3009 will be tested at 2 DLs: DL1 at CCI mg and DL2 at RP2D. GEN3013 will only be tested at a fixed DL at 48 mg.
- Expansion phase in R/R DLBCL: to assess the preliminary efficacy of the GEN3009 + GEN3013 combination regimen at the selected DL of GEN3009 from the safety run-in phase combined with GEN3013 at 48 mg. Safety, PK, and MRD will also be studied for the combination.

Starting with GEN3009 at CCI mg is considered to be appropriate based on the safety findings from subjects (N=18) treated with GEN3009 at up doses up to CCI mg. Specifically, IRRs observed with GEN3009 treatment were not dose-dependent and IRRs could be well managed. Laboratory abnormalities such as neutropenia were transient and neutrophil counts recovered within a few days. Granulocyte colony stimulating factor (G-CSF) administration at the onset of Grade 3 or Grade 4 neutropenia was sufficient for count recovery by the next dose.

Due to the non-overlapping MoAs for the individual study drugs (ie, GEN3009, GEN3013), it is deemed safe to start GEN3009 at CCI mg on C1D1 followed by the combination regimen from C1D8 and onward. The lead-in dose of GEN3009 can potentially reduce the risk of CRS with GEN3013.

It is hypothesized that a more robust (ie, deeper, earlier, and more durable) overall clinical benefit can be achieved with the GEN3009 + GEN3013 regimen. Target-mediated clearance of GEN3009 is expected to be reduced over the course of treatment given to the depletion of malignant cells as a result of a potentially deeper and earlier tumor response with the combination treatment, so that target saturation can be maintained with less frequent dosing. Thus, this trial will test a less frequent schedule of GEN3009 in the combination cohort as compared to the GEN3009

monotherapy cohorts (ie, every 4 weeks instead of q2w in Cycle 4 and onward, and a fixed duration of 12 months instead of continuous treatment until disease progression). Subjects who achieve SD or better at the completion of 12 months will have the option to receive GEN3013 until disease progression to maintain the clinical benefit based on the investigator's discretion.

4.4 End of Trial and End of Treatment Definitions

4.4.1 End of Trial

The trial is considered completed when the last subject dies or withdraws from the trial. However, the maximum trial duration is 5 years after the last subject's first treatment in the trial. Following trial termination, the sponsor will make their best effort to ensure provision of post-trial access to GEN3009 and/or GEN3013 for those ongoing trial subjects with a potential treatment benefit, in accordance with local laws and requirements.

4.4.2 Treatment Discontinuation

Treatment should continue until the subject fulfills 1 of the treatment discontinuation criteria (refer to Section 8.1).

4.4.3 Trial Stopping Rules

If any of the events listed below occur, a prompt cumulative review of safety data will be conducted by the DMC to determine whether the trial should be discontinued permanently.

- Events outside of the DLT window, in the Dose Escalation part and in the expansion part of the trial, that in the judgment of the sponsor are deemed serious enough to warrant an immediate comprehensive evaluation by the SC;
- If at any time, all DLs are considered unsafe as defined by the mBOIN;
- Any safety finding assessed as related to GEN3009 and/or GEN3009 + GEN3013 combination treatment that, in the opinion of the DMC, contraindicates further dosing of trial subjects.

Any recommendation of the DMC must be approved by the sponsor SC.

In addition, to ensure subject safety, the following stopping criteria are applicable to subjects who have completed the DLT period during the Dose Escalation, as well as subjects enrolled in Expansion:

- ≥33% of subjects experiencing Grade 3 or greater treatment-emergent IRRs, or
- ≥33% of subjects experiencing Grade 4 neutropenia lasting >7 days not attributable to underlying disease, or
- ≥33% of subjects experiencing Grade 3 or greater CRS or ICANS.

As noted in Section 10.8, the DMC will review the totality of the data and monitor safety for the trial on a quarterly basis or more frequently during the Dose Escalation and at pre-specified intervals during the Expansion (including safety run-in) as defined in the DMC charter.

For each individual subject who has already received GEN3009 or GEN3009 + GEN3013 combination and is currently in the trial at the time the trial stopping criteria are met, the benefit-risk whether to stop or continue treatment will be assessed. To allow continuation of treatment, DMC consultation will be considered. All subjects continuing GEN3009 or GEN3009 + GEN3013

combination after trial termination should continue to have investigator follow-up for safety until the subject's condition returns to baseline or until the start of a new anti-cancer therapy, whichever comes first.

Where applicable, regulatory authorities and independent ethics committees (IECs)/institutional review board (IRBs) will be notified of any significant actions taken with the trial.

4.4.4 Trial Termination

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or ICH Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial drug development

The sponsor may, based on available data, need to discontinue further development of GEN3009 and/or the combination of GEN3009 + GEN3013. Following trial termination, the sponsor will make their best effort to provision post-trial access to GEN3009 and/or GEN3013 for those ongoing trial subjects with a potential treatment benefit, in accordance with local laws and requirements.

5 TRIAL POPULATION(S)

5.1 Inclusion Criteria

5.1.1 Dose Escalation Inclusion Criteria

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

1. Be at least 18 years of age.
2. Must sign an informed consent form (ICF) prior to any screening procedures indicating that they understand the purpose of the trial, the procedures required for the trial, and are willing to participate in the trial prior to any other trial-related assessments or procedures.
3. Criterion updated as per Amendment 1

   3.1 Criterion updated as per Amendment 3

   3.2 Criterion updated as per Amendment 5

   3.3 Has histologically or cytologically confirmed relapsed or refractory B-cell NHL with no available standard therapy or is not a candidate for available standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN3009 may be beneficial. All subjects must have received at least 2 prior lines of systemic therapy, and,

   a. For all indolent NHL (FL, MZL, and SLL) as well as aggressive NHL (DLBCL, HGBCL, and PMBCL), at least 1 of the 2 prior lines of treatment must have been a CD20-containing systemic regimen;
   b. For MCL, subjects must have had or are otherwise ineligible for treatment with a BTK inhibitor, and;
   c. For CLL, subjects must have received at least 1 prior line of BTK inhibitor or BCL-2 inhibitor.
4. Criterion updated as per Amendment 5

   4.1 Has 1 of the following B-cell NHL subtypes for the Dose Escalation:

   a. DLBCL, de novo or histologically transformed
   b. HGBCL (Swerdlow et al., 2016)
   c. PMBCL
   d. FL, with advanced symptomatic disease and with a need for treatment
   e. MCL, without leukemic manifestation
   f. MZL, either nodal, extranodal, or mucosa associated, with a need for treatment initiation based on symptoms and/or disease burden
   g. SLL, with a need for treatment based on symptoms and/or disease burden
   h. CLL with active disease that needs treatment based on the International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria) (Hallek et al., 2018)

      i. Criterion updated as per Amendment 3

5. Criterion removed as per Amendment 5
6. Criterion updated as per Amendment 5

   6.1 Has measurable disease:

   i. B-cell NHL:

   a. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) computed tomography (CT) scan demonstrating positive lesion compatible with CT (or magnetic resonance imaging [MRI])-defined anatomical tumor sites

   and

   b. A CT scan (or magnetic resonance imaging [MRI]) with involvement of ≥2 clearly demarcated lesions/nodes with long axis >1.5 cm and short axis >1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and a short axis ≥1.0 cm.

   Note: Subjects who do not have FDG-avid lymphoma at screening will be eligible if they meet "criterion 5b".

   ii. CLL:

   c. ≥5 × 10^9/L (5,000/μL) B lymphocytes in peripheral blood, or
   d. Presence of measurable lymphadenopathy and/or organomegaly

7. Has active disease for CLL: Progressive or symptomatic disease with at least 1 of the following criteria being met (Hallek et al., 2018):

   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
   b. Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
   c. Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
   d. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months.
   e. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids
   f. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
   g. Disease-related symptoms as defined by any of the following:
      i. Unintentional weight loss ≥10% within the previous 6 months
      ii. Significant fatigue
      iii. Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
      iv. Night sweats for ≥1 month without evidence of infection.

8. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Criterion updated as per Amendment 5.

   9.1 Has acceptable laboratory parameters as follows:

Parameter		Result
a.	Creatinine clearance	>50 mL/min (Cockcroft-Gault) or serum creatinine ≤1.5 × upper limit of normal (ULN) (refer to Appendix 1)
b.	Serum alanine transaminase (ALT)	≤2.5 × upper limit of normal (ULN)
c.	Serum aspartate transaminase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤1.5 × ULN *Note: Subjects with Gilbert's syndrome may be included if total bilirubin is ≤3 × ULN and direct bilirubin is ≤1.5 × ULN*
e.	Hemoglobin	≥5.6 mmol/L (9.0 g/dL) *Note: Without transfusion within 7 days of determination of eligibility.*
f.	Absolute neutrophil count	B-cell NHL: ≥1.0×10^9/L (1,000/µL) CLL: ≥1.0×10^9/L (1,000/µL) unless due to bone marrow involvement *Note: Without growth factor support within 7 days of determination of eligibility (14 days if pegylated growth factor such as pegfilgrastim).*
g.	Platelet count	B-cell NHL: ≥ 75×10^9/L (75,000/µL) *Note: In presence of bone marrow involvement, platelets ≥50×10^9/L.* CLL: ≥30×10^9/L (30,000/µL) *Note: Without transfusion within 7 days of determination of eligibility.*
h.	Coagulation Status: PT/INR/aPTT	Prothrombin time (PT)/International normalized ratio (INR)/Activated partial thromboplastin time (aPTT) ≤1.5×ULN

10. Criterion updated as per Amendment 3

    10.1 A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3009 administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 12 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.

11. Criterion updated as per Amendment 3

    11.1 A woman of childbearing potential must have a negative serum beta-human chorionic gonadotropin (beta-hCG) at screening.

12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 12 months after receiving the last dose of GEN3009.

13. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, condom only and spermicidal foam/gel/film/cream/suppository, and partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 12 months after receiving the last dose of GEN3009.

14. Must be willing and able to adhere to the requirements and restrictions specified in the ICF and this protocol.
15. Subjects must have a life expectancy of at least 3 months.
16. **Sites in France only:** Must have a social security number or equivalent per local requirements.

5.1.2 Expansion (including Safety Run-in) Inclusion Criteria

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

1. Be at least 18 years of age.
2. Must sign an ICF prior to any screening procedures indicating that they understand the purpose of the trial, the procedures required for the trial, and are willing to participate in the trial prior to any other trial-related assessments or procedures.
3. Has histologically or cytologically confirmed relapsed or refractory B-cell NHL. All subjects must have received at least 2 prior lines of systemic therapy, and,
    a. For FL and DLBCL, at least 1 of the 2 prior lines of treatment must have been a CD20-containing systemic regimen;
    b. For CLL, subjects must have received at least one prior line of BTK inhibitor or BCL-2 inhibitor.

Note: See Section 11.8.1.3 for definitions of "relapsed" disease.

4. Has 1 of the following B-cell NHL subtypes for the Expansion (including safety run-in):
    a. DLBCL, de novo or histologically transformed
    b. FL Grade 1, 2 and 3a, with advanced symptomatic disease and with a need for treatment initiation
    c. CLL, must have active disease that needs treatment with at least 1 of the following criteria being met (Hallek et al., 2018):
        i. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
        ii. Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
        iii. Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy

        - Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or LDT <6 months
        - Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids
        - Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
        - Disease-related symptoms as defined by any of the following:
            - Unintentional weight loss ≥10% within the previous 6 months

- Significant fatigue
- Fevers ≥38.0°C (100.5°F) for 2 or more weeks without evidence of infection
- Night sweats for ≥1 month without evidence of infection

d. GEN3009 + GEN3013 combination cohort only: Documented CD20+ DLBCL or FL based on representative pathology report

5. Has measurable disease for B-cell NHL:
   a. A FDG-PET CT scan demonstrating positive lesion compatible with CT (or MRI)-defined anatomical tumor sites, and
   b. A CT scan (MRI) with involvement of ≥ 2 clearly demarcated lesions/nodes with long axis >1.5 cm and short axis >1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and a short axis ≥1.0 cm.

Note: Subjects who do not have FDG-avid lymphoma at screening will be eligible if they meet criterion "5b".

6. Has measurable disease for CLL with at least one of the following criteria:
   a. ≥5 × 10^9/L (5,000/μL) B lymphocytes in peripheral blood
   b. Presence of measurable lymphadenopathy and/or organomegaly
7. Has ECOG performance status of 0 or 1.
8. Has acceptable laboratory parameters as follows:

Parameter		**Result**
a.	Creatinine clearance	>50 mL/min (Cockcroft-Gault) or serum creatinine ≤1.5 × ULN (refer to Appendix 1)
b.	Serum alanine transaminase (ALT)	≤2.5 × ULN
c.	Serum aspartate transaminase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤1.5 × ULN *Note: Subjects with Gilbert's syndrome may be included if total bilirubin is ≤ 3 × ULN and direct bilirubin is ≤1.5 × ULN*
e.	Hemoglobin	≥5.6 mmol/L (9.0 g/dL) *Note: Without transfusion within 7 days of determination of eligibility.*
f.	Absolute neutrophil count	B-cell NHL: ≥1.0×10^9/L (1,000/μL) CLL: ≥1.0×10^9/L (1,000/μL) unless due to bone marrow involvement *Note: Without growth factor support within 7 days of determination of eligibility (14 days if pegylated growth factor such as pegfilgrastim).*
g.	Platelet count	B-cell NHL: ≥75×10^9/L (75,000/μL) *Note: In presence of bone marrow involvement, platelets ≥50×10^9/L.* CLL: ≥30×10^9/L (30,000/μL)

		Note: Without transfusion within 7 days of determination of eligibility.
h.	Coagulation status: PT/INR/aPTT	Prothrombin time (PT)/International normalized ratio (INR)/Activated partial thromboplastin time (aPTT) ≤1.5 × ULN

9. Subjects must have a life expectancy of at least 3 months.
10. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3009 and/or GEN3013 administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 12 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
11. A woman of childbearing potential must have a negative serum beta-hCG at screening.
12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 12 months after receiving the last dose of GEN3009 and/or GEN3013.
13. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, condom only and with spermicidal foam/gel/film/cream/suppository and partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 12 months after receiving the last dose of GEN3009 and/or GEN3013.
14. Must be willing and able to adhere to the requirements and restrictions specified in the ICF and this protocol.
15. **Sites in France only:** Must have a social security number or equivalent per local requirements.

5.2 Exclusion Criteria

5.2.1 Dose Escalation Exclusion Criteria

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

1. Prior treatment with a CD37-targeting agent.
2. Prior allogeneic HSCT.
3. Autologous HSCT within 3 months before the first dose of GEN3009.
4. Criterion updated as per Amendment 5

   4.1 Treatment with an anti-cancer biologic including anti-CD20 therapy, radio-conjugated or toxin-conjugated antibody or chimeric antigen receptor (CAR) T cell therapy within 4 weeks or 5 half-lives, whichever is shorter, before the first dose of GEN3009. Treatment with small molecules such as BTK inhibitors, BCL2 inhibitors, or PI3K inhibitors within 5 half-lives prior to the first dose of GEN3009.
5. Chemotherapy or radiation therapy within 2 weeks of the first dose of GEN3009.
6. Criterion updated as per Amendment 5.

6.1 Treatment with an investigational drug or an invasive investigational medical device within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3009, and at any time during the study treatment period.

7. Autoimmune disease or other diseases that require permanent or high-dose immunosuppressive therapy.
8. Received a cumulative dose of corticosteroids more than the equivalent of 250 mg of prednisone within the 2–week period before the first dose of GEN3009.

   Note: Refer to Section 6.6.2 for steroid dosing limitations during study treatment period.
9. Has uncontrolled intercurrent illness, including but not limited to:
   a. Ongoing or active infection requiring intravenous antibiotics treatment at the time of enrollment or within the previous 2 weeks prior to the first dose of GEN3009
   b. Symptomatic congestive heart failure (grade III or IV as classified by the New York Heart Association ([NYHA]), unstable angina pectoris or cardiac arrhythmia (refer to Appendix 2)
   c. Myocardial infarction, intracranial bleed, or stroke within the past 6 months
   d. Screening 12-lead electrocardiogram (ECG) showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec
10. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
11. Primary central nervous system (CNS) lymphoma or known CNS involvement at screening.
12. Has known past or current malignancy other than inclusion diagnosis, except for:
    a. Cervical carcinoma of Stage 1B or less
    b. Non-invasive basal cell or squamous cell skin carcinoma
    c. Non-invasive, superficial bladder cancer
    d. Prostate cancer with a current PSA level <0.1 ng/mL
    e. Criterion deleted as per Amendment 3
    f. Any curable cancer with a CR of >2 years duration
13. Criterion updated per Amendment 5

    14.1 Had allergic reactions to anti-CD20 or anti-CD37 monoclonal antibody treatment or intolerant to GEN3009 excipients (refer to the GEN3009 IB for more information).
14. Criterion updated per Amendment 5

    14.1 Has had major surgery, (eg, requiring general anesthesia) within 4 weeks before screening or will not have fully recovered from surgery, or has major surgery planned during the time the subject is expected to participate in the trial (or within 4 weeks after the last dose of GEN3009 and/or GEN3013).

    Note: Subjects with planned minor surgical procedures to be conducted under local anesthesia may participate.

15. Has known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    - Positive test for antibodies to the hepatitis B core antigen (anti-HBc)
      and
    - Negative test for antibodies to the hepatitis B surface antigen (anti-HBs).
16. Known medical history or ongoing hepatitis C infection that has not been cured.
17. Criterion updated per Amendment 5

    17.1 Known history of seropositivity for HIV infection. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
18. Is a woman who is pregnant or breast-feeding, or who is planning to become pregnant while enrolled in this trial or within 12 months after the last dose of GEN3009.
19. Is a man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3009.
20. Criterion updated as per Amendment 5

    20.1 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.
21. Prior treatment with live, attenuated vaccines within 4 weeks prior to initiation of GEN3009. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized SARS-CoV-2 vaccinations are not allowed.
22. Lymphomas leukemia phase: high absolute lymphocyte count or the presence of abnormal cells in the peripheral blood indicating circulating lymphoma cells.

5.2.2 Expansion (including Safety Run-in) Exclusion Criteria

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

1. Prior treatment with a CD37-targeting agent.
2. **GEN3009 + GEN3013 combination cohort only:** Prior treatment with a CD3 × CD20 bispecific antibody.
3. Prior allogeneic HSCT.
4. Autologous HSCT within 3 months before the first dose of GEN3009.
5. Lymphomas leukemia phase: high absolute lymphocyte count or the presence of abnormal cells in the peripheral blood indicating circulating lymphoma cells

6. Treatment with an anti-cancer biologic including anti-CD20 therapy, radio-conjugated or toxin-conjugated antibody or CAR T cell therapy within 4 weeks or 5 half-lives, whichever is shorter, before the first dose of GEN3009. Treatment with small molecules such as BTK inhibitors, BCL2 inhibitors, or PI3K inhibitors within 5 half-lives prior to the first dose of GEN3009.
7. Chemotherapy or radiation therapy within 2 weeks of the first dose of GEN3009.
8. Treatment with an investigational drug or an invasive investigational medical device within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3009, and at any time during the study treatment period
9. Autoimmune disease or other diseases that require permanent or high-dose immunosuppressive therapy.
10. Received a cumulative dose of corticosteroids more than the equivalent of 250 mg of prednisone within the 2–week period before the first dose of GEN3009.

    Note: Refer to Section 6.6.1 for steroid dosing limitations during the study treatment period.
11. Has uncontrolled intercurrent illness, including but not limited to:
    a. Ongoing or active infection requiring intravenous antibiotics treatment at the time of enrollment or within the previous 2 weeks prior to the first dose of GEN3009 or GEN3013
    b. Symptomatic congestive heart failure (grade III or IV as classified by the NYHA), unstable angina pectoris or cardiac arrhythmia (refer to Appendix 2) and/or known decrease ejection fraction of <45%
    c. Myocardial infarction, intracranial bleed, or stroke within the past 6 months
    d. Screening 12-lead ECG showing a baseline QTcF >480 msec
12. **GEN3009 + GEN3013 combination cohort only:** Seizure disorder requiring therapy (such as steroids or anti-epileptics)
13. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy.
14. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
15. Primary CNS lymphoma or known CNS involvement at screening.
16. Has known past or current malignancy other than inclusion diagnosis, except for:
    a. Cervical carcinoma of Stage 1B or less
    b. Non-invasive basal cell or squamous cell skin carcinoma
    c. Non-invasive, superficial bladder cancer
    d. Prostate cancer with a current PSA level < 0.1 ng/mL
    e. Any curable cancer with a CR of >2 years duration
17. Had allergic reactions to anti-CD20 or anti-CD37 monoclonal antibody treatment or intolerant to GEN3009 excipients (refer to the GEN3009 IB for more information)
18. **GEN3009 + GEN3013 combination cohort only:** Intolerant to GEN3013 excipients (refer to the GEN3013 IB for more information)

19. Has had major surgery, (eg, requiring general anesthesia) within 3 weeks before screening or will not have fully recovered from surgery, or has major surgery planned during the time the subject is expected to participate in the trial (or within 4 weeks after the last dose of GEN3009).

    Note: Subjects with planned minor surgical procedures to be conducted under local anesthesia may participate.

20. Has known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):

    - Positive test for anti-HBc

      and

    - Negative test for anti-HBs.

21. Known medical history or ongoing hepatitis C infection that has not been cured.
22. Known history of seropositivity for HIV infection. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
23. Is a woman who is pregnant or breast-feeding, or who is planning to become pregnant while enrolled in this trial or within 12 months after the last dose of GEN3009 and/or GEN3013.
24. Is a man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3009 and/or GEN3013.
25. 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.
26. Prior treatment with live, attenuated vaccines within 4 weeks prior to initiation of GEN3009. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non-authorized SARS-CoV-2 vaccinations are not allowed.

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 Section 5.1 and 5.2). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons) and any SAEs or AEs related to a trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. Screen failures may be rescreened only once. Subjects are required to sign a new ICF if updates have been made since signing the most recent ICF. All eligibility criteria must be re-assessed at the rescreening visit.

Previously submitted tumor biopsy samples are acceptable if obtained within 6 months prior to Cycle 1 Day 1. The following screening assessments may be used for rescreening if performed ≤3 weeks prior to Cycle 1 Day 1 or if approved by sponsor:

- Previously submitted FDG-PET CT, CT, or MRI scans with acquisition date ≤3 weeks prior to Cycle 1 Day 1. Scans that exceed the 3-week window may be used for trial enrollment with sponsor's approval.
- Screening laboratory assessments with the protocol-defined timelines as indicated in the visit assessment schedules (refer to Table 2 and Table 5).

6 TREATMENT

6.1 Treatment Assignment or Randomization

6.1.1 Subject Numbering

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

6.1.2 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Subjects will be assigned to a dose cohort based on slot availability.

During Dose Escalation, site personnel must contact the contract research organization (CRO) when a potential subject has been identified. If there is an available enrollment slot in any currently enrolling cohort, the site will be given approval to start the screening process. If there is no opening, the subject will be placed on a waiting list, and the site will be alerted of the next available opening either in the currently enrolling DL or at the next opened DL.

During the Expansion, subjects that meet the eligibility criteria will be assigned a subject number.

6.2 Premedication

6.2.1 Premedication in GEN3009 Monotherapy Cohorts

The purpose of premedication is to reduce the risk of IRRs. It is mandatory to premedicate subjects in the first treatment cycle with corticosteroids, antihistamines, antipyretics, and a leukotriene receptor antagonist before each infusion of GEN3009 (ie, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 1 Day 22). Premedication should be administered 30 minutes to 2 hours prior to the GEN3009 infusion:

1. Prednisolone 100 mg, or equivalent, administered IV. Only intermediate-acting and long-acting steroids are allowed (refer to Appendix 3 for the equivalent).
2. Antipyretics: Acetaminophen 650 to 1000 mg PO, or equivalent.
3. Antihistamine: Diphenhydramine 25 to 50 mg IV or PO, or equivalent.
4. A leukotriene receptor antagonist: Montelukast 10 mg PO.

In addition to the corticosteroid administered on the day of the GEN3009 infusion, dexamethasone 5 mg PO is allowed at the investigator's discretion for up to 3 days prior to the day of GEN3009 infusion.

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

If there is a Grade 3 IRR during the Cycle 1, corticosteroid is required for Cycle 2 but may be at a reduced dose, ie, prednisolone at 80 mg IV. The use of corticosteroid is optional for subsequent cycles.

Premedication with antipyretics and antihistamines should be administered at all cycles. The leukotriene receptor antagonist only needs to be given in Cycle 1.

6.2.2 Premedication and CRS Prophylaxis in GEN3009 + GEN3013 Combination Cohort

Premedication (ie, corticosteroids, antihistamines, antipyretics and a leukotriene receptor antagonist) and post-infusion corticosteroids are mandatory for GEN3009 and GEN3009 + GEN3013 doses in Cycle 1 and Cycle 2 Day 1 as described in Table 23. In subsequent treatment (ie., Cycle 2 Day 8 and beyond), steroid may be optional. Refer to Appendix 3 for corticosteroid equivalent. The leukotriene receptor antagonist only needs to be given in Cycle 1. Premedication with antipyretics and antihistamines should be administered at all cycles.

If there is a Grade 3 IRR during Cycle 1, corticosteroid is required for Cycle 2 but may be at a reduced dose ie, prednisolone at 80 mg IV. The use of corticosteroid is optional for subsequent cycles.

If CRS ≥ Grade 2 occurs following the fourth dose of epcoritamab administration (Cycle 2 Day 1 dose), premedication with corticosteroid and 3-day consecutive corticosteroid administration is recommended to continue for the rest of GEN3013 doses in Cycle 2. From Cycle 3 and onward, corticosteroid may be optional for premedication with antipyretics and antihistamines should be administered at all cycles.

Table 23 Premedication and Post-infusion Medication for GEN3009 + GEN3013 Combination

			Corticosteroids	Antihistamines	Antipyretics	Leukotriene receptor antagonist
Cycle 1	Premedication for GEN3009	Day 1 (Predose)*	Prednisolone 100 mg IV (or equivalent)	Diphenhydramine 50 mg IV or oral (PO) or equivalent)	Acetaminophen 650 to 1000 mg PO (or equivalent)	Montelukast, 10 mg PO
	Premedication for GEN3009 + GEN3013 (priming dose at 0.16 mg)	Day 08 (Predose)*	Prednisolone 100 mg IV (or equivalent)	Diphenhydramine 50 mg IV or PO (or equivalent)	Acetaminophen 650 to 1000 mg PO (or equivalent)	Montelukast, 10 mg PO
		Day 09	Prednisolone 100 mg IV or PO (or equivalent)			
		Day 10	Prednisolone 100 mg IV or PO (or equivalent)			
	Premedication for GEN3009 + GEN3013 (intermediate dose at 0.8 mg)	Day 15 (Predose)*	Prednisolone 100 mg IV (or equivalent)	Diphenhydramine 50 mg IV or PO (or equivalent)	Acetaminophen 650 to 1000 mg PO (or equivalent)	Montelukast, 10 mg PO
		Day 16	Prednisolone 100 mg IV or PO (or equivalent)			
		Day 17	Prednisolone 100 mg IV or PO (or equivalent)			
	Premedication for GEN3009 + GEN3013 administration 48 mg)	Day 22 (Predose)*	Prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or PO (or equivalent)	Acetaminophen 650 to 1000 mg PO (or equivalent)	Montelukast, 10 mg PO

			Corticosteroids	Antihistamines	Antipyretics	Leukotriene receptor antagonist
		Day 23	Prednisolone 100 mg IV or PO (or equivalent)			
		Day 24	Prednisolone 100 mg IV (or equivalent including oral dose)			
Cycle 2	Premedication for GEN3009 + 4th GEN3013 administration (48 mg)	Day 1 (Predose)*	Prednisolone 100 mg IV (or equivalent)	Diphenhydramine 50 mg IV or PO (or equivalent)	Acetaminophen 650 to 1000 mg PO (or equivalent)	
		Day 2	Prednisolone 100 mg IV or PO (or equivalent)			
		Day 3	Prednisolone 100 mg IV or PO (or equivalent)			
		Day 8 and beyond	If CRS ≥Grade 2 occurs following the 4th dose of epcoritamab administration (Cycle 2 Day 1 dose), premedication with corticosteroid and 3-day consecutive corticosteroid administration is recommended to continue for the rest of GEN3013 doses in Cycle 2. From Cycle 3 and onward, corticosteroid may be optional.			

* Premedication should be given 30 minutes - 1 hour prior to the trial treatment. On the days when both trial drugs are given, administer GEN3013 s.c. first, monitor the subject for 30 minutes to 1 hour, then start the GEN3009 infusion. GEN3013 will be administered prior to GEN3009.

6.3 Management of Infusion-Related Reactions

IRRs can occur with GEN3009 administration. All patients must receive premedication for IRRs as described in Section 6.2.1.

Table 24 GEN3009 Dose Modification Rules for IRRs

IRR Grade	Dose Modification
Grade 1 or 2	• Stop GEN3009 infusion immediately and treat the subject based on local institutional guidelines. • Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. • If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate. Please refer to Section 6.2.1 for premedication instructions.
Grade 3	• Stop GEN3009 infusion immediately and treat the subject based on local institutional guidelines • Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. • If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate. • If, after resumption of the infusion, symptoms return (irrespective of grade), permanently discontinue administration of GEN3009 and manage the IRR symptoms accordingly. Please refer to Section 6.2.1 for premedication instructions.
Grade 4 (life-threatening)	• Permanently discontinue administration of GEN3009 and institute appropriate emergency care.

Trained trial staff should be prepared to intervene in case of any IRRs occurring, with resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) available.

6.4 Dosage(s) and Administration

6.4.1 GEN3009 Monotherapy Cohorts

GEN3009 will be administered as an IV infusion according to the following schedule until 1 or more of the discontinuation criteria in Section 8.1 are met:

- Cycles 1 through 3: Days 1*, 8, 15, and 22 (once weekly for a 28-day cycle)
- Cycles 4 through 9: Days 1 and 15 (every 2 weeks for a 28-day cycle)
- Cycle 10 and beyond: Day 1 (every 4 weeks for a 28-day cycle)

*At dose levels≥CCI mg, the first dose of GEN3009 can be split into 2 consecutive days (eg, CCI mg at C1D1 and remaining amount at C1D2) after approval of the sponsor's medical monitor.

Refer to the GEN3009 investigational medicinal product (IMP) manual for additional information and guidance on dosage and administration.

Refer to Section 6.6 for information regarding concomitant therapy. Detailed dose modification guidance is provided in Section 7.

In the Dose Escalation, the DLs will be determined by the starting dose and the escalation steps taken in the trial (refer to Section 4.1.1).

During the Dose Escalation, all subjects must remain at the clinic for at least 4 hours after each GEN3009 administration in Cycle 1. Subjects must be instructed to contact the investigator should signs or symptoms of IRRs occur following discharge from the 4-hour observation period. An

observation of up to 24 hours postdose during Cycle 1 is permissible at the discretion of the investigator.

During the Expansion (including safety run-in), all subjects are required to remain at the clinic for at least 2 hours after the GEN3009 administration in Cycle 1. Subjects must be instructed to contact the investigator should signs or symptoms of IRRs and/or CRS (eg, fever, lightheadedness, shortness of breath, etc) occur following discharge.

6.4.2 GEN3009 + GEN3013 Combination Cohort

GEN3009 will be administered as an IV infusion and GEN3013 will be given as an s.c. injection.

A lead-in dose of GEN3009 will be given 7 days prior to the GEN3009 + GEN3013 combination. A step-up dosing of GEN3013 will be used to further reduce the risk of CRS: 0.16 mg on Day 8 of Cycle 1, 0.8 mg on Day 15 of Cycle 1, then 48 mg on Day 22 of Cycle 1 followed by 48 mg for the rest of the cycles.

On the days when both treatments were given, GEN3013 will be administered at least 1 hour prior to the GEN3009 infusion.

In the safety run-in, 2 DLs of GEN3009 (ie, CCI mg and RP2D) and 1 DL of GEN3013 (ie, 48 mg) will be tested. Detailed dosing and schedule are shown in Table 21.

After safety and tolerability of GEN3009 + GEN3013 in combination have been evaluated in the safety run-in, the Expansion of the combination will be opened to further evaluate the preliminary anti-tumor activity of GEN3009 at the recommended dose with GEN3013 at 48 mg in R/R DLBCL.

Refer to the IMP manual for additional information and stepwise guidance on dosage and administration.

Refer to Section 6.6 for information regarding concomitant therapy. Detailed dose modification guidance is provided in Section 7.

In the GEN3009 + GEN3013 combination cohort, all subjects are required to remain at the clinic for at least 2 hours after the GEN3009 infusion in Cycle 1. Subjects must be instructed to contact the investigator should signs or symptoms of IRRs and/or CRS (eg, fever, lightheadedness, shortness of breath, etc) occur following discharge. In addition, all subjects must be hospitalized for mandatory CRS monitoring for at least 24 hours after the third dose (first full dose) at Cycle 1 Day 22 of GEN3013 (ie, 48 mg). Additional or longer hospitalization are based on the investigator's discretion.

6.5 Treatment Compliance

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

6.6 Concomitant Medications and Therapies

6.6.1 Permitted Concomitant Medications and Therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.6.2).

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

- Local palliative radiotherapy on non-target lesions is allowed.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and neutropenia, when clinically indicated or at the investigator's discretion. In case of ≥ Grade 3 neutropenia, use of growth factors is mandated in the Dose Escalation and Safety Run-in parts of the study.
- Blood cell transfusion is allowed if clinically indicated.
- Intravenous immunoglobulin (IVIg) is permitted, if clinically indicated.
- Multivitamins, vitamin D, calcium, and supplements in prevention of weight loss. Prescribed medicinal cannabinoids as palliative therapy are allowed.
- Anti-hypertensives are allowed as concomitant medications. However, due to the transient hypotension observed in the monkey toxicology study, consider withholding anti-hypertensive medication for 12 hours prior to infusions.

The sponsor's medical monitor/designee should be contacted if there are any questions regarding concomitant medication or prior therapy. Refer to Section 7.4.3 for additional guidance on permitted/required treatments for toxicity management.

The trial site will supply supportive medications, eg, premedication, anti-viral medication, anti IL-6R. Immediate access to tocilizumab is mandated on site.

6.6.1.1 Antibiotic, Antiviral, and Antifungal Therapy

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

For subjects with a history of recurrent herpes virus infections, herpes infection during previous anti-lymphoma therapy, neutropenia and/or low CD4+ cell counts (<200 cells/µL) prophylactic antiviral therapy is mandatory, eg, acyclovir 400 mg 3 times a day PO. Prophylaxis against *P jiroveci*, eg, oral trimethoprim/sulfamethoxazole 160 mg/800 mg every other day is mandatory to subjects who are considered at increased risk, eg, subjects with low CD4+ cell counts (<350 cells/µL).

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

6.6.1.2 Immunizations

For subjects treated with GEN3009 and/or GEN3013, 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. Administer vaccines at least 4 weeks prior to start of treatment.

6.6.1.3 Immunoglobulin Therapies

Immunoglobulins administered at doses on the order of 1 g/kg body weight have the potential to alter the clearance of other antibodies. Investigators should therefore be aware that the efficacy of GEN3009 and/or GEN3013 may be decreased when administering immunoglobulins at these doses, for example for the treatment of immune thrombocytopenia, or other immune, inflammatory, or paraneoplastic conditions.

6.6.2 Prohibited Concomitant Therapy

The following medications are prohibited during the trial:

- Any anti-lymphoma therapy, eg, chemotherapy, radiotherapy or experimental therapy or other investigational drugs

  Note: Local palliative radiotherapy for pain relief may be allowed after discussion with the sponsor's medical monitor. Irradiated site cannot be used as measurable, target lesions when assessing response to treatment.
- Corticosteroid that exceed a total daily dose of 10 mg of prednisone or equivalent administered for more than 10 days unless for the management of AEs (eg, excluding corticosteroids given as premedication or CRS management)
- Herbal preparations or related OTC preparations containing herbal ingredients are not permitted during participation in the trial
- The use of live, attenuated vaccines is not allowed through the entire duration of trial. Killed virus vaccines are allowed. Note: SARS-CoV-2 vaccine is generally permitted, including mRNA-based, protein-based, or non-replicating viral vector-based vaccines. Consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired. **SARS-CoV-2 vaccine should not be administered during the DLT observation period.**
- Investigational agents

If a subject receives any of these during the trial, the sponsor must be notified for evaluation of whether the subject can continue treatment in the trial.

6.7 Investigational Medicinal Product Information

6.7.1 GEN3009 Information

GEN3009 is intended for administration by the IV route after dilution.

6.7.1.1 Physical Description of GEN3009

GEN3009 is supplied at CCI [redacted] mg/mL by the sponsor.

6.7.1.2 Packaging and Labeling

GEN3009 labels will contain information to meet the applicable regulatory requirements. For further details see the trial-specific IMP manual.

6.7.1.3 Preparation, Handling, and Storage

GEN3009 must be stored at controlled temperatures ranging from 2°C to 8°C (35.6°F to 46.4°F).

GEN3009 must be prepared aseptically at the site pharmacy. Refer to the IMP manual for additional guidance on trial drug preparation, handling, and storage.

6.7.2 Epcoritamab (GEN3013) Information

Epcoritamab (GEN3013) is to be administered as an s.c. injection by qualified site personnel. Injection site is preferably in the lower part of the abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during weekly administration.

6.7.2.1 Physical Description of Epcoritamab (GEN3013)

Epcoritamab (GEN3013) is supplied at 5 mg/mL or 60 mg/mL by the sponsor.

6.7.2.2 Packaging and Labelling

Epcoritamab (GEN3013) labels will contain information to meet the applicable regulatory requirements. For further details see the trial-specific IMP manual.

6.7.2.3 Preparation, Handling, and Storage

Epcoritamab (GEN3013) must be stored in a refrigerator at 2°C to 8°C (35.6°F to 46.4°F) until use.

Epcoritamab (GEN3013) is supplied as a concentrate for solution for s.c. injection. Priming and intermediate doses of epcoritamab must be diluted at the site/pharmacy using aseptic techniques. Detailed dose preparation instructions including the important dilution steps will be provided in the IMP manual.

6.7.3 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of trial drug in a drug accountability log. Drug accountability will be verified by the field monitor during site visits and at the completion of the trial. At trial close-out, and as appropriate during the trial, the investigator is to destroy all used and unused GEN3009 and/or epcoritamab (GEN3013), packaging, and drug labels, as per local regulations. A copy of the completed drug accountability log and documentation of drug destruction must be provided to the monitor or to the address provided in the investigator folder (unless otherwise agreed with sponsor).

6.8 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.8.1 Procedures

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

If the defect is combined with an AE, the trial-site personnel must report the AE to the sponsor according to the AE and SAE reporting process and timelines (Section 10.4) in addition to reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.8.2 Contacting Sponsor Regarding Product Quality

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

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

7.1 Dose-limiting Toxicities

7.2 Dose Escalation: Dose-limiting Toxicity

For the Dose Escalation, the DLT assessment period is defined as 28 days from the start of the first GEN3009 administration on C1D1.

The occurrence of any of the toxicities outlined in this section will be considered a DLT.

All Grade 5 toxicities

Hematologic:

- Thrombocytopenia Grade 4 (<25.0 × 10^9/L [<25,000/µL]) that is not due to underlying malignancy or extraneous cause
- Neutropenia Grade 4 (<0.5 × 10^9/L [<500/µL]) lasting >7 days **not attributable to underlying disease**
- Febrile neutropenia Grade 3 or 4 lasting >2 days (ie, absolute neutrophil count [ANC] <1.0 × 10^9 cells/L with a single temperature of >38.3°C [100.9°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour)
- Grade 3 or 4 hemorrhage associated with thrombocytopenia of ≥Grade 3 requiring platelet transfusion
- Anemia Grade 4.
- TLS Grade 4 (see Appendix 4 for additional information)

Non-hematologic:

- All non-hematological AEs of grade ≥ 3 (severe or life-threatening), **excluding** the following:
    a. Fever Grade 3 (>40.0°C [>104.0°F]) for ≤24 hours
    b. Hypotension Grade 3 (medical intervention indicated; hospitalization indicated) resolving in ≤24 hours
    c. Laboratory values out of normal range that do not have any clinical consequence, are clinically transient in nature and that resolve in ≤3 days (including electrolyte abnormalities that respond to medical intervention)
    d. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) Grade 3 returning to Grade 1 or baseline in ≤7 days
    e. Nausea Grade 3 that responds to adequate antiemetic treatment in ≤3 days
    f. Vomiting Grade 3 that responds to adequate antiemetic treatment in ≤3 days
    g. Diarrhea Grade 3 that responds to adequate antidiarrheal treatment in ≤3 days
    h. Fatigue/asthenia Grade 3 when fatigue/asthenia was present at baseline or that lasts for <14 days
    i. Alopecia (no grading)

Frequent laboratory monitoring of complete blood count including differential should be initiated to document start and resolution of hematological AEs. All AEs occurring during the defined DLT evaluation period will be assessed according to the criteria above. All AEs, including those not qualifying for a DLT, will be monitored and included in the evaluation of the toxicity profile of GEN3009 unless the event is clearly determined to be unrelated to GEN3009.

7.3 Safety Run-in for Expansion: Dose-limiting Toxicity

For the Expansion GEN3009 + GEN3013 combination cohort safety run-in, the DLT assessment period is defined as 28 days from the start of the first GEN3009 administration on C1D1.

The occurrence of any of the toxicities outlined in this section will be considered a DLT.

All Grade 5 toxicities

Hematologic:

- Thrombocytopenia Grade 4 (<25.0 × 10^9/L [<25,000/μL]) lasting >7 days not attributable to underlying disease
- Neutropenia Grade 4 (<0.5 × 10^9/L [<500/μL]) lasting >7 days not attributable to underlying disease
- Febrile neutropenia Grade 3 or 4 lasting >2 days (ie, ANC <1.0 × 10^9 cells/L with a single temperature of >38.3°C [100.9°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour)
- Grade 3 or 4 hemorrhage associated with thrombocytopenia of ≥Grade 3 requiring platelet transfusion
- Anemia Grade 4
- TLS Grade 4 (see Appendix 4 for additional information)

Non-hematologic:

- All non-hematological AEs of Grade ≥3 (severe or life-threatening), excluding the following:
  a. CRS Grade 3 according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee et al., 2019), which has improved to Grade ≤2 or resolved (Grade 0) within 48 hours
  b. ICANs Grade 3 according to ASTCT criteria (Lee et al., 2019), which has improved to Grade ≤2 or resolved (Grade 0) within 48 hours
  c. Fever Grade 3 (>40.0°C [>104.0°F]) for ≤24 hours (this applies to fever not considered a symptom of other toxicities such as CRS)
  d. Hypotension Grade 3 (medical intervention indicated; hospitalization indicated) resolving in ≤24 hours (this applies to hypotension not considered a symptom of other toxicities such as CRS)
  e. Laboratory values out of normal range that do not have any clinical consequence, are clinically transient in nature and that resolve in ≤ 7 days (including electrolyte abnormalities that respond to medical intervention)
  f. AST and/or ALT Grade 3 returning to Grade 1 or baseline in ≤7 days

g. Nausea Grade 3 that responds to adequate antiemetic treatment in ≤3 days
h. Vomiting Grade 3 that responds to adequate antiemetic treatment in ≤3 days
i. Diarrhea Grade 3 that responds to adequate antidiarrheal treatment in ≤3 days
j. Fatigue/asthenia Grade 3 when fatigue/asthenia was present at baseline or that lasts for <14 days
k. Alopecia (no grading)

Frequent laboratory monitoring of complete blood count including differential should be initiated to document start and resolution of hematological AEs. All AEs occurring during the defined DLT evaluation period will be assessed according to the criteria above. All AEs, including those not qualifying for a DLT, will be monitored and included in the evaluation of the toxicity profile of GEN3009 in combination with GEN3013 unless the event is clearly determined to be unrelated to GEN3009 and/or GEN3013.

7.4 Dose Modification Guidance and Safety Stopping Criteria

7.4.1 Dose Escalation Part (GEN3009 Monotherapy)

If a subject experiences a DLT, the subject may continue treatment with GEN3009, if the toxicity recovers to ≤ Grade 2 or baseline within 4 weeks from occurrence of the DLT. Continued administration of GEN3009 must be agreed to between the sponsor and the investigator based on a thorough assessment of the event, the duration of the event, and benefit-risk for the subject. In the event a subject experiences a second episode of a DLT with GEN3009, the treatment will be permanently discontinued. Treatment with GEN3009 will be discontinued in the event the DLT is not resolved within 4 weeks.

- If a subject experiences toxicity that qualifies as a DLT but occurs after the 4-week DLT evaluation period, the subject's benefit-risk must be thoroughly assessed. Continued treatment with GEN3009 must be agreed between the sponsor and the investigator.
- For the subject who receives more than 4 doses of GEN3009, ie, treatment beyond the DLT evaluation period, all corresponding AEs that meet the DLT criteria will be considered for the purpose of determining the MTD and/or the RP2D. For the declaration of the RP2D of GEN3009 in the Expansion and for further development, the totality of the data from Dose Escalation (including safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated).
- During the trial, a planned dose of GEN3009 can be postponed for up to 4 weeks from the last dose of trial drug for 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, GEN3009 should be discontinued, unless approved by the sponsor's medical monitor.
- During the trial, the GEN3009 dose can be held for the following laboratory results:
    a. If platelet count $<50\times10^9$/L, hold dose until platelet count is $\geq 50\times10^9$/L.
    b. If febrile neutropenia $<0.5\times10^9$/L, hold dose until neutrophil count is $\geq0.5\times10^9$/L.
    c. If hemoglobin is <8 g/dL (<5 mmol/L), hold dose until hemoglobin ≥8 g/mL (>5 mmol/L).

Note: If the investigator deems any of the above cytopenia as bone marrow involvement due to the disease, continuation of GEN3009 treatment can be discussed with the sponsor's medical monitor. Transfusion with blood products and/or administration with G-CSF is permitted if needed (refer to Section 6.6.1).

7.4.2 Expansion Part (Including Safety Run-in)

7.4.2.1 GEN3009 Dose Modification Rules

Dose reduction is not allowed for GEN3009.

Dose delay is allowed for GEN3009 for the management of toxicities. GEN3009 administration can be postponed up to 4 weeks from the next scheduled date.

- If a dose is delayed more than 4 weeks from the next scheduled dosing date due to toxicity, GEN3009 should be discontinued, unless approved by the sponsor's medical monitor.
- If a GEN3009 dose is delayed or withheld for any reason, GEN3013 may be continued, if clinically indicated, after consultation with the sponsor's medical monitor.
- If GEN3009 is discontinued, GEN3013 can be continued if approved by the sponsor's medical monitor.

7.4.2.2 GEN3013 Dose Modification Rules

Dose reduction is **not** allowed for GEN3013 on an individual subject level in this trial. Refer to Section 4.3 for dosing rationale.

If a dose is delayed more than 6 weeks, the subject should be asked to perform an unscheduled visit for collection of AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and a limited physical examination (as clinically indicated) after consultation with the sponsor's medical monitor.

A repriming cycle is necessary if dose is delayed at certain time points, as described below. A repriming cycle consists of a weekly schedule of a priming dose, intermediate dose, and 2 full doses. Refer to Table 15 for the repriming cycle Visit Assessment Schedule.

A repriming cycle should occur:

- For the second GEN3013 full dose onward (ie, C2D1), if the interval between the previous dose of GEN3013 and next planned dose exceeds 6 weeks.

During the repriming cycle, CRS prophylaxis must be resumed with 3 consecutive days of corticosteroids beginning at each GEN3013 dose, until at least 1 full dose of GEN3013 is administered without subsequent occurrence of CRS Grade ≥2 (see Section 6.2.2).

Once the full repriming cycle is completed, the subject should resume treatment with Day 1 of the next planned cycle (subsequent to the cycle during which the dosing was delayed). For example, if the subject experiences a 7-week delay after C3D1, the subject should receive a repriming cycle, then continue treatment at C4D1. GEN3009 dose will continue as scheduled.

If GEN3013 dose is delayed, withheld, or discontinued during the combination treatment period, GEN3009 can be continued if approved by the sponsor's medical monitor.

Refer to Section 7.4.3 for information about dose modifications due to AEs.

7.4.3 Dose Modification Guidelines for Toxicity Management

Refer to Section 6.2.1 and Section 6.2.2 for requirements on premedication, and Section 6.3, Section 6.6.1, Section 7.5, Appendix 13, and Appendix 14 for guidance on prevention and management of specific AEs.

7.4.3.1 Cytopenias (All Cohorts)

GEN3009 and/or GEN3013 dose (regardless of being monotherapy or combination therapy) will be held for up to 4 weeks for the following hematologic laboratory results:

Table 25 Dose Modification Rules for Cytopenias

Laboratory Parameter	Laboratory Value	
	Hold GEN3009 and/or GEN3013 Dose	**Resume GEN3009 and/or GEN3013 Dose**
Platelet count[a]	$<50 \times 10^9$/L	$\geq 50 \times 10^9$/L
Neutrophil count	$<0.5 \times 10^9$/L	$\geq 0.5 \times 10^9$/L
Hemoglobin	<8 g/dL (<5 mmol/L)	≥8 g/dL (>5 mmol/L)

No dose-reduction is allowed for GEN3009 or GEN3013, but a repriming cycle may be needed if the interval between the previous dose of GEN3013 and next planned dose exceeds 6 weeks.

a. In subjects with CLL having platelets $\geq 30 \times 10^9$/L (30,000/μL) can be dosed after the consultation with the sponsor's medical monitor.

Note: If the investigator deems any of the above cytopenias are secondary to bone marrow involvement by the disease, continuation of study treatment can be discussed with the sponsor's medical monitor. Transfusion with blood products (eg, RBC, platelets) and/or administration with G-CSF is permitted if needed. G-CSF must be used in case of ≥Grade 3 neutropenia during Dose Escalation and safety run in parts of the study. See Sections 6.6.1 and 7.5.1.

7.4.3.2 Cytokine Release Syndrome (the GEN3009 + GEN3013 Combination Cohort)

CRS has been reported with the use of GEN3013. To date, CRS is not a known/identified risk with GEN3009. Refer to Section 7.5.2 and Appendix 13 for guidelines for grading and supportive care for CRS management.

CRS must be graded according to the ASTCT grading for CRS (Lee et al., 2019).

Table 26 GEN3013 Dose Modification for Cytokine Release Syndrome (GEN3009 + GEN3013 Combination Cohort)

CRS ASTCT Grade	Dose Modification
Grade 1	• Hold GEN3013 (and GEN3009 if given in combination) until resolution of CRS event and treat the subject (see Appendix 13)
Grade 2	• Hold GEN3013 (and GEN3009 if given in combination) until resolution of CRS event and treat the subject. • If Grade 2 or higher CRS occurs with the second full dose or beyond, administer CRS prophylaxis with the next dose until a GEN3013 dose is given without subsequent CRS (of any grade)
Grade 3 lasting less than 72 hours	• Hold GEN3013 (and GEN3009 if given in combination) until resolution of CRS event and treat the subject. • Continue with the next planned GEN3013 dose at the planned date and hospitalize the subject for at least 72 hours following this GEN3013 administration. • If Grade 2 or higher CRS occurs with the second full dose or beyond, administer CRS prophylaxis with the next dose until a GEN3013 dose is given without subsequent CRS (of any grade)
Grade 3 lasting longer than 72 hours	• Permanently discontinue administration of GEN3013 and treat the subject (see Appendix 13)
Grade 3, second occurrence (ie, 2 separate Grade 3 events)	• Permanently discontinue administration of GEN3013 even if each event resolved to Grade 2 within 72 hours, and treat the subject (see Appendix 13)
Grade 4 CRS	• Permanently discontinue administration of GEN3013 and treat the subject (see Appendix 13)

7.4.3.3 Tumor Lysis Syndrome (All Cohorts)

In cases of TLS, hold GEN3009 and/or GEN3013 (regardless of being monotherapy or combination therapy) until the TLS has resolved.

TLS should be reported as an AE, using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading, whereas clinical TLS should be reported as an AESI, using Cairo-Bishop grading (see Appendix 4).

Refer to Section 7.5.4 for prevention and management of TLS.

7.4.3.4 Immune Effector Cell-Associated Neurotoxicity Syndrome (GEN3009 + GEN3013 Combination Cohort)

ICANS has been reported with the use of GEN3013. To date, ICANS is not a known/identified risk with GEN3009. See Table 27 for information on GEN3013 dose modification for ICANS. Refer to Section 7.5.3 for supportive care and Appendix 13 grading of ICANS.

Table 27 GEN3013 Dose Modification for ICANS (GEN3009 + GEN3013 Combination Cohort)

ICANS ASTCT Grade	Dose Modification
Grade 1 or 2	• Hold GEN3013 (and GEN3009 if given in combination) until resolution of ICANS to Grade 0 and treat the subject appropriately.
Grade 3 or 4	• Permanently discontinue administration of GEN3013 and treat the subject appropriately.

7.4.3.5 All Other AEs Related to GEN3009 and/or GEN3013

Relationship assessment will be based on the Investigator's judgement.

Table 28 Dose Modification for All Other GEN3009 and/or GEN3013-Related AEs

CTCAE Grade	Dose Modification
Grade 1	• Continue study drug
Grade 2	• Continue study drug
Grade 3*	• First episode: May hold treatment until improvement to ≤ Grade 2 or resolution to baseline. • Second episode of the same AE considered related to study drug: Hold treatment until improvement to ≤ Grade 2 or resolution to baseline and permanently discontinue if no improvement within 14 days unless otherwise agreed upon with the sponsor's medical monitor.
Grade 4[a]	• First episode: Hold treatment until improvement to ≤ Grade 2 or resolution to baseline. • Second episode of same AE considered related to study drug: Permanently discontinue study drug unless otherwise agreed upon with the sponsor's medical monitor.

a. This may exclude any asymptomatic isolated laboratory abnormalities without any clinical consequences such as hypoalbuminemia, hypophosphatemia, hyponatremia, etc.

7.5 Management of Specific Adverse Events

7.5.1 Neutropenia and Other Cytopenias (All Cohorts)

G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and neutropenia, when clinically indicated or at the investigator's discretion.

- In case of ≥ Grade 3 neutropenia, use of growth factors is mandated during Dose Escalation and Safety Run-in parts of the study.

Neutropenic fever should be evaluated immediately for any potential underlying reason (eg, blood cultures, imaging, etc) and managed based on local institutional guidelines ensuring appropriate anti-infective prophylaxis.

For other cytopenias, blood or platelet transfusion should be given based on local institutional guidelines.

Complete blood counts should be monitored until count recovery.

7.5.2 Supportive Care for Cytokine Release Syndrome (Expansion GEN3009 + GEN3013 Combination Cohort Only)

Rescue medication in terms of an antidote to reverse the action of GEN3013 is not available. Potential adverse effects of GEN3013 have to be treated symptomatically. For treatment of CRS patients should receive supportive care according to Appendix 13.

The supportive care can include, but is not limited to:

- Infusion of saline
- Systemic glucocorticosteroid, antihistamine, antipyretic
- Support for blood pressure (vasopressin, vasopressors)
- Support for low-flow and high-flow oxygen and positive pressure ventilation
- Monoclonal antibody against IL-6R, IL-6 or IL-1 (eg, tocilizumab, siltuximab, and/or anakinra)
- Blood product support, analgesics, skin and mouth care, etc, should be according to local guidelines and investigator's discretio.

7.5.3 Supportive Care for Immune Effector Cell-Associated Neurotoxicity Syndrome (Expansion GEN3009 + GEN3013 Combination Cohort Only)

Close monitoring of mental status during treatment is important to secure a timely start of supportive care as needed. Supportive care can include, but is not limited to:

- Initiation of IV hydration
- Withhold oral intake
- Avoid medications that cause central nervous system depression
- Initiation of corticosteroids
- Anti-cytokine therapy
- Anti-convulsive therapy

7.5.4 Tumor Lysis Syndrome Prevention and Management (All Cohorts)

To prevent TLS, all subjects should receive appropriate hydration and allopurinol according to local standards or available guidelines (Coiffier et al., 2008). Subjects who are considered to have an increased risk for TLS, eg, due to the type of lymphoma, the tumor burden (bulky disease and/or elevated lactate dehydrogenase), 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. If signs of TLS occur, supportive therapy, including rasburicase, may be used as clinically indicated at the investigator's discretion. In addition, close monitoring of laboratory parameters to allow for early diagnosis of a possible TLS is recommended.

For details, refer to Table 4 and Table 15 for the minimum sampling time points for tumor lysis. Definition of TLS and guidance for grading of TLS events are provided in Appendix 4.

7.5.5 Tumor Flare Reaction Management (All Cohorts)

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

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

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that ≥Grade 2 TFR be treated with corticosteroids at the investigator's discretion. NSAIDs (ie, ibuprofen 400 to 600 mg orally every 4 to 6 hours as needed) and/or narcotic analgesics for pain management may also be administered as needed. In mild to moderate cases, it is suggested that GEN3009 and/or GEN3013 be continued along with symptomatic treatment as indicated above.

8 DISCONTINUATION, FOLLOW-UP AND COMPLETION

8.1 Discontinuation of Treatment

A subject's trial drug may be discontinued for any of the following reasons:

- Unacceptable AE requiring treatment discontinuation (refer to Section 7)*
- Subject non-compliance
- Sponsor decision
- Subject request to discontinue treatment*
- Pregnancy
- Clinical progression*
- Disease progression according to response criteria
- Other

*Imaging should continue to be performed until evidence of radiographic disease progression despite treatment discontinuation. When a subject discontinues trial drug, they are to remain on trial and are to be followed until death, initiation of subsequent therapy, or any other reason listed in Section 8.2.

Subjects should be examined regularly according to the protocol schedule, or more frequently, as needed. If the decision to discontinue trial drug treatment occurs around the time of the next planned treatment administration visit, the assessment schedule for the treatment discontinuation visit should be followed. Subjects should be followed for safety within 30 days of the last administration of trial drug in GEN3009 monotherapy cohorts and 60 days of the last administration of trial drug in GEN3009 + GEN3013 combination cohort

8.2 Withdrawal from the Trial

Subjects are to be withdrawn from the trial (Dose Escalation or Expansion) for the following reasons:

- Death
- Lost to follow-up (refer to Section 8.4)
- The investigator or sponsor believes (eg, that for safety or tolerability reasons [eg, AE]) it is in the best interest of the subject to discontinue the trial intervention
- Subject withdraws consent from the trial
- Other

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected or generated before such a withdrawal of consent. A subject may choose to discontinue from any future trial assessments (eg, dosing, imaging, blood sampling, etc) but agree to remain in the trial and to be followed for survival follow-up, without withdrawal of consent. If a subject withdraws consent from the trial, they may request destruction of any samples (including those collected for biomarker testing) taken and not tested, and the investigator must document this in the site trial records. When a subject withdraws consent, the reason for withdrawal is to be documented in the source document. Trial drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. The

investigator and sponsor will make every effort to ensure subject data are followed for completion of all trial safety assessments including the safety follow-up visit and survival follow-up (refer to Table 3, Table 6, and Table 11) at the time of trial discontinuation.

8.3 Safety Follow-up Visit

Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days after the last dose of trial drug in GEN3009 monotherapy cohorts and 60 days after the last administration of trial drug in the GEN3009 + GEN3013 combination cohort. If the subject initiates new anti-lymphoma therapy after the discontinuation of treatment, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once the safety follow-up visit is completed, the subject will move into survival status follow up (refer to Section 9.3.6).

8.4 Lost to Follow-Up

For subjects whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show “due diligence” by contacting the subject, family, or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow up until due diligence has been completed (minimum of 3 documented attempts).

9 TRIAL ASSESSMENTS

9.1 Demography and Baseline Assessments

9.1.1 Demographics

Demographic details will be assessed and recorded at screening.

9.1.2 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, prior evidence of CD20 positivity (the GEN3013 + GEN3009 combination arm), and staging criteria (ie, Ann Arbor staging for B-cell NHL [refer to Appendix 5] and Rai or Binet staging for CLL/SLL [refer to Appendix 6]) will be recorded at screening.

9.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3009 and/or GEN3013 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to the first GEN3009 and/or GEN3013 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of GEN3009 and/or GEN3013 will be documented as an AE. See additional details in Section and 10.2.

9.1.4 Concomitant Medication and Procedures

Any medication or therapy (including OTC or prescription medicines, vitamins, and/or herbal supplements, vaccinations, and blood transfusions) other than GEN3009 is considered concomitant medication and must be recorded. Relevant prior concomitant medication administered and/or procedures during the trial must be recorded from <21 days prior to the first dose of GEN3009 and up to 30 days after the last dose of GEN3009 in the monotherapy arms and 60 days after the last dose of GEN3009 + GEN3013 in the combination arm. The subject must be instructed to notify the investigational site about any new medications he or she takes after the start of the trial drug. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy/procedures.

9.1.5 Prior Cancer Therapy and Surgery

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

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

9.2 Efficacy Assessment

9.2.1 Definition of Measurable and Assessable Disease

Eligible subjects with B-cell NHL must have at least 1 measurable site of disease (refer to inclusion criteria Section 5.1) for disease evaluations. Measurable sites of lymphoma are defined as lymph nodes, lymph node masses, or extranodal sites. The measurement must be determined by imaging evaluation by the local radiologist. Up to 6 measurable sites will be followed as indicator (target) lesions for each subject. All other sites of disease will be considered assessable by objective evidence of disease (ie, radiographic imaging, bone marrow assessment, physical examination, or other procedures as necessary), but is not measurable (nontarget) as defined above. Examples of accessible disease may include bone marrow involvement, bone lesions, effusions, or thickening of bowel wall.

9.2.2 Evaluations

Efficacy assessments will be conducted as specified in the visit assessment schedules (refer to Table 2, Table 3, Table 5, Table 6, Table 10, and Table 11 will include the following: imaging assessments (including hepatic involvement and splenic involvement [size by vertical: cranial to caudal]), bone marrow assessment (as applicable), physical exam including constitutional symptoms, ECOG performance status, MRD status, and other procedures as necessary. All efficacy assessments should be conducted throughout the trial until disease progression, the start of new anti-cancer therapy, death or withdrawal of consent from trial participation, whichever occurs first.

Response assessment for B-cell NHL will be according to revised response criteria (Cheson et al., 2014) (refer to Appendix 7) and for CLL according to the iwCLL (Hallek et al., 2018) (refer to Appendix 8).

9.2.2.1 Radiographic Assessment

For B-cell NHL excluding CLL, an ^{18F}-FDG-PET CT (or CT/MRI and FDG-PET when PET CT not available) must be performed at screening (ie, within 3 weeks prior to the first dose of GEN3009). For subjects with FDG-avid tumors at screening, all subsequent disease assessments will be performed with FDG-PET CT using the 5-point scale (Barrington et al., 2014). For subjects with non-avid or variably FDG-avid tumors, CT scan with IV contrast of neck/chest/abdomen/pelvis/additional known lesions will be performed. The CT component of the PET CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET CT is not available, a standalone diagnostic CT/MRI and a standard FDG-PET should be performed. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast so as to not 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.

For CLL, CT/MRI must be performed at screening (ie, within 3 weeks prior to the first dose of GEN3009) and subsequent response assessments.

MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, 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.

In monotherapy cohorts, an MRI or CT scan of the brain (with lumbar puncture) at screening and during the course of trial should be performed if clinically indicated. In the combination cohort with GEN3013, an MRI or CT scan of the brain is mandatory during screening within 21 days of C1D1, and lumbar puncture is required only if clinically indicated and required within 21 days of C1D1.

Imaging assessment schedules in both the Dose Escalation and Expansion are: at screening, on Cycle 2 (Week 6), Cycle 3 (Week 12), Cycle 5 (Week 18), Cycle 6 (Week 24), Cycle 9 (Week 36), Cycle 12 (Week 48), and every 24 weeks (Cycle 18, 24, etc.) thereafter until confirmation of disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. All assessments will be determined from the first dose date and will follow the counting of calendar days and not the dosing cycles. Refer to Table 29 for details. Refer to Appendix 9 for PET positivity evaluation.

Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a subject as necessary. 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.

Table 29 Imaging Assessments During Dose Escalation and Expansion

Subject Diagnosis	Imaging	Screening	On-treatment Assessment
B-cell NHL	FDG-PET CT	Required within 3 weeks (ie, 21 days) before Cycle 1 Day 1	Required at: Cycle 2 (Week 6±7 days), Cycle 3 (Week 12±7 days), Cycle 5 (Week 18±7 days), Cycle 6 (Week 24±14 days), Cycle 9 (Week 36±14 days) Cycle 12 (Week 48±14 days) then every 24 weeks thereafter (ie, Cycle 18, 24, 36±14 days, etc) until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first
B-cell NHL including CLL	CT/MRI (neck, chest, abdomen, and pelvis) Note: For subjects with non-avid or variably FDG-avid tumors, CT scan with IV contrast of neck/chest/abdomen/p	Required within 3 weeks (ie, 21 days) before Cycle 1 Day 1	Required at: Cycle 2 (Week 6±7 days), Cycle 3 (Week 12±7 days), Cycle 5 (Week 18±7 days), Cycle 6 (Week 24±14 days), Cycle 9 (Week 36±14 days) Cycle 12 (Week 48±14 days)

Subject Diagnosis	Imaging	Screening	On-treatment Assessment
	elvis/additional known lesions will be performed MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT		then every 24 weeks thereafter (ie, Cycle 18, 24, 36±14 days, etc.) until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first
B-cell NHL including CLL	CT/MRI of brain	1. Required at screening if clinically indicated to rule out CNS involvement in GEN3009 monotherapy cohorts 2. Required at screening in all subjects in GEN3009 + GEN3013 combination cohort	Required as clinically indicated

9.2.2.2 Bone Marrow Assessment

For all CLL subjects and B-cell NHL subjects with bone marrow involvement, fresh bone marrow biopsy and bone marrow aspirate must be obtained at screening (ie, within 3 weeks prior to the first dose of GEN3009) and at the time of CR or as clinically indicated. However, archival bone marrow biopsy obtained as routine SOC taken within 28 days before the first dose of GEN3009 is acceptable. Fresh bone marrow aspirate is mandatory at screening.

- Bone marrow evaluation must include morphological examination and either flow cytometry or immunohistochemistry (IHC).
- For CLL subjects and B-cell NHL subjects with bone marrow involvement, a portion of the bone marrow aspirate collected at screening and to confirm CR will be used for MRD assessments.
- For B-cell NHL subjects with no bone marrow involvement at baseline, no bone marrow for MRD is required.
- If a subject is MRD-positive in the bone marrow but maintains CR, an additional bone marrow aspirate will be collected after 3 months, if clinically feasible.

A bone marrow biopsy with aspirate from CLL subjects should be obtained during the trial for the following:

- To confirm a CR or nodular partial remission that is supported by physical examination findings, laboratory evaluations and radiographic evaluations (Hallek et al., 2018);
- If progression is only shown in 1 parameter to confirm cytopenic progression (ie, neutropenia, anemia, and/or thrombocytopenia and to distinguish from autoimmune and treatment-related cytopenias).

Refer to Table 30 for details.

Table 30 Bone Marrow Biopsy and Aspirate Collection During Dose Escalation and Expansion

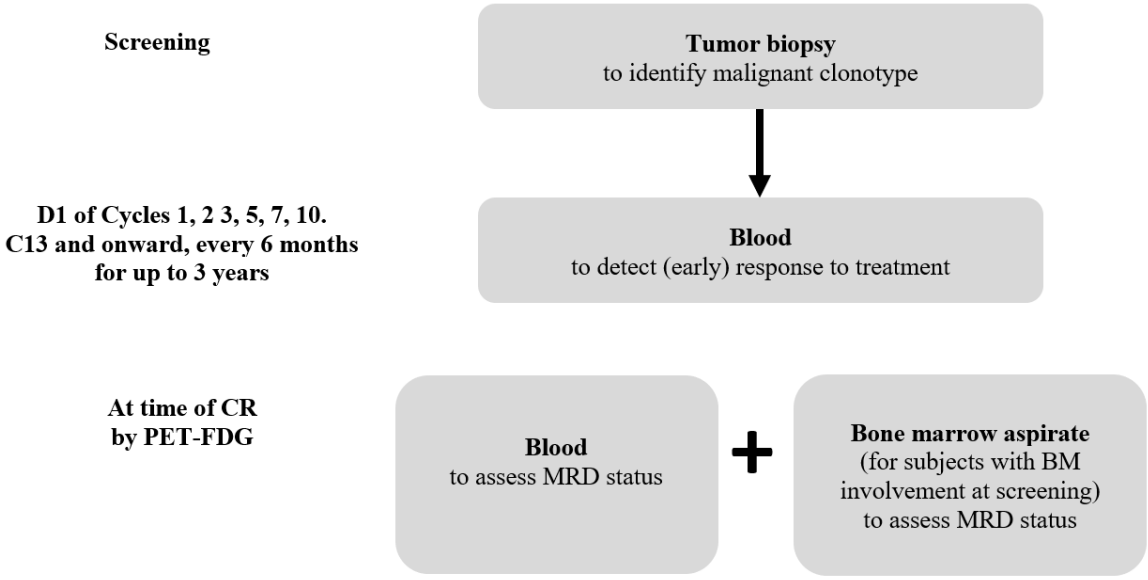
Subject Diagnosis	Procedure	Screening	On-treatment Assessment
• CLL • Lymphomas with bone marrow involvement	• Bone Marrow Aspirate	• Fresh bone marrow aspirate is required.	• Bone marrow aspirate is required at the time of CR or as clinically indicated. • If at CR, bone marrow has MRD, additional aspirate will be collected after 3 months, if clinically feasible • For CLL only: bone marrow biopsy is required to confirm nodular partial remission; or if progression is shown in 1 parameter to confirm cytopenic progression
	• Bone Marrow Biospy	• Fresh bone marrow biopsy is required. Archival bone marrow biopsy obtained as routine standard of care within 28 days of Cycle 1 Day 1 is acceptable	

9.2.2.3 Minimal Residual Disease Assessment (MRD)

MRD will be assessed by tracking the presence of DNA that encodes the B cell receptor (BCR) expressed specifically by the cancer cells. The DNA sequence of this BCR will be identified in the tumor biopsy that is requested at screening and/or in bone marrow aspirate using next-generation sequencing (NGS) (see Figure 2). After start of treatment, blood samples are requested at fixed timepoints and at time of CR to assess whether the amount of cancer DNA is declining, as a potential measure of (early) response, and to assess MRD.

As an exploratory analysis, when a subject reaches a CR by FDG-PET (or by CT/MRI for non-FDG avid disease) and having bone marrow involvement documented at screening, a portion of the aspirate collected to confirm CR will be used to assess MRD. Subjects having no bone marrow involvement at screening will not require further bone marrow examination for MRD.

Figure 2 MRD Assesment by Tracking Malignant Clonotype



Note: After start of treatment, blood samples are requested at fixed timepoints to assess whether the amount of cancer DNA is declining, as a potential measure of (early) response, and to assess MRD at time of PET/CT response assessments. When a patient reaches a CR by PET-FDG (or by CT/MRI for FDG PET non-avid disease), MRD will be measured in blood to assess whether the cancer is still detectable or not.

9.2.3 Assessment of Disease Response and Progressive Disease

9.2.3.1 Assessment of Response

Tumor response according to imaging assessment as described in visit assessment schedules (refer to Table 2, Table 3, Table 5, Table 6, Table 10, and Table 11) will be performed by the investigators at the site to make decisions for continuation of treatment.

For B-cell NHL, tumor response will be determined according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin Lymphoma and Non-Hodgkin Lymphoma (Cheson et al., 2014) (refer to Appendix 7 and Appendix 10). For timepoints when FDG-PET assessment (metabolic response) is available, the FDG-PET (metabolic response) assessment trumps the CT-response in FDG-avid histologies. For timepoints 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 timepoint, with no worsening, does not preclude prior FDG-PET CR [metabolic response] and response can stay as CR).

For CLL, response will be assessed per guidelines for diagnosis, indications for treatment, response assessment and supportive management of CLL (Hallek et al., 2018) (refer to Appendix 8).

For response assessment, imaging studies including FDG-PET CT, CT or MRI will be performed on Cycle 2 (Week 6), Cycle 3 (Week 12), Cycle 5 (Week 18), Cycle 6 (Week 24), Cycle 9 (Week 36), Cycle 12 (Week 48), and every 24 weeks (Cycle 18, 24, etc) thereafter until disease progression, the start of a new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first.

In the Dose Escalation and Expansion (including safety run-in), response assessment will be conducted locally by investigators.

As local palliative radiotherapy on non-target lesions is permitted (refer to Section 6.6), if given during the trial, these lesions should no longer be included in the response assessment.

9.2.3.2 Progressive Disease

Imaging findings suggestive of progressive disease (PD) despite evidence of clinical benefit have been described with immunomodulatory agents, eg, tumor flare or pseudo-progression (Cheson et al., 2016). Currently, the potential for similar effect of GEN3009 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 GEN3009 treatment, may represent pseudo-progression and may not be designated as PD, unless there is continued increase in size on subsequent imaging studies or confirmed with biopsies. Hence, in order to avoid premature termination, subjects can remain on the GCT3009-01 trial at investigator and subject discretion until the response or lack thereof is confirmed on subsequent imaging.

9.3 Clinical Safety Assessments

9.3.1 Physical Examination

The investigator or qualified designee will perform a full physical examination according to SOC during the screening period and report any relevant findings as medical history. Report any medical conditions as an AE if they were assessed by the investigator to have been caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications. After the first dose of trial drug, report any new or worsening findings since the last assessment as AEs. The time points for full physical examinations are described in Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15.

In addition to the above, the physical examination should evaluate the presence of palpable lymph nodes and tumor masses. Specifically, the bidimensional diameters of the largest palpable lymph nodes in each of the following sites should be documented: cervical, axillary, and inguinal. To assess for enlargement, the dimensions of the liver and spleen below their respective costal margins, as assessed by palpation, should also be documented.

Height (without shoes) rounded to nearest centimeter, and body weight will be measured as described in Table 2, Table 5, and Table 10. Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.1.1 Immune Effector Cell-Associated Neurotoxicity Syndrome Assessment (GEN3009 + GEN3013 Combination Cohort only)

Assessment for neurotoxicity must be performed during therapy with GEN3013 by the trial site staff. An assessment according to ICANS evaluation (Lee et al., 2019) should be performed as indicated in Table 10, Table 10, and Table 15. ICANS assessment must be performed daily in case of unscheduled hospitalization due to symptoms associated with CRS. Finally, additional ICANS assessment should always be performed when clinically indicated.

ICANS is a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused immune

effector cells, including T cells. Symptoms can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema (Lee et al., 2019).

The grading of ICANS requires assessment of the 10-point immune effector cell-associated encephalopathy (ICE) score as well as evaluation of 4 other neurological domains: level of consciousness, seizures, motor symptoms, and signs of raised intracranial pressure/cerebral edema, which may occur with or without encephalopathy (see Appendix 14 for additional details).

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

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

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

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

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

9.3.2 Vital Signs

Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) should be measured with the subject in a sitting position. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed as indicated in Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15. On non-infusion days, vital signs should be assessed any time during the visit.

More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

9.3.3 Electrocardiograms

The ECGs will be recorded digitally at the sites by using the standard 12-leads as outlined in Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15. ECGs will be performed in accordance with the ECG manual issued by the vendor. The digital ECGs will be transmitted from the sites electronically to a central laboratory for a measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the print out. In case of discrepancy between central and the investigator ECG readings, the central reading will be used for trial analysis purposes.

For the ECG recordings, the subjects must be resting and in a supine or reclined position for at least 10 minutes. ECGs should be done in triplicate, 5 minutes apart (±5 minutes). In case any

irregularity (eg, vomiting or cough) occurs during the recording of the ECG, the ECG should be repeated.

9.3.4 ECOG Performance Status

The ECOG performance status will be assessed by the investigator as indicated in Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15. Performance status will be scored using the ECOG performance status scale index (refer to Appendix 11).

9.3.5 Constitutional Symptoms (B Symptoms)

Constitutional symptoms will be evaluated at screening and before GEN3009 administration as indicated in Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15. Constitutional symptoms include night sweats, weight loss > 10% over 6 months, and extreme fatigue and/or fever without infection.

9.3.6 Survival Status

Survival status will be assessed every 3 months via telephone contact, email, or on-site visit, after the last administration of GEN3009 and/or GEN3013 and will continue until the subject dies or withdraws from the trial. Data will be collected as reported by the subject regarding disease status, new anti-lymphoma treatment, any other malignancy other than the disease under study (ie, a second primary malignancy), and survival status, if available. If the subject is not available for this assessment, the response should be entered as “lost to follow up” (Section 8.4).

9.4 Clinical Laboratory Assessments

9.4.1 Laboratory Parameters

The laboratory parameters listed in Table 31 must be performed as indicated in the visit assessment schedules (refer to Table 2, Table 3, Table 5, Table 6, Table 10, Table 11, and Table 15). Any local or central laboratory values leading to a dose modification/delay should be recorded as an AE (Section 10.2.5).

Laboratory abnormalities are to be recorded as AEs also if considered clinically relevant by the investigator (see Section 10.2.5).

Local Laboratory Assessments

Local laboratory values for hematology, biochemistry and coagulation must be obtained within 3 days prior to the first dose of each subject and reviewed by the investigator prior to the first dose to ensure that the subject is still eligible. For the subsequent doses, these laboratory values must be obtained within 1 day, preferably on the same day prior to each GEN3009 and/or GEN3013 administration, and reviewed by the investigator prior to each administration to ensure the subject can be dosed in line with the dosing instructions as defined in the protocol. As this is a FIH trial, the timing of safety laboratory assessments may be adjusted during the trial based on emerging data.

Additional local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions of the subject.

Local laboratory assessments outlined in Table 31 must be recorded.

Central Laboratory Assessments

Central laboratory assessments include immunophenotyping for lymphocytes (Section 9.8.3.1), PK (Section 9.5), immunogenicity assessments (ADAs) (Section 9.6), and cytokine measurements (Section 9.8.3.2). Additional biopsy and blood samples for exploratory biomarker analyses will be collected (refer to Sections 9.8.2 and 9.8.3) and shipped for centralized testing.

Table 31 Protocol-Required Laboratory Assessments

Local Laboratory Assessments	
Test Category	**Test Name**
Hematology	Hemoglobin, hematocrit, white blood cells including differential (neutrophils, basophils, eosinophils, lymphocytes [both percent and absolute]), monocytes (absolute values for differential are preferred), reticulocytes and platelets. Reporting the proportion of prolymphocytes is desirable when these are present.
Quantitative lymphocyte subsets	B cells, T cells, and NK cells (both absolute and percent)
Biochemistry	Albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, lactate dehydrogenase (LDH), calcium, chloride, magnesium, inorganic phosphorus (phosphate), sodium, potassium, creatinine, total bilirubin, blood urea nitrogen (BUN) or urea, uric acid, glucose (non-fasting), total protein, C-reactive protein (CRP), D-dimer, ferritin. Tumor lysis sample includes uric acid, potassium, inorganic phosphorus (phosphate), calcium and creatinine.
Coagulation	Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen
Serology	Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). If positive serology, PCR for HBV-DNA to be performed. Hepatitis C virus (HCV) antibody. If positive serology PCR for HCV RNA to be performed. Cytomegalovirus (CMV) serology (IgG and IgM) at screening. If positive, further surveillance, ie, PCR for CMV-DNA to be performed at the investigator's discretion. Note: HIV testing is required at screening only if required per local health authorities or institutional standards. .
Additional tests	Beta2-microglobulin (at screening only). Immunoglobulins: IgA, IgG and IgM (at screening, at start of each cycle, and at the treatment discontinuation visit).
Urinalysis	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, specific gravity.
Pregnancy test	For female subjects with childbearing potential, a serum pregnancy test (beta-hCG) must be performed at screening; urine OR serum pregnancy test must be performed at the start of each cycle, at the treatment discontinuation visit, and safety follow up visit.
DLBCL or CLL	For subjects with DLBCL, major biologically distinct molecular subtypes (germinal center B-cell (GCB) and activated B-cell [ABC]), MYC positivity (IHC and FISH data), chromosomal rearrangements of MYC plus BCL2 (double-hit lymphoma) and overexpression of MYC and BCL2 proteins (double-expressor lymphoma) will be collected. For subjects with CLL/SLL, FISH data for del(13q), del(11q), del(17p), and DNA sequencing for TP53 and IGHV mutational status will be collected.
Bone marrow biopsy and/or aspirate	For subject response assessments, perform locally.

Central Laboratory Assessments/Specialty Laboratories	
Test Category	**Test Name**
Immunophenotyping	Absolute blood cell counts leukocytes such as B cells, NK cells, monocytes and T cells; immune cell functional and activation markers (eg, CD69, CD25, CD86, CD16, CD32), target (CD37, CD3, CD20) and mCRP expression on leukocytes (Section 9.8.3.1)
PK	Plasma levels of GEN3009 and GEN3013
Cytokines	Plasma or serum levels of cytokines CCI [redacted] (Section 9.8.3.2)
Immunogenicity	Serum presence of antibodies against GEN3009 and/or GEN3013 (ADAs)
Complement	CH50 measurements in serum (Section 9.8.3.3)
Protein expression analysis	CD37 protein expression in tumor biopsies during dose escalation CD37, CD59, CD68/CD163, CD56, CD20 expression in tumor biopsies during expansion CD37, CD3, CD68/CD163, CD56, CD20 expression in tumor biopsies during expansion for combination GEN3009 + GEN3013 (Section 9.8.2.1)
BCR sequencing (MRD assessment)	Quantification of malignant B-cell DNA in peripheral blood to detect MRD (Section 9.2.2.3)
Saliva DNA	Genomic DNA control for tumor DNA sequencing (Sections 9.8.3.4)
DNA/RNA and ctDNA sequencing	Mutational and gene expression profiling in tumor and/or plasma (Sections 9.8.2.2, 9.8.2.3, and 9.8.3.4)

9.5 Pharmacokinetics

Venous blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of GEN3009 or GEN3013 as specified in Table 4 (Dose Escalation), Table 7 (Expansion Monotherapy) or Table 12 (Expansion Combination). Additional samples may be collected during the trial if warranted and agreed upon between investigator and sponsor, eg, for safety monitoring. Instructions for the collection and handling of biological samples will be provided by the sponsor in the laboratory manual.

Samples collected for analyses of GEN3009 or GEN3013 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

Plasma samples will be analyzed to determine concentrations of GEN3009 or GEN3013. Validated, specific, and sensitive ligand binding assays/immunoassays will be used under the supervision of the sponsor at an assay CRO.

9.6 Immunogenicity

Venous blood samples will be collected for measurement of serum concentrations of ADAs as specified in Table 4 (Dose Escalation), Table 7 (Expansion), or Table 12 (Expansion Combination). In the Expansion Combination cohort, 1 sample each for GEN3009 and GEN3013 are to be drawn.

Samples should also be collected at the final visit from subjects who discontinued trial drug or were withdrawn from the trial. At visits where ADAs will be evaluated, 1 blood draw of sufficient volume can be used.

Each serum sample for ADA evaluation will be divided into 2 aliquots (one for ADA analysis and a back-up). Plasma concentrations of GEN3009 or GEN3013 will be analyzed (refer to Section 9.5) and those data will be used 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.

Samples may be stored according to local regulations at a facility selected by the sponsor to enable further analysis of immune responses to GEN3009 or GEN3013.

Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

The detection and titer characterization of ADAs will be performed using validated, specific and sensitive Electrochemiluminescence Immunoassay (ECLIA) methods and the titer of confirmed positive samples will be reported. The analysis will be performed under the supervision of the sponsor at an assay CRO. Neutralization characterization of ADAs will be performed at sponsor laboratories using appropriate methods.

9.7 Tumor Biopsy

During both Dose Escalation and Expansion, for subjects with accessible tumors, tumor samples are required for biomarker assessments. A fresh lymph node biopsy is preferable at screening and the biopsy can be a whole lymph node or core biopsy. A fine needle biopsy will not be sufficient. An archival lymph node tumor biopsy, which is the most recently collected lymph node biopsy after most recent therapy prior to enrollment, is also acceptable if taken within 6 months of C1D1 (Table 32).

During Expansion two fresh core tumor biopsies at C2D1 (±1 week) for GEN3009 + GEN3013 cohorts and C2D15 (±1 week) for GEN3009 monotherapy cohorts are mandatory for all patients with accessible tumors, where it is considered feasible without a high risk of complications for the patient based on the discretion of the investigator. Additionally, where feasible, a biopsy should be collected at the end of treatment visit. All tumor biopsies should be formalin-fixed, paraffin-embedded. Tumor biopsies will be examined as described in Section 9.2.2.3 and 9.8.2.

Table 32 Tumor Biopsy Collection During Dose Escalation and Expansion

Subject Diagnosis	Requirement
B-cell NHL, SLL or CLL	Fresh whole lymph node biopsy or fresh core tumor biopsies (2 cores) is required. If a fresh biopsy is not clinically feasible, an archival lymph node biopsy (FFPE) is acceptable, which is the most recently collected lymph node biopsy after most recent therapy prior to enrollment, if taken within 6 months of Cycle 1 day 1.

9.8 Biomarkers

Biomarker investigations in this trial will include safety markers, candidate predictive biomarkers, which may predict outcome to the treatment, and pharmacodynamic biomarkers. Biomarker assessments performed in the Dose Escalation and Expansion will focus on complement activation (primarily as pharmacodynamics marker), circulating cytokine levels (as safety assessment), CD37 versus membrane complement regulatory protein (mCRP) expression on leukocyte subsets (as candidate predictive markers for treatment efficacy), frequencies of (CD37-expressing) expressing leukocyte subsets (as pharmacodynamics markers for B lymphocytes expressing high CD37 levels,

and as safety assessment for other leukocyte subsets expressing lower CD37 levels), and activation marker expression on circulating immune effector cells (as potential pharmacodynamic marker). In the GEN3009 + GEN3013 Combination Cohort additional GEN3013 specific biomarker assessments will be added that will focus on T cell activation/exhaustion as potential safety and/or pharmacodynamic biomarkers and evaluation of CD3 and CD20 expression as potential predictive biomarkers for outcome to GEN3013 treatment. Additional biomarker assessments in the Expansion may be performed on tumor tissues and/or whole blood samples to expand on the understanding of MoAs of GEN3009 and GEN3013, predict subjects' outcome to GEN3009 monotherapy or GEN3009 + GEN3013 combination therapy, or deepen the understanding of CD37 and/or CD20 biology in lymphoma. All biomarker assessments will be performed at a central laboratory.

9.8.1 Sample Collections

Samples for biomarker analyses will be collected as specified in Table 4, Table 8, Table 9, Table 13, and Table 14. Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

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

9.8.2 Biomarker Assessments in Tumor Samples

Biomarker analyses in tumor samples at baseline and during treatment with GEN3009 monotherapy or GEN3009 + GEN3013 combination therapy may help confirm the MoAs of GEN3009 or GEN3009 combined with GEN3013 and enable the identification of biomarkers predictive of response to GEN3009 or GEN3009 + GEN3013. Tumor biopsies will be evaluated for CD37, CD3, and CD20 expression (protein or ribonucleic acid [RNA]), as well as molecular profiling to identify potential mechanisms of tumor response and/or treatment-induced changes in the immune microenvironment. The DNA that encodes the BCR expressed specifically by the cancer cells will be identified in the tumor biopsy at baseline to allow MRD assessment as described in Section 9.2.2.3.

9.8.2.1 Protein Expression Analyses

CD37, CD59, CD20, CD3 (combination arm), and expression of other proteins related to lymphoma biology CCI [redacted] or GEN3009's MoA CCI [redacted] may be evaluated in tumor biopsies by IHC/immunofluorescence 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.

9.8.2.2 RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine CD37, CD3, and CD20 RNA expression levels, as well as to evaluate other potential genes associated with CD37 biology CCI [redacted] with immune effector cell activation, or with lymphoma biology in general, such as gene signatures characteristic of lymphoma subtypes CCI [redacted] for exploratory biomarker analyses.

9.8.2.3 DNA Analyses

Tumor biopsies may also be analyzed using NGS for analyses of DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements or polymorphisms CCI [redacted] in genes associated with CD37 expression or function, CCI [redacted] proposed MoAs of GEN3009 and GEN3013, or lymphoma biology, CCI [redacted].

9.8.3 Biomarker Assessments in Blood Samples

Biomarker assessments will also be performed using whole blood samples to investigate safety markers and potential pharmacodynamic markers and explore the relationship to efficacy, AEs and/or MoA of GEN3009.

9.8.3.1 Immunophenotyping Analyses

Absolute counts of immune cells such as B cells (both benign B cells as well as circulating malignant cells), NK cells, monocytes, and T cells will be measured in whole blood and/or peripheral blood mononuclear cells (PBMC) samples using flow cytometry to monitor changes in frequency and/or phenotype (activation status) of these cells during GEN3009 monotherapy treatment. CD37 expression (in relation to mCRP expression), as well as CD37 occupancy by GEN3009, may be monitored to enable correlation analysis of target expression or GEN3009 binding with pharmacodynamic and efficacy assessments. The activation of immune effector cells (including NK cells, granulocytes and monocytes) may be monitored using activation markers such as CD69, CD25, or CD86, as well as markers related to effector function (such as CD16 or CD32 expression). For the GEN3009 + GEN3013 cohort additional immunophenotypes of circulating immune cells will be determined in fresh whole blood and/or PBMC samples using flow cytometry to monitor changes during GEN3009 + GEN3013 combination treatment. The T-cell activation and exhaustion phenotype will be evaluated using flow cytometry and markers such as CD69, CD25, and PD-1 in order to evaluate the association of such markers with drug target engagement, treatment efficacy and/or safety of GEN3009 + GEN3013. Additional immunophenotypes of circulating immune cells (eg, the levels of regulatory T cells which can suppress T-cell function) may be determined in fresh whole blood using flow cytometry to evaluate association of such markers with T-cell activation/exhaustion phenotype, patient response, and GEN3013's MoA.

9.8.3.2 Cytokine and Endothelial Activation Marker Analyses

As GEN3009 may activate immune effector cells or induce cytokine production resulting from lysis of immune cells and T-cell activation following initial GEN3013 administrations may lead to cytokine release causing CRS, cytokine levels will be monitored closely. The levels of cytokines, CCI [redacted] will be measured in plasma or serum samples. Additional cytokines and soluble markers of endothelial activation CCI [redacted] may also be determined to evaluate the association of such markers with treatment-emergent AEs and outcome to GEN3009 or GEN3009 + GEN3013.

9.8.3.3 Complement Analyses

As complement-mediated cytotoxicity is an anticipated key MoA of GEN3009, activation of the complement pathway will be assessed as a pharmacodynamics marker potentially predictive of clinical responses. Complement pathway activity will be monitored by CH50 measurements in serum, while individual complement pathway components such as C2 may be monitored in plasma for depletion following complement activation.

9.8.3.4 Cell-free DNA/RNA and Tumor-derived DNA (ctDNA) Analyses

Circulating cell-free DNA and/or RNA, including circulating tumor-derived DNA (ctDNA) and/or exosomal RNA (exoRNA), may be measured, and analyses such as RNA expression levels, DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements in genes may be performed to evaluate the association of such biomarkers with the MoA of GEN3009, MoA of GEN3013, subject response, or lymphoma disease biology.

A saliva sample may also be evaluated to confirm the tumor specificity of any genomic alterations that are identified. Where required by local law, a separate consent will be used for DNA/RNA research.

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

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

10.1 Adverse Event Definitions

10.1.1 Definition of Adverse Events

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

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

10.1.2 Definition of Serious Adverse Events

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

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- 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. Medical and scientific judgment must be exercised in deciding whether an AE is "medically significant"
- Requires inpatient hospitalization or prolongation of existing hospitalization[2] (Planned hospitalization for observation following GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) administration during Cycle 1 should not be reported as an SAE).

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

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

- Routine treatment or monitoring of the underlying disease, 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 informed consent
- Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

10.1.3 Definition of Adverse Events of Special Interest

AESIs are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid

communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

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

10.1.4 Definition of Infusion-Related Reactions

IRRs are defined as any AEs occurring during infusion or where the onset of the event occurs within 24 hours after the ended infusion. For IRRs, the causality of the event should be judged as "related" by the investigator.

Investigators should consider the clinical picture and isolated events, such as "fatigue," occurring within 24 hours after the end of infusion, and assess whether they do or do not constitute an IRR.

10.2 Adverse Event Reporting

All AEs, whether serious or nonserious (see definition in section 10.1.2), will be documented from the first dose of GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort only) until 30 days after the last GEN3009 and 60 days after the last dose of GEN3013, subject withdrew consent, subject started new anti-cancer treatment, or the subject died, whichever comes first. Refer to the electronic case report form (eCRF) completion guidelines for additional information on reporting and stepwise guidance.

Medical conditions (signs, symptoms, and diagnoses) that occur after the ICF is signed and prior to the first GEN3009 and/or GEN3013 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

The investigator will use the CTCAE Version 5.0 (NCI, 2017) to describe the intensity of AEs, except for TLS (refer to Appendix 4), CRS (refer to Appendix 13) and ICANS (refer to Appendix 14). Changes in intensity of an ongoing AE should be assessed at each visit or more frequent if deemed necessary and must be reported.

SAEs still ongoing after the safety follow-up visit(s) should be followed on a regular basis according to the investigator's clinical judgment until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved. Only SAEs judged by the investigator as related to GEN3009 (all cohorts) and/or GEN3013 (the combination cohort only) should be reported after the safety follow-up visit.

The investigator must assess whether or not the event is related to the trial drug. 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 caused the AE; this means there is evidence to suggest a causal relationship between the trial drug and the AE (ie, considered related).

Note:

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

10.2.1 Pre-existing Condition

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

10.2.2 Diagnosis

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

10.2.3 Disease Progression or Death

Progression of malignancy, if only documented by use of an appropriate method (as per CT/PET or MRI criteria), with no clinical symptoms, should not be reported as an AE or SAE. However, all hospitalizations and deaths caused by clinical manifestations of disease progression should be reported as SAEs.

10.2.4 Unrelated Procedures

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

10.2.5 Laboratory Test Abnormalities

Laboratory abnormalities that are considered clinically significant, ie, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial drug should be recorded as an AE in a timely manner in the eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin, neutropenia instead of decreased neutrophil count). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

10.3 Adverse Events of Special Interest

The following are considered AESIs:

GEN3009:

- IRRs

GEN3009 + GEN3013
- IRRs
- CRS
- Clinical TLS
- ICANS

AESIs are to be entered in the eCRF and reported to the safety CRO within 24 hours if they meet seriousness criteria or entered in eCRF within 72 hours if not serious.

10.4 Events Requiring Immediate Reporting

10.4.1 Serious Adverse Events

All SAEs occurring during the safety reporting period must be reported from the trial site to the sponsor no later than 24 hours following:

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

Grade 3 and 4 abnormal laboratory test values, if deemed serious (refer to Section 10.1.2), must be reported as SAEs when these are assessed as clinically significant by the reporting investigator.

Refer to the eCRF completion guidelines for additional information on reporting and stepwise guidance.

10.4.2 Serious Adverse Events With Onset After Ended Trial Participation

Information on any SAE with onset at any time after the subject has terminated trial participation that is suspected to be related to the trial drug by the investigator should be collected and emailed to the safety CRO.

10.4.3 Overdose and Medication Errors

An overdose is defined as a subject receiving a dose of GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) in excess of 10% of that specified in this protocol. All cases of overdose, whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event. Overdose of concomitant medication should only be reported if associated with AEs, whether serious or not.

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

Overdose and/or medication errors with GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) must be recorded as an AE , whether associated with an AE or not, within 24 hours after awareness.

Refer to the eCRF completion guidelines for additional information on reporting and stepwise guidance.

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

Rescue medication to reverse the action of GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) is not available. In case of overdose, medication errors, misuse, and/or abuse of trial drug, subjects should be monitored closely for potential side effects of GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) and receive supportive care according to local guidelines for the management of the potential side effects.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities, and ensure timely reporting of those, until GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) can no longer be detected systemically.
- Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

10.4.4 Pregnancy

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

All reports of pregnancy in female subjects or partners of male subjects must be reported on a pregnancy form to sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to the GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only), must be promptly reported to the sponsor or designee.

10.4.5 Timelines for Immediate Reporting

All SAEs, events of overdose and/or medication errors with GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only), serious AESIs, and pregnancy must be reported to the sponsor within 24 hours after sites' awareness. Completed Safety Reporting documents must be forwarded to the safety CRO within 24 hours.

10.5 Suspected Unexpected Serious Adverse Reactions

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

The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) is recorded and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional 8 days.

The investigator should be aware of local reporting regulations to the IEC/IRB. The sponsor or the safety 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.

10.6 Follow Up on Adverse Events

All AEs should be followed until they are resolved, until the end of the safety follow-up period, or the start of new anti-cancer treatment, whichever comes first. However, GEN3009 and/or GEN3013 (GEN3009 + GEN3013 cohort 4 only) related AESIs qualifying for safety reporting and all SAEs (independent of causality) still ongoing after the safety follow-up visit must be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

10.7 Warnings and Precautions

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

10.8 Data Monitoring Committee

This trial will institute a DMC, which will function independently of all other individuals associated with the conduct of this clinical trial, including the investigators participating in the trial. The functions and responsibilities of the DMC will be described in the DMC charter, which will be signed by the DMC.

During the Dose Escalation, the DMC will review the totality of the data and monitor safety for the trial on a quarterly basis or more frequently as defined in the DMC charter (escalation).

During the Expansion of the trial, the DMC will review the totality of the data at pre-specified intervals as defined in the DMC charter (expansion). The DMC will evaluate the safety profile with particular emphasis on any safety signals.

The DMC will also be available on an ad hoc basis, ie, to advise and recommend actions in relation to urgent safety signals, mitigation plans, etc or if requested by the DEC or sponsor SC.

The DMC will provide written feedback following periodic reviews and ad-hoc reviews. If a DMC meeting is scheduled, it will include both an open and closed session to discuss available data. During the open session, sponsor employees and investigators could participate together with the DMC. During the closed session, only DMC members will participate. The sponsor SC will hereafter meet to evaluate the recommendations provided by the DMC.

10.9 Dose Escalation Committee and the Safety Committee

In the Dose Escalation (monotherapy cohorts) and safety run-in (combination cohort) parts of the trial, subject safety will be monitored by the DEC and the sponsor SC. The sponsor SC is a cross-functional committee chaired by Global Drug Safety & Pharmacovigilance (GDS&PV) and consists of project-specific staff such as the Medical Director, Medical Scientist, Safety Physician and Safety Scientist, Regulatory Lead, Non-clinical Safety Representative, Head of Medical Department, Head of GDS&PV, Head of Regulatory Affairs, and Head of Pharmacology. The DEC will be chaired by the sponsor medical monitor and membership will include at a minimum the trial principal investigators, members of the sponsor medical and safety departments, as well as additional staff as appropriate.

The DEC will meet throughout the Dose Escalation and the safety run-in, after completion of the DLT evaluation period (ie, 28 days) by subjects enrolled in each dose level cohort. Dose escalation decisions will be proposed by the DEC in conjunction with the participating investigators. The DEC will convene when all subjects in a DL cohort complete the DLT evaluation period to make a decision regarding further dose escalation and when a decision regarding RP2D must be made.

The sponsor SC will meet immediately following DEC meetings and DMC periodic reviews to evaluate the recommendations from the DEC and DMC and determine how to proceed. The sponsor SC will monitor all available treatment-emergent data to ensure subject safety. The sponsor SC is responsible for ensuring that participation in the trial is safe for trial subjects, evaluating the outcome of ongoing safety surveillance, evaluating outcomes of DEC and DMC meetings, performing benefit-risk assessments, evaluating regulatory impact of decisions made, and for ensuring that appropriate actions are taken when new safety issues emerge.

11 STATISTICS

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

In general, data from the Dose Escalation and Expansion (including safety run-in) parts, from GEN3009 monotherapy and GEN3009 + GEN3013 combination therapy will be summarized separately.

In the reporting of the Dose Escalation and safety run-in, tables will report by cohort while in the Expansion tables will report by indication.

Milestone analyses will be timed as follows:

Dose Escalation and Safety Run-in:

- At the end of the DLT observation period for the last dosed subject in a dose-escalation cohort, a DEC report will be created to support the decision for escalation/de-escalation.

Expansion:

- An analysis will be performed when all subjects have sufficient data to evaluate response (and safety) in expansion.
- Additional analysis, such as supporting regular DMC meetings, may also be performed during the trial.
- The final analysis across all indications will be conducted at the end of the trial, up to 5 years after the last subject's first treatment in the trial.

11.1 Analysis Sets

11.1.1 Full Analysis Set

The full analysis set (FAS) and safety set are defined in the same way and comprise all subjects to whom trial drug has been assigned and who received at least 1 dose of trial drug. Subjects will be analyzed according to actual treatment received.

11.1.2 Dose-Determining Analysis Set

In GEN3009 Dose Escalation, the dose-determining set (DDS) consists of all subjects from the safety set who have either received between 80% and 125% of the planned dose and have completed the DLT observation period, or have experienced a DLT during Cycle 1. A treated subject who discontinues due to toxicity during the DLT observation period should be included in the DDS, regardless of the amount of dose received. This constitutes an evaluable subject for the determination of MTD statistical analyses. Subjects enrolled in parallel cohorts during escalation will not be included in DDS, but will be reported in the FAS for decision making.

In GEN3009 + GEN3013 safety run-in, the DDS includes all FAS subjects in the safety run-in part who meet the minimum exposure criterion and have sufficient safety evaluations or experience a DLT during the DLT observation period. The DLT observation period consists of the 4 weeks, ie, 28 days, following the first GEN3009 dose.

A subject will meet the minimum exposure criterion if the subject takes at least 3 out of 4 pre-planned GEN3009 doses and one full dose of GEN3013 within the first cycle .

11.1.3 Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who receive at least 1 dose of trial drug and who provide at least 1 evaluable PK sample.

11.1.4 Immunogenicity Analysis Set

The immunogenicity analysis set will include all subjects who receive at least 1 dose of trial drug and have a baseline and at least 1 evaluable on-treatment ADA sample.

11.1.5 Response Evaluable Set

The response evaluable set (RES) will consist of all subjects who:

- receive at least 1 dose of trial drug;
- have measurable disease at baseline; and
- have at least 1 post-baseline disease evaluation or die within 60 days of first trial treatment.

11.2 Subject Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term, by DL and expansion cohort.

11.3 Treatments

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to GEN3009 and combination with GEN3013, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics.

The number of subjects with dose adjustments and the reasons will be summarized, and all dosing data will be listed.

Concomitant medications will be summarized.

11.4 Primary Objectives

The primary objectives of the Dose Escalation and Expansion safety run-in are to:

- Determine the MTD and/or determine the RP2D
- Establish the safety profile

The primary objective of the Expansion is to:

- Evaluate (preliminary) anti-tumor efficacy

11.4.1 Primary Endpoints

11.4.1.1 Escalation and Safety Run-in in Expansion

11.4.1.1.1 DLTs and AEs

- Number of DLTs during the DLT period (initial 28 days of treatment).
- Summary tables for AEs will include only AEs that started or worsened during the on-treatment period (the TEAEs).
- The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (CTCAE grade), type of AE, and relationship to GEN3009 (Dose Escalation) or GEN3009 + GEN3013 (safety run-in).
- SAEs, non-serious AEs, and AESIs during the on-treatment period will be tabulated.
- All deaths (on treatment and post treatment) will be summarized.
- All AEs, deaths and SAEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment periods will be flagged.

Further summaries of AEs will be specified in the SAP.

11.4.1.1.2 Severity of Changes in Laboratory Values

Grading of laboratory values will be assigned programmatically as per the CTCAE Version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only; clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by the CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

For laboratory tests where grades are defined by the CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by the CTCAE:

- Shift tables using the low/normal/high (low and high) (or other project-specific) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, eg, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

11.4.1.1.3 Frequency of Dose Interruptions, Delays and Dose Intensity

See Section 11.3.

11.4.1.2 Expansion

For all efficacy analyses the FAS will be used. The RES may also be used for presentation of results, in particular for responder rates while the trial is ongoing.

For GEN3009 monotherapy cohorts in Expansion (R/R DLBCL, FL and CLL cohorts), ORR will be determined per (Cheson et al., 2014) for lymphomas and per (Hallek et al., 2018) for CLL. Subjects with PR and CR are considered as responders while all other categories, including "not evaluable," are considered as non-responders. ORR will be calculated together with its 95% CI. For GEN3009 + GEN3013 R/R DLBCL cohort, CR rate will be summarized. CR rate is defined as the proportion of patients with CR. Analysis will be based on response assessment by Lugano (Cheson et al., 2014).

11.4.2 Statistical Hypothesis, Model, and Method of Analysis

Results will be presented using descriptive statistics. No formal statistical hypotheses are formulated in this trial. Any P values will be considered as hypothesis-generating results to be considered for future trials.

11.5 Secondary Safety Objectives

11.5.1 Other Safety Data

11.5.1.1 ECG

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each subject during the trial in accordance with Table 2 and Table 3 (Dose Escalation), Table 5, Table 6, Table 10, Table 11, and Table 15 (Dose Expansion). ECG data will be read and interpreted centrally. Categorical analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced.

11.5.1.2 Vital Signs

Data on vital signs will be tabulated and listed; notable values will be flagged.

11.6 Pharmacokinetics

Individual curves of plasma concentration of GEN3009 or GEN3013 versus time after end of infusion will be presented for all subjects, including information on actual administered dose. All available data will be shown in these figures. Concentrations below the limit of quantification will be marked separately.

PK parameters (Table 33) will be calculated based on non-compartmental methods and will be calculated separately for Cycle 1 and Cycle 2. Elimination half-life ($T_{1/2}$) and parameters based on $T_{1/2}$ (area under the curve $[AUC]_{inf}$, CL) will be calculated only if a sufficient number of observations are available above LLOQ.

The relation between derived PK parameters and covariates such as actual dose, weight and dose, and selected laboratory parameters will be evaluated graphically.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Descriptive statistics of PK endpoints will include arithmetic and geometric means, standard deviations, CV%, median, minimum and maximum.

Further exploratory analyses of PK data may be performed.

Table 33 Non-compartmental Pharmacokinetic Parameters

$AUC_{0\text{-}7days}$	The AUC from time zero to Day 7 (mass × time × volume^{-1})
AUC_{inf}[a]	The AUC from time zero to infinity (mass × time × volume^{-1})
AUC_{last}	The AUC from time zero to last quantifiable measurement (mass × time × volume^{-1})
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume^{-1})
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
C_{trough}	Observed concentration at the end of the dosing interval (mass × volume^{-1})
$T_{1/2}$[a]	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time)
CL[a]	The total body clearance of drug from the plasma (volume × time^{-1})

[a] Calculated only if feasible.

11.6.1 Pharmacodynamics

The FAS will be used to summarize the pharmacodynamic parameters.

Selected cytokine results will be summarized by cytokine and time point. Median cytokine results, and their standard errors, may be plotted by time and cytokine.

11.7 Immunogenicity of GEN3009/GEN3013

Immunogenicity analysis samples will be scored ADA positive or ADA negative and subsequently reported. From positive ADA samples, titer values and neutralizing antibody scores (positive or negative) will be determined and reported. ADA negative samples with drug on board above the drug tolerance limits of the ADA method will be scored inconclusive due to possible drug interference. The association between positive/non-positive ADA and PK (predose, AUC, C_{max}), major safety signals (CTCAE ≥Grade 3) and efficacy information (change in tumor size by CT scan) may be explored.

11.8 Secondary Efficacy Objectives

The secondary efficacy objectives are to:

- Further evaluate the anti-tumor activity of GEN3009 or the combination of GEN3009 + GEN3013
- Evaluate clinical efficacy

11.8.1 Definition of Response

11.8.1.1 Response in B-cell NHL Other Than CLL

Objective and best response will be classified according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The

Lugano Classification (Cheson et al., 2014). Subjects with PR and CR are considered as responders while all other categories, including "not evaluable," are considered as non-responders. Subjects with CR, PR, or SD are considered to be in disease control.

11.8.1.2 Response in CLL/SLL

Assessment of response to therapy will be classified according to iwCLL guideline (Hallek et al., 2018) and should include careful physical examination and evaluation of the blood and bone marrow. To define the response to therapy, 2 groups of parameters need to be assessed and documented: parameters of group A assess the lymphoid tumor load and constitutional symptoms; parameters of group B assess the hematopoietic system.

Any response to therapy (eg, CR, PR) should be sustained for at least 2 months before using this response in the assessment. In addition, where appropriate, a further assessment of response (ie, marrow assessment) may be performed at least 2 months after the subject has cleared MRD from the peripheral blood.

CR and PR are considered clinically beneficial; all others (eg, SD, nonresponse, PD, death from any cause) will be rated as a treatment failure (Hallek et al., 2018).

11.8.1.3 Definitions of Relapsed/Refractory

Relapsed disease is defined as disease responding (CR or PR) to therapy that have progressed ≥6 months after completion of therapy. Refractory disease is defined as disease not responding to therapy that have progressed or disease responding to therapy that have progressed during therapy or within 6 months (<6 months) of completion of therapy. For CLL, "relapsed disease" is defined as evidence of disease progression in a subject who has previously achieved a CR or PR for ≥6 months. "Refractory disease" is defined as treatment failure (not achieving a CR or PR) or as progression within 6 months from the last dose of therapy.

11.8.2 Duration of Response

DoR only applies to subjects whose best objective response is CR or PR and is defined as the number of days from the first documentation of objective tumor response (CR or PR) to the date of first PD or death.

DoR will be censored and summarized in the same way as PFS (section 11.8.4). The detailed censoring rules are specified in the SAP.

11.8.3 Time to Response

TTR is defined as the time from C1D1 to first documentation of objective tumor response (CR or PR). Descriptive statistics will be presented.

11.8.4 Progression-free Survival

PFS is defined as the number of days from C1D1 to of the first documented progression or death due to any cause.

PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will

be the date of the last adequate tumor assessment prior to cut-off/start of new anti-neoplastic therapy. The detailed censoring rules are specified in the SAP.

PFS will be derived for all subjects and presented graphically as well as summarized using survival analysis methods.

The quartile estimates of PFS from the Kaplan Meier product limit algorithm will be presented. The 2-sided 95% confidence interval will be presented as well. The number of events may be small, and thereby limit use of the Kaplan Meier method to provide reliable information. In this case, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum) for PFS will be presented.

11.8.5 Overall Survival

Overall survival (OS) is defined as the number of days from Day 1 of Cycle 1 to death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date)

11.8.6 Minimal Residual Disease

The rate of MRD-negativity is defined as the proportion of patients with at least 1 MRD-negative sample. Duration of MRD-negativity is defined as the number of days from the first documentation of MRD-negativity to the date of MRD status change (not MRD-negativity).

11.9 Exploratory Endpoints

Only descriptive analyses will be performed on exploratory endpoints. Further details for the specific endpoints will be defined in the SAP.

11.10 Interim Analyses

No formal interim analysis is planned for this trial.

11.11 Sample Size Calculation

Sample size for the Dose Escalation is expected to be up to 90 subjects based on simulations of the mBOIN design in order to provide adequate information for MTD estimation and the planning and design of future trials. The expected number of subjects depends on the true relationship between dose and DLT probability but is expected to lie between 30 to 40 subjects in realistic scenarios. Approximately 49 additional subjects may be recruited to DLS below the MTD where it is found relevant to further explore the PK, toxicity, and efficacy.

Table 34 shows 4 different scenarios for the probability of a subject having a DLT at the 10 DLs. For each scenario the total expected number of subjects, when following the mBOIN design, is shown in the rightmost column. The mBOIN design method behaves as intended with most subjects exposed to the DLs with DLT probability close to the target DLT rate and fewer subjects exposed in total if the toxicity is high at the lowest DLs.

Table 34 Modified BOIN Design Characteristics

Simulation Scenario		Probability of DLT, Expected Number of Subjects at Each Dose Level										Expected Number of Subjects
		1	2	3	4	5	6	7	8	9	10	
1	Prob(DLT)	0%	1%	1%	2%	3%	4%	5%	10%	20%	30%	
	Num of subjects	1.0	1.1	1.1	3.2	3.4	3.5	3.8	5.1	5.9	4.6	32.7
2	Prob(DLT)	0%	1%	1%	2%	3%	4%	5%	20%	25%	35%	
	Num of subjects	1.0	1.1	1.1	3.3	3.4	3.5	4.9	6.2	4.7	2.9	32.0
3	Prob(DLT)	0%	1%	1%	2%	3%	4%	5%	20%	40%	60%	
	Num of subjects	1.0	1.0	1.1	3.3	3.3	3.5	5.0	7.3	4.8	1.0	31.3
4	Prob(DLT)	0%	1%	1%	2%	3%	4%	5%	10%	12%	15%	
	Num of subjects	1.0	1.0	1.1	3.2	3.4	3.5	3.8	4.3	4.4	6.6	32.2

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial, 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 informed consent. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. 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/randomization number
- Trial identification
- Eligibility of participation in the trial (inclusion/exclusion)
- Medical history
- Date of each visit
- Any assessment performed, ie, results of safety and efficacy parameters
- Concomitant medications
- Occurrence of any AEs/SAEs (including description and duration)
- Receipt, dilution, dispensing and return of IMP
- Status of the subject at the end of trial
- Reason for discontinuation/withdrawal, if applicable

Any worksheets used to capture data to facilitate completion of the eCRF will become part of the subject's source documentation.

An electronic source system may be utilized, which contains data maintained in a hospital medical record to document medical care (eg, electronic source documents) as well as the clinical trial-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the case report form (CRF) in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

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

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

12.2 Case Report Form Completion

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

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

All eCRF entries, 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:

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

12.3 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory, ECG data from the ECG vendor, and review of radiographic scans, pathology reports (as applicable) from the central imaging vendor (Expansion only) into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

12.4 Record Retention

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

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

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

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

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

13 ETHICS

13.1 Trial-Specific Design Considerations

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

This trial is being conducted to evaluate the safety and multiple-dose PK of GEN3009 monotherapy and GEN3009 + GEN3013 combination therapy in subjects with relapsed, progressive and/or refractory B-cell NHL. The results of this trial will provide useful information on the PK of GEN3009 and/or GEN3013. These data will assist in developing dosage adjustment guidance for future trials.

As with all clinical and PK trials, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which may cause additional discomfort, the use of IV indwelling catheters is permitted in this trial. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the PK of GEN3009 and GEN3013. Additionally, there are medical risks related to obtaining fresh biopsies. To mitigate such risks, fresh biopsies in this trial are performed only where it is considered feasible without a high risk of complications for the subject based on the discretion of the investigator.

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

13.2 Regulatory Ethics Compliance

13.2.1 Investigator Responsibilities

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

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

13.2.2 Independent Ethics Committee or Institutional Review Board

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

Approval for the collection of samples for research and for the corresponding ICF must be obtained from the IEC/IRB, as required by local regulations. Approval for the protocol can be obtained independent of this optional research component.

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

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

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

13.2.3 Informed Consent

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

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

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

A separate ICF will be used for the required DNA/RNA research component of the trial if required by local regulations.

13.2.4 Privacy of Personal Data

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 purpose and the objectives of the trial. 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.

Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

The subject has the right to request, through the investigator, access to his or her personal data and the right to request rectification of any data that are not correct or complete. Furthermore, the subject has the right to withdraw consent at any time throughout the duration of the trial. Personal data collected prior to the subject's withdrawal will still be used but no new personal data will be collected or processed for trial purposes unless it relates to reportable safety events. Reasonable steps will be taken by the investigator to respond to such requests, taking into consideration the nature of the request, the conditions of the trial, the applicable laws and regulations, and the investigator's obligations stated in the clinical trial agreement, including the data processor agreement.

13.2.5 Return of Exploratory Research Data to Subjects and Investigators

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects or investigators. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Amendments

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

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

14.2 Regulatory Documentation

14.2.1 Regulatory Approval/Notification

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

14.3 Subject Identification, Enrollment, and Screening Logs

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

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

14.4 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial-site visit log that will be kept at the trial site. In the Dose Escalation the first post-initiation visit will be made as soon as possible after enrollment has begun.

At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with local regulations, (eg, in the event of a national emergency) and in agreement with the investigator, remote source data verification may be performed.

The investigator must permit the monitor direct 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 contacts 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.

14.5 On-Site Audits

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

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

14.6 Publication

All information, including but not limited to information regarding GEN3009 and/or GEN3013 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 pharmacogenomic or exploratory biomarker 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.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN3009 and/or GEN3013, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the

information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be reported in a clinical trial report generated by the sponsor and will contain eCRF data from all trial sites that participated in the trial and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the clinical trial report (CTR) has been issued will be reported in a separate report and will not require a revision of the CTR. 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, 2018), the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish trial site-specific data after the primary data are published. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work (ICMJE, 2010).

14.7 Registration of Clinical Trials and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

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16 APPENDICES

Appendix 1 Calculation of Glomerular Filtration Rate

Glomerular filtration rate (GFR) may be estimated based on commonly used and accepted formulae, ie

,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], FS is a correction Factor for Sex: in males F_S=1, in females F_S=0.85

Modification of Diet in Renal Disease (MDRD) formula

$$GFR = 170 \times Serum\ Creatinine^{-0.999} \times Age^{-0.176} \times BUN^{-0.170} \times Albumin^{+0.318} \times F_S$$

Units: GFR [ml/min], age [years], serum creatinine [mg/dl], FS is a correction Factor for Sex: in males F_S=1, in females F_S=0.762

Variations of the MDRD formula

$$GFR = 186 \times Serum\ Creatinine^{-1.154} \times Age^{-0,203} \times F_S$$

Units: GFR [ml/min], age [years], serum creatinine [mg/dl], FS is a correction Factor for Sex: in males F_S=1, in females F_S=0.742

Appendix 2 New York Heart Association Criteria

Class	Subject Symptoms	Objective Assessment
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Appendix 3 Corticosteroid Dose Equivalents

Steroid	Approximate Equivalent Dose	
Betamethasone	12 mg	Long-acting
Dexamethasone	15 mg	Long-acting
Methylprednisolone	80 mg	Intermediate-acting
Triamcinolone	80 mg	Intermediate-acting
Prednisone	100 mg	Intermediate-acting
Prednisolone	100 mg	Intermediate-acting

Appendix 4 Tumor Lysis Syndrome

Presence of TLS is not clearly defined by CTCAE. For this trial the Cairo-Bishop classification will be used to define the presence of TLS. Laboratory TLS (Table 35) will not be considered as presence of TLS in the absence of the specified clinical complications (Coiffier et al., 2008). Clinical TLS should be graded according to Table 36. Individual symptoms should be graded according to CTCAE.

As noted in Section 7.1, during Dose Escalation, Grade 4 TLS is considered a DLT. Refer to Sections 7.4.3.3 and 7.5.4 for relevant management and dose modification guidelines.

Table 35 Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

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

Note: 2 or more laboratory changes within 3 days before or 7 days after treatment with GEN3009. Based on (Coiffier et al., 2008).

Table 36 Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine*†	1.5 x ULN	> 1.5–3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x 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)	

* Not directly or probably attributable to GEN3009
† If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.
Based on (Coiffier et al., 2008).

Appendix 5 Ann Arbor Staging

Stage	Area of Involvement
I	Single lymph node or lymph node region
II	Two or more lymph node regions on same side of diaphragm
III	Lymph node regions on both sides of the diaphragm are affected
IV	Disease is wide spread, including multiple involvement at 1 or more extranodal sites (beyond the lymph node, spleen, tonsils and Waldeyer's ring), such as the bone marrow, liver or pleura
A	Without disease symptoms
B	With symptoms like night sweats, weight loss > 10% over 6 months, fever without infection
E	Extranodal disease

Appendix 6 Rai and Binet Staging

Rai Staging System

Low-risk disease	Lymphocytosis with leukemia cells in the blood and/or marrow
Intermediate-risk disease	Peripheral blood lymphocytosis, enlarged lymph nodes in any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not)
High-risk disease	Disease-related anemia (as defined by a Hb level <1 g/dL) or thrombocytopenia (as defined by a platelet count of <100 × 10^9/L)

Hallek et al., 2018

Binet Staging System

Stage	
A	Hb ≥10 g/dL and platelets ≥100×10^9/L and up to 2 areas involved
B	Hb ≥10 g/dL and platelets ≥100×10^9/L and 3 or more lymphoid areas involved
C	Hb <10 g/dL and/or a platelet count <100 × 10^9/L)

Areas of involvement considered for staging include:
1. Head and neck, including the Waldeyer ring (this counts as 1 area, even if ≥1 group of nodes is enlarged)
2. Axillae (involvement of both axillae counts as just 1 area)
3. Groins, including superficial femorals (involvement of both groins counts as just 1 area)
4. Palpable spleen
5. Palpable liver (clinically enlarged)

Hallek et al., 2018

Appendix 7 Response Criteria for B-cell NHL by CT Scan

Response	Lymph Nodes	Non-Measurable Lesion	Organ Enlargement	New Lesions	Bone Marrow
CR	Target nodes/nodal masses regression ≤1.5 cm in longest diameter	Absent	Regress to normal	None	Normal by morphology; if indeterminate, IHC negative
PR	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	Absent/normal, regressed, but no increase	Spleen regressed >50% in length beyond normal	None	Not applicable
No response or SD	<50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	No increase consistent with progression	No increase consistent with progression	None	Not applicable
PD	>1.5 cm and increase by ≥50% from nadir and increase from nadir • 0.5 cm for lesions ≤2 cm • 1.0 cm for lesions >2 cm	New or clear progression of pre-existing lesions	Spleen length increase of >50% from baseline or if no prior splenomegaly, must increase by at least 2 cm from baseline	Regrowth of previously resolved lesions; new nodes >1.5 cm in any axis; new extranodal site >1.0 cm in any axis; assessable disease of any size unequivocally attributable to lymphoma	New or recurrent involvement

(Cheson et al., 2014)

Appendix 8 Response Criteria for CLL

Group and Parameters	Complete Remission (CR)**	Partial Remission (PR)**	Progressive Disease (PD)	Stable Disease (SD)
Group A – assess the lymphoid tumor load and constitutional symptoms				
Lymph nodes	None ≥1.5 cm	Decrease ≥50% from baseline*	Increase ≥50% from baseline or from response	Change of -49% to +49%
Liver and/or spleen size†	Liver size normal; spleen size <13 cm	Decrease ≥50% from baseline	Increase ≥50% from baseline or from response	Change of -49% to +49%
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	$< 4 \times 10^9$/L	Decrease ≥50% from baseline	Increase ≥50% from baseline	Change of -49% to +49%
Group B – assess the hematopoietic system				
Platelet count	$\geq 100 \times 10^9$/L (≥ 00,000 µL)	$\geq 100 \times 10^9$/L (≥100,000 µL) or increase ≥ 50% over baseline	Decrease ≥50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11.0 g/dL or increase of ≥50% over baseline	Decrease of ≥2.0 g/dL from baseline, secondary to CLL	Increase <11.0 g/dL or <50% over baseline or decrease <2.0 g/dL
Bone marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells or B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltration

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation and recorded.

**CR, (all of the criteria have to be met); PD (at least 1 of the criteria of group A or group B has to be met); PR (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD (all of the criteria have to be met; constitutional symptoms alone do not define PD).

Nodular partial remission is defined as a bone marrow biopsy showing residual nodules or suspicious lymphocytic infiltrates in subjects who are in remission; which often indicates a residual disease.

(Hallek et al., 2018)

Appendix 9 PET Positivity Evaluation

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

The 5-PS was intended as a simple, reproducible scoring method, with the flexibility to change the threshold between good or poor response according to the clinical context and/or treatment strategy. For example, a lower level of FDG uptake might be preferred to define a so-called negative result in a clinical trial exploring de-escalation to avoid undertreatment. A higher level of uptake might be preferred to define a so-called positive result in a trial exploring escalation to avoid overtreatment. The 5-PS has been validated for use at interim and the end of treatment.

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

1 no uptake

2 uptake ≤ mediastinum

3 uptake > mediastinum

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

Appendix 10 Response Criteria for B-cell NHL by FDG-PET CT scan

Response	Lymph Nodes	Non-Measurable Lesion	Organ Enlargement	New Lesions	Bone Marrow
CR	Score 1, 2 or 3 with or without a residual mass on 5-PS*	Not applicable	Not applicable	None	No evidence of FDG-avid disease in marrow
PR	Score 4 or 5* with reduced uptake compared to baseline and residual mass of any size	Not applicable	Not applicable	None	Residual uptake higher than uptake in normal marrow but reduced compared to baseline
No response or SD	Score 4 or 5 with no significant change in FDG uptake	Not applicable	Not applicable	None	No change from baseline
PD	Score 4 or 5 with an increase in intensity of uptake from baseline	None	-	New FDG-avid foci consistent with lymphoma	New or recurrent FDG-avid foci

*PET 5-PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum; 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.

Appendix 11 ECOG Performance Status

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

(Oken et al., 1982)

Appendix 12 Definition of Reproductive Potential and Contraception

Female subjects of reproductive potential must agree to use adequate contraception during and for 12 months after the last GEN3009 and/or GEN3013 administration. Adequate contraception is defined as highly effective methods of contraception in the table that follows. Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

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 follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 12 months after receiving the last dose of GEN3009 and/or GEN3013.

Highly Effective Methods of Contraception

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

[1] Hormonal contraception may be susceptible to interaction with GEN3009 and/or GEN3013, which may reduce the efficacy of the contraception method and therefore must be supplemented with a barrier method for the non-vasectomized male partner (preferably a condom with spermicidal foam/gel/film/cream/suppository).

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

[3] 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.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The

reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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

Appendix 13 Grading and Management of Cytokine Release Syndrome

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

Grading of Cytokine Release Syndrome

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever[1]	>38.0°C	>38.0°C	>38.0°C	>38.0°C	Death due to CRS in which another cause is not the principal factor leading to this outcome
With hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)	
And/or hypoxia[2]	None	Requiring low-flow (≤6 L/minute) nasal cannula or blow-by	Requiring high-flow (>6 L/minute) nasal cannula, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure ventilation3 (eg, CPAP, BiPAP, intubation and mechanical ventilation)	

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

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

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)

Grading and Management of Cytokine Release Syndrome

CRS Grade	Defining Features of Grade	Management
Grade 1	Fever with temperature ≥38°C but no hypotension or hypoxia	Antipyretics and IV hydration Diagnostic work-up to rule out infection Consider growth factors and antibiotics if neutropenic
Grade 2	Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula	Supportive care as in grade 1 IV fluid boluses and/or supplemental oxygen Tocilizumab +/− dexamethasone or its equivalent of methylprednisolone
Grade 3	Fever with hypotension requiring 1 vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or venturi mask	Supportive care as in grade 1 Consider monitoring in intensive care unit Vasopressor support and/or supplemental oxygen Tocilizumab + dexamethasone 10-20 mg IV every 6 hours or its equivalent of methylprednisolone
Grade 4	Fever with hypotension requiring 2 vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure ventilation (eg, CPAP, BiPAP, intubation and mechanical ventilation)	Supportive care as in grade 1 Monitoring in intensive care unit Vasopressor support and/or supplemental oxygen via positive pressure ventilation Tocilizumab + methylprednisolone 1000 mg/day

Source: (Neelapu, 2019)

Appendix 14 Grading of Neurotoxicity Associated with Immune Effector Cells

Harmonized definitions and grading criteria for neurotoxicity, per the ASTCT, formerly ASBMT, are presented below.

Grading for Immune Effector Cell-associated Neurotoxicity Syndrome

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ICE score[1]	7-9	3-6	0-2	0 (subject is unrousable and unable to perform ICE)	Death due to ICANS in which another cause is not the principal factor leading to this outcome
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unrousable 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[3]	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[4]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy, or papilledema, or Cushing's triad	

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.

1. 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.
2. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
3. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE Version 5.0, but they do not influence ICANS grading.
4. 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 Version 5.0.

Source: (Lee et al., 2019)

Immune Effector Cell-Associated Encephalopathy Assessment Tool

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

Source: Based on (Lee et al., 2019)

INVESTIGATOR AGREEMENT AND SPONSOR MEDICAL OFFICER SIGNATURE

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

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD, PhD

Institution: Genmab

Signature: PPD Date: PPD

(DD-Mmm-YYYY)