CLINICAL TRIAL PROTOCOL

An Open-Label, Multicenter, Phase 1/2 Trial of GEN3014 (HexaBody®-CD38) in Relapsed or Refractory Multiple Myeloma and Other Hematologic Malignancies

Short Title: Phase 1/2 trial of GEN3014 in relapsed or refractory hematologic malignancies

Protocol Number:		GCT3014-01
Sponsor Name:		Genmab*
Regulatory Agency Identifier Number(s)		IND 146079; EudraCT 2020-003781-40
Genmab investigational medicinal product (IMP):		GEN3014
Development Phase:		Phase 1/2
Protocol Approver**	**Name**	Jenny Chen, MD, PhD
	Title	Senior Medical Director
Date of Protocol; version:		31-Aug-2023 (Amendment 3_RS-1, v1.0) 18-Feb-2022 (Amendment 3, v5.0) 18-Aug-2021 (Amendment 2, v4.0) 04-Feb-2021 (Amendment 2, v3.0) – version 3.0 never distributed 16-Nov-2020 (Amendment 1, v2.0) 08-Sep-2020 (Original Protocol, v1.0)

*Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab Holding B.V.; Genmab A/S; or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following sponsor information page.

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

SPONSOR INFORMATION PAGE

Sponsor information for countries in the European Economic Area, the United Kingdom, and Serbia	Genmab A/S Carl Jacobsens Vej 30 2500 Valby Denmark
Sponsor information for all other countries	Genmab US, Inc. 777 Scudders Mill Road Plainsboro, New Jersey 08536 United States of America

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PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 3_RS-1, version 1.0 (TMF-456592)	31 Aug 2023
Global Amendment 3, version 5.0 (TMF-73915)	18 Feb 2022
Global Amendment 2, version 4.0 (Note: version 3.0 never distributed) (TMF-73915)	18 Aug 2021
Global Amendment 1, version 2.0 (TMF-73915)	16 Nov 2020
Original Protocol, version 1.0 (TMF-73915)	08 Sep 2020

Amendment 3_RS-1 (31 Aug 2023):

This amendment is considered to be nonsubstantial 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 because it neither significantly impacts the safety or right of the subjects nor the data reliability and robustness of data.

Overall Rationale for Regional Amendment:

The GCT3014-01 protocol was amended to update the new address of Genmab A/S for submission to the regulatory authorities.

The amendment changes are summarized below.

List of Changes in the Protocol and Their Rationale

Section No. and Name	Description of Change	Brief Rationale
Sponsor Information Page	The new address of Genmab A/S has been updated and Serbia has been added to the list of countries for which Genmab A/S is the sponsor.	For submission to the regulatory authorities
Title Page and Investigator Agreement Page	The title page has been updated to include the name and title of the protocol approver and a note indicating that the electronic signature approval page can be found appended to the document. The Responsible Medical Officer signature box has been removed from the Investigator Agreement page.	Alignment with the current Genmab Protocol SOP and template

STATEMENT OF COMPLIANCE

GCP Compliance

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

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Title	An Open-Label, Multicenter, Phase 1/2 Trial of GEN3014 (HexaBody®-CD38) in Relapsed or Refractory Multiple Myeloma and Other Hematologic Malignancies
Short Title	Phase 1/2 trial of GEN3014 in relapsed or refractory hematologic malignancies
Clinical Phase	Phase 1/2
Purpose and Rationale	GEN3014 (HexaBody®-CD38) is a fully human immunoglobulin (Ig)G1 monoclonal antibody (mAb) targeting the cluster of differentiation (CD)38 antigen. The E430G mutation in the fragment crystallizable (Fc) region of GEN3014 facilitates the formation of antibody hexamer upon binding to CD38 on the plasma membrane thus leading to enhanced C1q binding and complement-dependent cytotoxicity (CDC) activity. Similar to daratumumab, GEN3014 induces tumor cell death through Fc-mediated effector mechanisms including CDC, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), programmed cell death after antibody crosslinking, immunomodulatory activity, and inhibition of the CD38 ectoenzymatic activity. As compared to daratumumab, GEN3014 has a higher affinity for CD38, more potent CDC activity, and stronger inhibition of the CD38 cyclase activity. It is hypothesized that GEN3014 may trigger stronger reversion of the immune suppression in the tumor microenvironment. Preclinical data have shown: In vitro, GEN3014 has shown superior CDC activity. Efficient tumor cell lysis of multiple myeloma (MM), acute myeloid leukemia (AML), and B-cell non-Hodgkin lymphoma (B-NHL) cell lines was induced by GEN3014, including lysis of cell lines that were insensitive to daratumumab. Ex vivo, GEN3014 showed enhanced CDC activity against MM cells harvested from patients with newly diagnosed MM and relapsed or refractory MM (RRMM) as compared to daratumumab. In vivo, the anti-tumor activity of GEN3014 was observed in a Daudi cell line-derived xenograft model, a diffuse large B-cell lymphoma (DLBCL) patient-derived xenograft (PDX) model, and 2 AML PDX models. The aim of this phase 1/2 trial is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary anti-tumor activity of GEN3014 in subjects with RRMM and other hematologic malignancies. In the Dose Escalation, dose-limiting toxicities (DLTs) will be monitored to determine the recommended phase 2 dose (RP2D), and if reached, the maximum tolerated dose (MTD), for both RRMM and relapsed or refractory (R/R) AML. Following the Dose Escalation, in the Expansion Part A (GEN3014 Single Cohorts), the clinical activity of GEN3014 at the RP2D in anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, R/R DLBCL, and R/R AML will be assessed, as well as safety, tolerability, PK, pharmacodynamics, and biomarkers. After an interim analysis of the efficacy and safety data among anti-CD38 mAb-naive subjects with RRMM treated with GEN3014 at 16 mg/kg and 24 mg/kg, the Expansion Part B (Randomized H2H) will be initiated and the clinical activity of GEN3014 intravenous (IV) at the RP2D will be evaluated in a head-to-head manner as compared to daratumumab subcutaneous (SC) in anti-CD38 mAb-naive RRMM subjects. It is hypothesized that the preclinical observation of stronger complement-mediated tumor cell killing by GEN3014 may be translated into the clinic; specifically, subjects with lower CD38 levels or higher expression of complement inhibitory proteins may benefit from the GEN3014 treatment.

Objectives and Endpoints (Dose Escalation)	**Objectives**	**Endpoints**
	Primary	
	• Determine the RP2D and if reached, the MTD of GEN3014	• Incidence of DLTs
	• Evaluate the safety and tolerability of GEN3014	• Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory values, vital signs, electrocardiograms (ECGs) • Tolerability: Dose interruptions, delay, and dose intensity
	Secondary	
	• Characterize the PK properties of GEN3014	• Noncompartmental PK parameters (if feasible): o Maximum concentration (C_{max}) o Time to C_{max} (t_{max}) o Predose concentration (C_{trough}) o Area under the concentration-time curve from time zero to last quantifiable sample ($AUC_{0\text{-}last}$) and from time zero to 168 h ($AUC_{0\text{-}168h}$) o Accumulation ratios in C_{max} ($R_{A,Cmax}$) and AUC ($R_{A,AUC}$) • In addition, a population PK modeling approach may be employed
	• Characterize the pharmacodynamic properties of GEN3014	• Pharmacodynamic markers in blood and tumor samples, including frequencies of natural killer (NK) cells and other leukocyte subsets and complement analyses
	• Evaluate immunogenicity	• Anti-GEN3014 antibodies
	• Assess the preliminary anti-tumor activity of GEN3014	• Objective response rate (ORR) • Clinical benefit rate (CBR) • Duration of response (DOR) • Time-to-response (TTR)
	• Assess the clinical efficacy of GEN3014	• Progression-free survival (PFS) • Overall survival (OS)
	Exploratory	
	• Assess potential biomarkers predictive of clinical response to GEN3014	• Expression of CD38 and other molecular markers on tumor cells at baseline and during treatment
	• Assess minimal residual disease (MRD) status	• Rate of MRD-negative remission in RRMM
	• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

Objectives and Endpoints (Expansion Part A [GEN3014 Single Cohorts])	**Objectives**	**Endpoints**
	Primary	
	• Assess the preliminary anti-tumor activity of GEN3014	• ORR
	Secondary	
	• Assess the anti-tumor activity and efficacy of GEN3014	• CBR • DOR • TTR • PFS • OS
	• Evaluate safety of GEN3014	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs • Immunogenicity: Anti-GEN3014 antibodies
	• Characterize the PK of GEN3014	• Noncompartmental PK parameters (if feasible): ○ C_{max} ○ t_{max} ○ C_{trough} ○ $AUC_{0\text{-}last}$ and $AUC_{0\text{-}168h}$ ○ $R_{A,Cmax}$, $R_{A,AUC}$, and $R_{A,Ctrough}$ • In addition, a population PK modeling approach may be employed
	• Evaluate the pharmacodynamic profiles of GEN3014	• Pharmacodynamic markers in blood and tumor samples, including frequencies of NK cells and other leukocyte subsets and complement analyses
	Exploratory	
	• Assess potential biomarkers predictive of clinical response to GEN3014 and evaluate potential surrogacy with PFS and OS	• Baseline CD38 expression • Immune cell profiling • Deoxyribonucleic acid (DNA) mutation status and gene profile (ribonucleic acid [RNA]-seq)
	• Assess MRD status	• Rate and duration of MRD-negative remission in RRMM, R/R AML, R/R DLBCL
	• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

Objectives and Endpoints (Expansion Part B [Randomized H2H])	**Objectives**	**Endpoints**
	Primary	
	• Compare overall response of GEN3014 IV vs daratumumab SC in anti-CD38 mAb-naive RRMM subjects	• ORR
	Secondary	
	• Compare time dependency in PK between GEN3014 IV vs daratumumab SC	• C_{trough} levels of GEN3014 IV, or daratumumab SC, on Cycle 3 Day 1
	• Assess the anti-tumor activity of GEN3014 IV vs daratumumab SC	• VGPR or better • CR or better • DOR • TTR • PFS • OS • Time to next therapy (TTNT)
	• Assess safety of GEN3014 IV vs daratumumab SC	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs • Immunogenicity: Anti-GEN3014 antibodies, anti-daratumumab antibodies, anti-rHuPH20 antibody
	Exploratory	
	• Evaluate the pharmacodynamic profiles of GEN3014 and compare with those of daratumumab	• Pharmacodynamic markers in blood and tumor samples, including frequencies of NK cells and other leukocyte subsets, and complement analyses
	• Assess potential biomarkers predictive of clinical response to GEN3014 and evaluate potential surrogacy with PFS and OS	• Baseline CD38 expression • Immune cell profiling • DNA mutation status and gene profile (RNA-seq)
	• Assess MRD status	• Rate and duration of MRD-negative remission
	• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship
Trial Design	This is a phase 1/2, open-label, multicenter, multinational trial to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3014 in subjects with RRMM and other hematologic malignancies including R/R AML and R/R DLBCL. The trial will be conducted in 3 parts: Dose Escalation (phase 1), Expansion Part A (GEN3014 Single Cohorts) (phase 2), and Expansion Part B (Randomized H2H) (phase 2). Each part will consist of a Screening period (up to 21 days prior to Cycle 1 Day 1), a Treatment period (Cycle 1 Day 1 until trial drug discontinuation), and a Follow-up period (ie, 30-day safety follow-up from the last dose of trial drug and survival follow-up). In Dose Escalation, GEN3014 will be evaluated in RRMM and R/R AML using the modified Bayesian Optimal Interval (mBOIN) design. At each dose level (DL), DLTs	

	will be assessed in the first treatment cycle, ie, a DLT evaluation period of 28 days from Cycle 1 Day 1. The RRMM Cohort will be opened first. Preliminary data from the RRMM Cohort at DLs up to 16 mg/kg including PK, pharmacodynamic, receptor occupancy, and safety will be analyzed. After the DL of 16 mg/kg has been cleared for the RRMM Cohort, the R/R AML Cohort may be initiated. Predictive PK-pharmacodynamic modeling for R/R AML, together with the preliminary data of GEN3014 in RRMM, will be used to further guide modification of the proposed starting dose for the R/R AML Cohort. For both RRMM and R/R AML, population PK modeling may be explored to facilitate selection of the optimal dosing and dosing schedule. The RP2D and MTD (if reached) for the 2 disease indications will be determined based on the observed toxicity with each. In Expansion Part A (GEN3014 Single Cohorts), GEN3014 will be further evaluated in 4 cohorts: anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, R/R DLBCL, and R/R AML at the RP2D identified from the Dose Escalation. The clinical activity of GEN3014 will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers. Specifically, for the anti-CD38 mAb-naive cohort, daratumumab-naive subjects who received GEN3014 at the 16 mg/kg or 24 mg/kg dose during the Dose Escalation phase of the trial will be counted toward the 10-subject lead-in analysis prior to starting the H2H arm. In Expansion Part B (Randomized H2H), GEN3014 IV will be compared to daratumumab SC to evaluate whether GEN3014 IV may be more potent in anti-CD38 mAb-naive RRMM subjects. A total of 80 subjects will be randomized in a 1:1 ratio to receive either GEN3014 IV at the RP2D or daratumumab SC at 1800 mg. Subjects will be stratified by body weight (≤70 kg and >70 kg) and number of prior lines of therapy (≤4 prior lines and >4 prior lines). During the Dose Escalation, a Dose Escalation Committee (DEC) will assess the available data (including safety) according to DEC Charter and make recommendations on the next DL and/or propose the RP2D/MTD to the Safety Committee. A Data Monitoring Committee (DMC) will assess the totality of safety information of the trial and identify additional safety signal according to a DMC charter.
Population and Sample Size	In the Dose Escalation: • Up to 54 (maximum 9 subjects on each of 6 DLs) subjects with RRMM will be treated including subjects who are anti-CD38 mAb-naive. • Up to 18 subjects with R/R AML will be treated. Expansion Part A will be conducted in 4 parallel cohorts: • Anti-CD38 mAb-naive RRMM (N=approximately 10 subjects) • Anti CD38 mAb-refractory RRMM (N=20 subjects) • R/R DLBCL (up to 40 subjects) • R/R AML (N=20 subjects) Expansion Part B: • After 10-subject lead-in of GEN3014, 80-subject H2H of GEN3014 IV vs daratumumab SC will be conducted among anti-CD38 mAb-naive RRMM subjects.
Inclusion Criteria (Dose Escalation)	Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Dose Escalation part of the trial: • Must be at least 18 years of age. • Must sign an informed consent form (ICF) prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA). • Must have fresh bone marrow samples collected at Screening.

- Eastern Cooperative Oncology Group (ECOG) performance status score 0, 1, or 2.
- Has acceptable laboratory test results during the Screening period, as follows:

Parameter		Result
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥50 mL/min estimated by Cockcroft-Gault or serum creatinine ≤1.5 × upper limit of normal (ULN)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN *Note: A subject with Gilbert's syndrome may be included if total bilirubin is ≤3 × ULN and direct bilirubin is ≤1.5 × ULN*
e.	Hemoglobin	≥8 g/dL (≥80 g/L or ≥5 mmol/L) *Note: Red blood cell transfusion may be administered during Screening to meet this requirement*
f.	Absolute neutrophil count	>1.0 × 10^9/L (>1,000/μL) *Note: G-CSF may be administered during Screening to meet this requirement*
g.	Platelet count	>50 × 10^9/L (>50,000/μL) *Note: Platelet transfusion may be administered during Screening to meet this requirement*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

- A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 administration. Adequate contraception is defined as highly effective methods of contraception. In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
- A woman of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) at Screening.
- 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 GEN3014.
- 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014.

Specific Inclusion Criteria for RRMM:

	• Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria: o Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma. **and** o Measurable disease at baseline as defined by any of the following: ▪ IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours; **or** ▪ Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio. Note: Subjects with RRMM must have exhausted standard therapies, at the investigator's discretion. • For anti-CD38 mAb-naive RRMM subjects: Subject received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory imide drug (IMiD) in any order, or is double refractory to a PI and an IMiD; or subject received ≥2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody. Anti-CD38 mAb-naive subjects with RRMM may be recruited from Sweden, France, Spain, Netherlands, and Australia, and from countries where anti-CD38 therapies are not available. • For anti-CD38 mAb-treated RRMM subjects: Subject has received at least 2 prior lines of therapy and must have discontinued daratumumab or isatuximab for at least 4 weeks prior to the first dose of GEN3014. Note: Subjects should not have received any other anti-CD38 antibody except daratumumab or isatuximab. • Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L). **Specific Inclusion Criteria for R/R AML:** • Relapsed or refractory AML, both de novo or secondary; must have failed all conventional therapy. Acute promyelocytic leukemia (APL) is excluded from this trial. Note: Relapse is defined by BM blasts ≥5% in patients who have been in CR previously, or reappearance of blasts in the blood, or development of extramedullary AML. Refractory is defined as not being able to achieve a CR after the initial therapy. • Subject with relapsed AML who received at least 2 prior therapies for AML with the exception of hydroxyurea. • Subject with refractory AML who received at least 1 prior line of therapy for AML with the exception of hydroxyurea. • Subject's life expectancy at Screening is judged to be at least 3 months.
Inclusion Criteria (Expansion Part A [GEN3014 Single Cohorts])	Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part A of the trial: • Must be at least 18 years of age. • Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA). • ECOG performance status score 0, 1, or 2 for MM and AML; ECOG PS 0 or 1 for DLBCL. • Must have fresh bone marrow samples collected at Screening. • Has acceptable laboratory test results during the Screening period (see above list in Inclusion Criteria, Dose Escalation).

- A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 administration. Adequate contraception is defined as highly effective methods of contraception. In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
- A woman of childbearing potential must have a negative serum β-hCG at Screening.
- 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 GEN3014.
- 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014.

Specific Inclusion Criteria for RRMM:

- Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:
  - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

  and

  - Measurable disease at baseline as defined by any of the following:
    - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

    or

    - Light chain myeloma: Serum Ig FLC ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

  Note: Subjects with RRMM must have exhausted standard therapies, at the investigator's discretion.
- For anti-CD38 mAb-naive RRMM Cohort: Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD, or subjects received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).
- For anti-CD38 mAb-refractory RRMM Cohort: Prior to trial entry, subject received daratumumab or a daratumumab-containing regimen or an isatuximab-containing regimen and had evidence of progressive disease (PD) during the treatment or within 90 days of treatment cessation.
- Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); or corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

Specific Inclusion Criteria for R/R DLBCL:

- Relapsed or refractory DLBCL, both de novo or histologically transformed. Note: Relapsed disease is defined as the reappearance or growth of lymphoma after at least 6 months duration of response. Refractory disease is defined as failure to achieve response after at least 2 cycles of therapy or reappearance after a duration of response of <6 months. Subjects with R/R DLBCL must have exhausted standard therapies, at the investigator's discretion.
- Received at least 2 prior lines of systemic therapy, with 1 being a CD20-containing chemoimmunotherapy.
- Have at least 1 measurable site of disease:

<table>
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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

<u>and</u>

A CT scan (or 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.

Must have available archival or fresh tumor tissue or both to submit to a central laboratory for CD38 assay.

<u>Specific Inclusion Criteria for R/R AML:</u>

(Please refer to the “Specific Inclusion Criteria for R/R AML” in the Dose Escalation)

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<tr><td>Inclusion Criteria (Expansion Part B [Randomized H2H])</td><td>
Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part B of the trial:

Must be at least 18 years of age.
Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA).
ECOG PS score 0, 1, or 2.
Must have fresh bone marrow samples collected at Screening.
Has acceptable laboratory test results during the Screening period, as follows:

<table>
<tr><th colspan="2">Parameter</th><th>Result</th></tr>
<tr><td>a.</td><td>Creatinine clearance (Clcr) or serum creatinine</td><td>Clcr ≥20 mL/min (Cockcroft-Gault formula or EGFR (MDRD) or CKD-epi)</td></tr>
<tr><td>b.</td><td>Serum alanine aminotransferase (ALT)</td><td>≤2.5 × ULN</td></tr>
<tr><td>c.</td><td>Serum aspartate aminotransferase (AST)</td><td>≤2.5 × ULN</td></tr>
<tr><td>d.</td><td>Total bilirubin</td><td>≤2 × ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 × ULN</td></tr>
<tr><td>e.</td><td>Hemoglobin</td><td>≥7.5 g/dL (≥4.65 mmol/L)
Note: Red blood cell transfusions are not permitted within 7 days before the laboratory test for eligibility review; recombinant human erythropoietin use is permitted</td></tr>
<tr><td>f.</td><td>Absolute neutrophil count</td><td>>1.0 × 10^9/L (>1,000/μL)
Note: (Granulocyte colony stimulating factor [GCSF] use is permitted)</td></tr>
<tr><td>g.</td><td>Platelet count</td><td>>50 × 10^9/L (>50,000/μL) if bone marrow is >50% involved in myeloma. Otherwise ≥75 × 10^9/L
Note: Platelet transfusions are not permitted within 7 days before the laboratory test for eligibility review</td></tr>
<tr><td>h.</td><td>Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated</td><td>PT/INR/aPTT ≤1.5 × ULN</td></tr>
</table>
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	partial thromboplastin time (aPTT)	

- A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 IV or daratumumab SC administration. Adequate contraception is defined as highly effective methods of contraception. In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
- A woman of childbearing potential must have a negative serum β-hCG at Screening and within 72 hours of the first dose of study treatment prior to dosing.
- 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 GEN3014 IV or daratumumab SC.
- 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014 IV or daratumumab SC.
- Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:
  - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

  and

  - Measurable disease at baseline as defined by any of the following:
    - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

    or

    - Light chain myeloma: Serum Ig FLC ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
- Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD; or subject received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).
- Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

Exclusion Criteria (Dose Escalation and Expansion Part A [GEN3014 Single Cohorts])

Any potential subject who meets any of the following criteria will be excluded from being treated in the Dose Escalation and/or Expansion Part A (GEN3014 Single Cohorts) of the trial.

- Prior treatment with any anti-CD38- directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) in anti-CD38 mAb-naive RRMM Cohort. Note: Prior daratumumab or isatuximab exposure is allowed for anti-CD38 mAb-treated RRMM subjects in the Dose Escalation and anti-CD38 mAb-refractory RRMM Cohort in the Expansion Part A.
- Treatment with an anti-cancer agent (eg, small molecule, antibody, chimeric antigen receptor T cell [CAR-T] cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to the first dose of GEN3014.

- Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3014.
- Cumulative dose of corticosteroids more than the equivalent of ≥140 mg of prednisone within 2-week period before the first dose of GEN3014.
- Has clinically significant cardiac disease, including:
  - Myocardial infarction within 1 year prior to the first dose of GEN3014, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV) uncontrolled cardiac arrhythmia (CTCAE v5.0 grade 2 or higher) or clinically significant ECG abnormalities.
  - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec.
- 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) tumor or known CNS involvement at Screening.
- Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig 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).
- Known medical history or ongoing hepatitis C infection that has not been cured.
- Known history of seropositivity of human immunodeficiency virus (HIV).
- Currently receiving any other investigational agents.
- 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 GEN3014.
- A man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3014.

Specific Exclusion Criteria for RRMM:

- Prior allogeneic HSCT.
- Autologous HSCT within 3 months of the first dose of GEN3014.

Specific Exclusion Criteria for R/R AML:

- <5% blasts in blood or bone marrow at Screening.
- Prior autologous HSCT.
- Allogenic HSCT within 3 months of the first dose of GEN3014.
- Active graft-versus-host-disease requiring immunosuppressive treatment. Any immunosuppressive medication (eg, calcineurin inhibitors) must be stopped ≥4 weeks prior to the first dose of GEN3014.

Additional Exclusion Criteria for All Subjects:

- History of allergic reactions attributed to compounds of similar active substance or excipients.
- Has known past (within 3 years) 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. • Prior treatment with live, attenuated vaccines within 28 days prior to initiation of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not allowed. **Additional Exclusion Criterion for RRMM:** • Known allergies, hypersensitivity, or intolerance to mAbs, human proteins, hyaluronidase, or excipients (refer to GEN3014 IB and daratumumab IB).
Exclusion Criteria (Expansion Part B [Randomized H2H])	Any potential subject who meets any of the following criteria will be excluded from being treated in the Expansion Part B (Randomized H2H) of the trial. • Prior or concurrent treatment with any CD38-directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) for RRMM. • Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to randomization. Note different timeframe requirements as per local health authorities. • Treatment with an investigational drug (including anti-cancer investigational vaccines) within 4 weeks or 5 half-lives, whichever is longer, prior to the randomization. • Radiation therapy for treatment of plasmacytoma within 14 days of randomization (palliative radiation for pain control secondary to lytic lesion is allowed). • A maximum cumulative dose of dexamethasone 160 mg within 28 days of randomization. • Has clinically significant cardiac disease, including: o Myocardial infarction within 6 months before the date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV uncontrolled cardiac arrhythmia (CTCAE v5.0 grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities. o Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec. • 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) tumor, current or history of CNS involvement by the disease under investigation. • Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig therapy): o Positive test for antibodies to the hepatitis B core antigen (anti-HBc) **and** o Negative test for antibodies to the hepatitis B surface antigen (anti-HBs). • Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy. • Known to be positive for human immunodeficiency virus (HIV), with 1 or more of the following:

	a. Not receiving highly active antiretroviral therapy (ART) b. Had a change in ART within 6 months of the start of Screening c. Receiving ART that may interfere with trial treatment (consult sponsor for review of medication prior to enrollment) d. CD4 count <350 cells/mm^3 at Screening e. Acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of start of Screening f. Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled). • Pulmonary a. COPD with a FEV1 <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal. b. Moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the trial. • Contraindications or life-threatening allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products. • Prior treatment with live, attenuated vaccines within 28 days prior to initiation of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not allowed. • Major surgery within 2 weeks before randomization, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the trial. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question about whether a procedure is considered a major surgical procedure, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the trial. • Plasmapheresis within 28 days before randomization. • Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the trial procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this trial. • Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject 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. Subject is taking any prohibited medications. • Currently receiving any other investigational agents. • 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 GEN3014 or daratumumab SC.

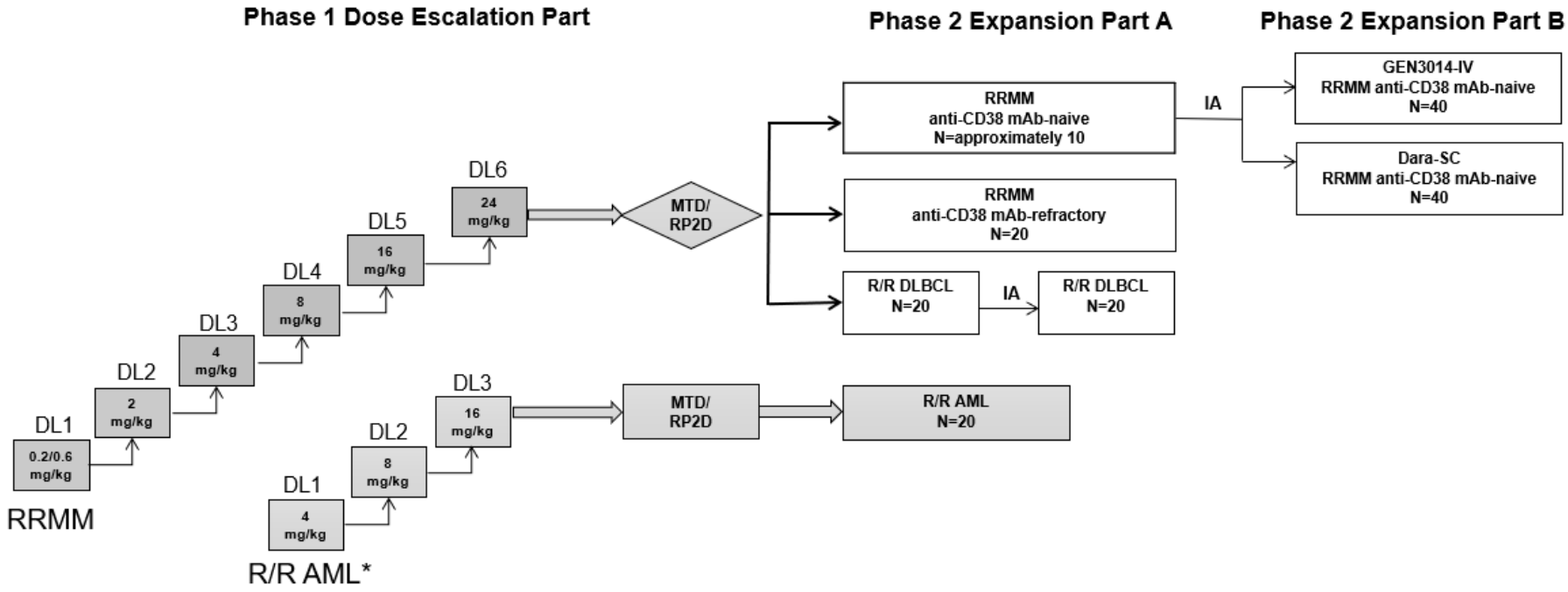
	• A man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3014 or daratumumab SC. • Prior allogeneic HSCT. • Autologous HSCT within 3 months of the first dose of GEN3014 or daratumumab SC. • Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any trial treatment or its excipients, or any of its metabolites (refer to GEN3014 and daratumumab IBs). • Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are: a. non-invasive cervical cancer treated within the last 24 months that is considered completely cured. b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured. c. non-muscle invasive bladder cancer (NMIBC). d. localized prostate cancer (N0M0). o with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance, o with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, o or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence. e. Breast cancer: o adequately treated lobular carcinoma in situ or ductal carcinoma in situ, o or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence. f. Malignancy that is considered cured with minimal risk of recurrence. **NOTE:** Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after Screening but before the first dose of trial treatment is given such that subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the trial.

Trial drug	GEN3014 will be administered intravenously and daratumumab will be administered subcutaneously (daratumumab SC). Both GEN3014 and daratumumab SC will be administered in 4-week (ie, 28-day) cycles until disease progression, unacceptable toxicity, or withdrawal of consent: once every week (Q1W) in Cycles 1-2; every 2 weeks (Q2W) in Cycles 3-6; and every 4 weeks (Q4W) in Cycles 7 and beyond. The first dose of GEN3014 in Cycle 1 will be split into 2 doses and administered in 2 consecutive days. Premedication (corticosteroids, antipyretics, antihistamines, a leukotriene receptor antagonist) and post-medication (corticosteroids) will be given to reduce the risk of infusion-related reactions (IRRs) and systemic administration-related reactions (sARRs). In the Dose Escalation, GEN3014 will be tested at 6 DLs in RRMM with the first 2 DLs being single-subject followed by standard 3-subject DLs. Intrasubject dose escalation will be performed for the first RRMM cohort (MM-DL1). From MM-DL3 and onward (ie, DL 4, 8, 16 and 24 mg/kg), the initial DL size is 3 subjects. In the Dose Escalation, 3 DLs (4, 8, and 16 mg/kg) are planned in R/R AML, with standard 3-subject cohorts. The R/R AML Cohort will be initiated after the trial has cleared the DL of 16 mg/kg in the RRMM Cohort with preliminary data on safety, PK, and pharmacodynamics in subjects with RRMM who have been treated with GEN3014 at DLs up to 16 mg/kg. DLs and the dosing schedule for the R/R AML Cohort may be modified based on emerging PK, pharmacodynamic, and safety data. In the Expansion Part A, 3 cohorts of subjects (anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, and R/R DLBCL) will be treated with GEN3014 at the RP2D identified for RRMM from the Dose Escalation and a fourth cohort of subjects with R/R AML will be treated with GEN3014 at the RP2D identified for AML from the Dose Escalation. If the preliminary efficacy and safety are judged to be favorable in the initial 10 anti-CD38 mAb-naive subjects with RRMM who received 16 mg/kg or 24 mg/kg (in the Dose Escalation or Expansion Part A), additional subjects in the anti-CD38 mAb-naive RRMM cohort will be randomized to receive: either GEN3014 at the RP2D or daratumumab SC at 1800 mg.
Statistics	<u>Dose Escalation:</u> During dose escalations of GEN3014, by utilizing an mBOIN, recommendations will be provided to the DEC to either escalate, remain or de-escalate next DL in the escalation part of the trial. The mBOIN aims to characterize the DLT rate at each DL such that the RP2D (and possibly the MTD) can be determined. Escalation data will be summarized by DL and indication (RRMM or R/R AML). <u>Expansion Part A</u> The Expansion Part A will be conducted in 4 parallel cohorts: • Anti-CD38 mAb-naive RRMM (N=approximately 10 subjects) • Anti CD38 mAb-refractory RRMM (N=20 subjects) • R/R DLBCL (up to 40 subjects): Based on a Simon's 2-stage design, up to 40 subjects with R/R DLBCL may be treated with GEN3014. The initial stage consists of 20 subjects and if least 5 of 20 subjects respond to GEN3014, the futility bar is passed. • R/R AML (N=20 subjects) The response assessment for each disease indication, for the primary endpoint of ORR, will be: • The International Myeloma Working Group consensus criteria (IWMG) 2016 for MM,

	• The revised response criteria for Hodgkin and non-Hodgkin lymphoma (Lugano classification) for DLBCL, and • The International Working Group (IWG) response criteria for AML. The ORR for each expansion cohort will be presented with the exact 2-sided 95% confidence intervals (CI) (using the Clopper-Pearson method). Expansion Part B (Randomized H2H) After a 10-subject lead-in of GEN3014, an 80-subject H2H comparison of GEN3014 IV vs daratumumab SC will be conducted among anti-CD38 mAb-naive RRMM subjects. (The randomized H2H comparison will be conducted if at least 2 out of the 10 subjects respond to GEN3014.) The ratio in ORR between the 2 arms in Expansion Part B will be described using the Miettinen-Nurminen method. The data will be evaluated by sponsor to guide further clinical development. AEs will be described using summary statistics. Safety stopping guidance based on the rate of Grade ≥4 treatment-related AEs and treatment-related deaths is established for the expansion cohorts. Individual curves of plasma concentration for GEN3014 will be presented for all subjects. PK parameters will be calculated based on non-compartmental methods and calculated separately.
GCP Compliance	This trial will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), in compliance with the principles of the Declaration of Helsinki, and other applicable regulatory requirements.

1.2 Schema

Figure 1-1 Schematic Overview of the Trial



*R/R AML cohort to be opened after GEN3014 has been tested in DL of 16 mg/kg in RRMM
DL=dose level; IA=interim analysis; IV=intravenous; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose; RRMM=relapsed or refractory multiple myeloma; R/R AML=relapsed or refractrory acute myeloid leukemia; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; SC=subcutaneous

1.3 Schedule of Activities

Table 1-1 through Table 1-11 list all of the assessments, and indicate with an "X" the evaluations performed by visit.

Dose Escalation:

- Table 1-1 Schedule of Activities – Subjects With RRMM – Dose Escalation
- Table 1-2 Schedule of Activities – Subjects With R/R AML – Dose Escalation
- Table 1-3 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – All Subjects – Dose Escalation
- Table 1-4 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Dose Escalation

Expansion:

- Table 1-5 Schedule of Activities – Subjects With RRMM – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-6 Schedule of Activities – Subjects With R/R AML – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-7 Schedule of Activities – Subjects With R/R DLBCL – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-8 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – All Subjects – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-9 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-10 Minimal Residual Disease Schedule – Subjects with R/R AML – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-11 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with R/R DLBCL – Expansion Part A (GEN3014 Single Cohorts)
- Table 1-12 Schedule of Activities – Subjects with RRMM – Expansion Part B (Randomized H2H)
- Table 1-13 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – GEN3014 IV-Treated Subjects – Expansion Part B (Randomized H2H)
- Table 1-14 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – Daratumumab SC-Treated Subjects – Expansion Part B (Randomized H2H)
- Table 1-15 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Expansion Part B (Randomized H2H)

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.

Table 1-1 Schedule of Activities – Subjects With RRMM – Dose Escalation

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X													
Eligibility criteria	5.1, 5.2		X													
Demographics	8.1.1		X													
Medical history[5]	8.1.3		X[5]	X												
Disease status	8.1.2	Includes diagnosis and staging criteria	X													
Constitutional symptoms	8.3.7	At Screening and before GEN3014 dosing	X	X		X		X	X	X	X	X				
ECOG PS	8.3.5		X	X						X		X	X	X		
Prior anti-cancer therapy	6.7.1		X													
Prior/concomitant medications and therapies	6.7		X	X	X	X	X[4]	X	X	X	X	X	X	X		
Height	8.3.2		X													
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X		X	X	X	X	X	X			

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Vital signs	8.3.3	On GEN3014 dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X[4]	X	X	X	X	X	X	X	X	
Physical examination	8.3.1	At Screening, perform complete physical exam. At subsequent visits, a symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X						X		X		X	X	
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X		X	X	X	X	X	X	X		
Adverse Events[5,6]	8.4		X[5]	X	X	X	X	X	X	X	X	X	X	X	X[6]	
TRIAL DRUG ADMINISTRATION																
Post-infusion monitoring[7]	4.1.1.2			X[7] (C1)	X[7]	X[7] (C1)	X[4,7]	X[7] (C1)	X[7] (C1)							

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Pre-infusion and post-infusion medication	6.2	Pre- and post-infusion medications required before all GEN3014 infusions.		X	X	X	X[4]	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[8]	X[8]	X[8]	X[4,8]	X	X	X	X	X				
LOCAL LABORATORY ASSESSMENTS																
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X[4]	X	X	X	X	X	X	X	X	
Biochemistry	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X[4]	X	X	X	X	X	X	X	X	
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X[4]	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X						X		X	X	X		
β2-microglobulin	8.3.6	Also see Table 10-1	X													

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X						X		X	X	X		
HBV and HCV serology	8.3.6	Also see Table 10-1	X													
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X													
CMV serology	8.3.6	Also see Table 10-1	X													
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X[4]	X	X	X (C3)			X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X													

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Cytogenetics	8.1.2.1, 8.3.6.1	Also see Table 10-1	X													
Molecular mutational status	8.1.2.1, 8.3.6.1	Also see Table 10-1	X													
CENTRAL LABORATORY																
PK	8.6		See Table 1-3													
ADA	8.9															
Biomarkers	8.8															
MRD/ctDNA	8.8		See Table 1-4													
MM DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS																
Quantitative serum Ig panel	8.2.1.1, 8.3.6.2	All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Also see Table 10-1.	X													
SPEP and UPEP (24-h urine sample) and interference assay sample[9]	8.2.1.1, 8.3.6.4	Perform Screening SPEP and UPEP within 14 days prior to C1D1. Also see Table 10-1.	X[9]	X[9]						X[9]		X[9]	X	X[9]		
Serum FLC and serum/urine IFE[10]	8.2.1.1, 8.3.6.4	Also see Table 10-1.	X	X[10]						X[10]		X[10]	X	X[10]		
Serum calcium corrected for albumin	10.7	Also see Table 10-1	X	X						X		X	X	X		
Skeletal survey[11]	8.2.1.5		X[11]	As clinically indicated[11]												

				Q1W (Weekly)						Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
Cycle(s)	**Pro-tocol Section**	**Notes**	**Screen-ing**	**Cycle 1-2**						**Cycles 3-6**		**Cycle 7 onward**				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D9[4] (C1 only)**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window								**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Bone marrow aspirate[12,13] and/or bone marrow biopsy	8.2.1.3	Needed to confirm CR/sCR, assess MRD, and for biomarker evaluations (see Table 1-3)	X[12]	Collect at C4D1 ±7 days for all subjects, and at time of suspected CR/sCR. Also collect at 6, 12, 18, 24 and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. At investigator's discretion, may be repeated if clinically indicated.[13]									X			
Assess extramedullary plasmacytomas[14]	8.2.1.4	Subject with history of plasmacytomas, or if clinically indicated at Screening.	X[14]	Measure every 4 weeks for physical examination (if applicable) and every 12 weeks for imaging assessment[14]									X			
Response Assessment	8.2.1	To be performed starting C2D1		X (C2)						X		X	X	X		
END OF TREATMENT																
New anti-cancer therapy	7.1.1														X	X
Survival Status	7.1.2															X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FLC=free light chain; FFPE=formalin-fixed, paraffin-embedded; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; min=minute(s); IRR=infusion-related reaction; MRD=minimal residual disease; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; sCR=stringent complete response; SPEP=serum protein electrophoresis; TLS=tumor lysis syndrome; UNS=unscheduled; UPEP=urine protein electrophoresis.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 30 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.
2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. To be performed at Cycle 1 Day 9 only for the MM-DL1 cohort (who is receiving a split dose on Days 8 and 9).

5. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
6. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
7. During Cycle 1, subjects in the first 2 dose levels (MM-DL1 and MM-DL2) are required to remain in the clinic for at least 8 hours after each GEN3014 infusion so that they can be observed closely. During treatment Cycle 1, all other subjects must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
8. For MM Dose Level 1 (MM-DL1), during Cycle 1, the C1D1 first dose is split between C1D1 and C1D2; the C1D8 second (escalated) dose is split between C1D8 and C1D9; the full dose is administered on C1D15, C1D22, and all dosing days for subsequent cycles. For MM-DL2 and subsequent cohorts, during Cycle 1, the C1D1 dose is split between C1D1 and C1D2; the full dose is administered on C1D8, C1D15, C1D22, and all dosing days for subsequent cycles.
9. SPEP and UPEP must be performed within 14 days prior to C1D1, and on C1D1. If Screening assessment performed within 3 days prior to C1D1, it is not necessary to repeat at C1D1. Subsequent on-treatment SPEP and UPEP are to be performed every 28 (±3) days on the scheduled assessment day. All responses based on biochemical investigations, including PD, require 2 consecutive assessments by local lab for confirmation. Once PD is confirmed, subsequent disease assessments are not required. Additional aliquots will be collected for IFE reflex testing, in case of potential interference of GEN3014 with interpretation of M-protein levels.
10. Perform serum FLC and serum/urine IFE when CR is suspected or maintained. To confirm CR (undetectable M-protein electrophoresis studies in both serum and urine will trigger central laboratory to perform IFE studies in both serum and urine and FLC in serum. Perform serum FLC on Day 1 of every cycle for all subjects.
11. A skeletal survey, including cranium, is required during Screening. Results from skeletal survey performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Additional imaging will be performed as clinically indicated.
12. At baseline (Screening) only, non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy) up to 42 days prior to enrollment may be collected for MRD assessment if the fresh aspirate fails to calibrate during testing.
13. To confirm CR/sCR, assess MRD, and for other biomarker evaluations. Samples to be collected at C4D1 ±7 days for all subjects. Also collect samples at time of suspected CR/sCR, and at 6, 12, 18, 24 and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. If 1 of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. The bone marrow tests for CR/sCR and beyond will only be required if subject's response is near CR or better by blood and urine evaluations.
14. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Results from radiologic plasmacytoma assessment performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Imaging methodology used for evaluation should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will only be monitored for PD.

Table 1-2 Schedule of Activities – Subjects With R/R AML – Dose Escalation

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X												
Eligibility criteria	5.1, 5.2		X												
Demographics	8.1.1		X												
Medical history[4]	8.1.3		X[4]	X											
Disease status	8.1.2	Includes diagnosis and staging criteria	X												
Constitutional symptoms	8.3.7	At Screening and before GEN3014 dosing	X	X		X	X	X	X	X	X				
ECOG PS	8.3.5		X	X					X		X	X	X		
Prior anti-cancer therapy	6.7.1		X												
Prior/concomitant medications and therapies	6.7		X	X	X	X	X	X	X	X	X	X	X		
Height	8.3.2		X												
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X	X	X	X	X	X	X			
Vital signs	8.3.3	On GEN3014 dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	8.3.1	At Screening, perform complete physical exam. At subsequent visits, a	X	X					X		X		X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
		symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).													
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X	X	X	X		X	X	X		
Adverse Events[4,5]	8.4		X[4]	X	X	X	X	X	X	X	X	X	X	X[5]	
TRIAL DRUG ADMINISTRATION															
Post-infusion monitoring[6]	4.1.1.2			X[6] (C1)	X[6]	X[6] (C1)	X[6] (C1)	X[6] (C1)							
Pre-infusion and post-infusion medication	6.2	Pre- and post-infusion medications required before all GEN3014 infusions.		X	X	X	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[7]	X[7]	X	X	X	X	X	X				
LOCAL LABORATORY ASSESSMENTS															
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
		authorities (see Appendix 10.15).													
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X					X		X	X	X		
β2-microglobulin	8.3.6	Also see Table 10-1	X												
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X					X		X	X	X		
HBV and HCV serology	8.3.6	Also see Table 10-1	X												
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X												
CMV serology	8.3.6	Also see Table 10-1	X												
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X	X	X	X		X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X												
Cytogenetics	8.1.2.2, 8.3.6.1	Also see Table 10-1	X												
Molecular mutational status	8.1.2.2, 8.3.6.1	Also see Table 10-1	X												

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
CENTRAL LABORATORY															
PK	8.6		See Table 1-3												
ADA	8.9														
Biomarkers	8.8														
AML DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS															
Immunoglobulins (IgA, IgG, IgM)	8.3.6.2	Also see Table 10-1. Local laboratory.	X												
Bone marrow aspirate[8] and bone marrow biopsy	8.2.2.2		X	During treatment, collect at Cycle 2 Day 1 (+3 days), Cycle 3 Day 1 (±7 days), then every 3 cycles (±1 cycle).[8]								X			
Peripheral blood assessment[9]	8.2.2.1		X	X[9]					X[9]		X[9]	X			
CT/MRI for extramedullary disease[10]	8.2.2.3	Subject with history of plasmacytomas or if clinically indicated at Screening.	X[10]	Measure every 8 weeks, and when clinically indicated[10]								X			
Response assessment	8.2.2	Response assessment to be performed on Day 1 of each cycle, starting with C2D1		X (C2)					X		X	X	X		
END OF TREATMENT															
New anti-cancer therapy	7.1.1													X	X
Survival Status	7.1.2														X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CBC=complete blood count; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; Ig=immunoglobulin; IRR=infusion-related reaction; min=minute(s); MRD=minimal residual disease; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; R/R AML=relapsed or refractory acute myeloid leukemia; SAE=serious adverse event; TLS=tumor lysis syndrome; UNS=unscheduled.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 60 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.

2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
5. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
6. During Cycle 1, subject must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
7. During Cycle 1, C1D1 dose is split between C1D1 and C1D2; full dose is administered on C1D8, C1D15, C1D22.
8. Additional sampling may be performed at other times at the investigator's discretion.
9. Perform during Screening and at Day 1 of each cycle. Include AML blast cell count and CBC with differential including promyelocytes, myelocytes, and metamyelocytes.
10. Extramedullary disease should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening.

Table 1-3 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – All Subjects – Dose Escalation

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immuno-pheno-typing	Explora-tory PBMCs	DNA-seq control sample (saliva)	Bone marrow for target engagement: Immunopheno-typing and DNA/ RNA seq (MM and AML), and IHC (AML only)
Screening	**Day -21 to Day -1**			X					X	X
Cycle 1	**Day 1**	Predose (-30 min)	X		X	X	X	X		
		End of infusion (+5 min)	X[1]							
		End of infusion +4 h (±30 min)			X	X				
	Day 2	Predose (-30 min) Day 2	X		X	X	X	X		
		End of Day 2 infusion (+5 min)	X[1]							
		End of Day 2 infusion +2 h (±15 min)	X							
		End of Day 2 infusion +4 h (±30 min)	X		X	X				
	Day 3	End of Day 2 infusion +24 h (±2 h)	X		X	X	X	X		
	Day 5	End of Day 2 infusion +72 h (±24 h)	X				X			
	Day 8	Predose (-30 min)	X		X	X	X			
		End of infusion (+5 min)	X[1]							
		End of infusion +2 h (±15 min)								
		End of infusion +4 h (±30 min)			X	X				
	Day 9	Predose (-30 min)	X[2]		X[2]	X[2]	X[2]			
		End of infusion (+5 min)	X[1,2]							
		End of infusion +2 h (±15 min)								
		End of infusion +4 h (±30 min)	X[2]		X[2]	X[2]				
		End of Day 8 infusion +24 h (±2 h)			X[3]	X[3]				
	Day 10	End of Day 9 infusion +24 h (±2 h)	X[2]		X[2]	X[2]	X[2]			
	Day 15	Predose (-30 min)	X	X	X	X	X			
		End of infusion (+5 min)	X[1]							
		End of infusion +2 h (±15 min)								
		End of infusion +4 h (±30 min)			X	X				
	Day 16	End of Day 15 infusion +24 h (±2 h)			X	X				
	Day 22	Predose (-30 min)	X		X	X	X			
		End of infusion (+5 min)	X[1]							
		End of infusion +4 h (±30 min)			X	X				
	Day 23	End of Day 22 infusion +24 h (±2 h)			X	X				

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immuno-pheno-typing	Explora-tory PBMCs	DNA-seq control sample (saliva)	Bone marrow for target engagement: Immunopheno-typing and DNA/ RNA seq (MM and AML), and IHC (AML only)
Cycle 2 to Cycle 6	**Day 1**	Predose (-30 min)	X	X[4]			X	X[4]		X[6]
		End of infusion (+5 min)	X[1]							
		End of infusion +2 h (±15 min)	X[5]							
		End of infusion +4 h (±30 min)	X[5]							
	Day 2	End of infusion +24 h (±2 h)	X[5]					X[5]		
	Day 4	End of infusion +72 h (±24 h)	X[5]							
	Day 8 (+2d)	Predose (-30 min)	X[5]				X[5]			
		End of infusion (+5 min)	X[1,5]							
	Day 15 (+2d)	Predose (-30 min)	X				X			
		End of infusion (+5 min	X[1]							
	Day 22 (+2d)	Predose (-30 min)	X[5]				X[5]			
		End of infusion (+5 min)	X[1,5]							
Cycle 7 and Beyond	**Day 1 (+3d)**	Predose (-30 min)	X	X[4]			X[4]	X[4]		
		End of infusion (+5 min)[a]	X[1]							
End of Treatment			X	X						
UNS			X	X	X	X	X	X		

ADA=anti-drug antibody; C=cycle; D/d=day; DNA=deoxyribonucleic acid; h=hour(s); min=minutes; MM-DL1=multiple myeloma dose level 1; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic(s); RNA=ribonucleic acid; R/R AML=relapsed or refractory acute myeloid leukemia; RRMM=relapsed or refractory multiple myeloma; seq=sequencing; UNS=unscheduled.

1. After flush.
2. Cycle 1 only, for MM-DL1 only.
3. All cohorts except MM-DL1.
4. ADA and biomarker samples in even cycles only.
5. Cycle 2 only.
6. For R/R AML, collect samples on C2D1 and C3D1. For RRMM, only collect sample on C4D1. Testing at these time points is for immunophenotyping only.

Table 1-4 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Dose Escalation

Screening or Treatment Cycle (28 days per cycle)	**Screening**	**Post-treatment Collections**
Day (window)	**Day -21 to Day -1**	**±1 month**
Bone marrow aspirate for MRD	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial
Whole blood MRD and ctDNA	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial

C=cycle; CR=complete remission; ctDNA=circulating tumor DNA; D/d=day; MRD=minimal residual disease; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response.

Table 1-5 Schedule of Activities – Subjects With RRMM – Expansion Part A (GEN3014 Single Cohorts)

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X												
Eligibility criteria	5.1, 5.2		X												
Demographics	8.1.1		X												
Medical history[4]	8.1.3		X[4]	X											
Disease status	8.1.2	Includes diagnosis and staging criteria	X												
Constitutional symptoms	8.3.7	At Screening and before GEN3014 dosing	X	X		X	X	X	X	X	X				
ECOG PS	8.3.5		X	X					X		X	X	X		
Prior anti-cancer therapy	6.7.1		X												
Prior/concomitant medications and therapies	6.7		X	X	X	X	X	X	X	X	X	X	X		
Height	8.3.2		X												
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X	X	X	X	X	X	X			
Vital signs	8.3.3	On GEN3014 dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
		authorities (see Appendix 10.15).													
Physical examination	8.3.1	At Screening, perform complete physical exam. At subsequent visits, a symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X					X		X		X	X	
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X	X	X	X		X	X	X		
Adverse Events[4,5]	8.4		X[4]	X	X	X	X	X	X	X	X	X	X	X[5]	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
TRIAL DRUG ADMINISTRATION															
Post Infusion Monitoring[6]	4.1.1.2			X[6] (C1)	X[6]	X[6] (C1)	X[6] (C1)	X[6] (C1)							
Pre-infusion and post-infusion medication	6.2	Pre- and post-infusion medications required before all GEN3014 infusions.		X	X	X	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[7] (C1)	X[7]	X	X	X	X	X	X				
LOCAL LABORATORY ASSESSMENTS															
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X					X		X	X	X		

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
β2-microglobulin	8.3.6	Also see Table 10-1	X												
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X					X		X	X	X		
HBV and HCV serology	8.3.6	Also see Table 10-1	X												
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X												
CMV serology	8.3.6	Also see Table 10-1	X												
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X	X	X (C3)			X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X												
Cytogenetics	8.1.2.1, 8.3.6.1	Also see Table 10-1	X												
Molecular mutational status	8.1.2.1, 8.3.6.1	Also see Table 10-1	X												

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
CENTRAL LABORATORY															
PK	8.6		see Table 1-8												
ADA	8.9														
Biomarkers	8.8.1														
MRD/ctDNA	8.8		see Table 1-9												
MM DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS															
Quantitative serum Ig panel	8.2.1.1, 8.3.6.2	All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Also see Table 10-1.	X												
SPEP and UPEP (24-h urine sample) and interference assay sample[8]	8.2.1.1, 8.3.6.4	Perform Screening SPEP and UPEP within 14 days prior to C1D1. Also see Table 10-1.	X[8]	X[8]					X[8]		X[8]	X	X[8]		
Serum FLC and serum/urine IFE[9]	8.2.1.1, 8.3.6.4	Also see Table 10-1.	X	X[9]					X[9]		X[9]	X	X[9]		
Serum calcium corrected for albumin	8.2.1.2, 10.7	Also see Table 10-1	X	X					X		X	X	X		
Skeletal survey[10]	8.2.1.5		X[10]	As clinically indicated[10]											
Bone marrow aspirate[11,12] and/or bone marrow biopsy	8.2.1.3	Needed to confirm CR/sCR, assess MRD, and for other biomarker evaluations (see Table 1-8)	X[11]	Collect at C4D1 ±7 days for all subjects, and at time of suspected CR/sCR. Also collect at 6, 12, 18, 24 and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. At investigator's discretion, may be repeated if clinically indicated.[12]								X	X[12]		

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Assess extramedullary plasmacytomas[13]	8.2.1.4	Subject with history of plasmacytomas, or if clinically indicated at Screening.	X[13]	Measure every 4 weeks for physical examination (if applicable) and every 12 weeks for imaging assessment[13]								X			
Response Assessment	8.2.1	To be performed starting C2D1		X (C2)					X		X	X	X		
END OF TREATMENT															
New anti-cancer therapy	7.1.1													X	X
Survival Status	7.1.2														X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FFPE=formalin-fixed, paraffin-embedded; FLC=free light chain; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; Ig=immunoglobulin; IRR=infusion-related reaction; min=minute(s); MRD=minimal residual disease; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; sCR=stringent complete response; SPEP=serum protein electrophoresis; TLS=tumor lysis syndrome; UNS=unscheduled; ; UPEP=urine protein electrophoresis.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 60 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.
2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
5. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
6. During Cycle 1, subject must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
7. During Cycle 1, C1D1 dose is split between C1D1 and C1D2; full dose is administered on C1D8, C1D15, C1D22.
8. SPEP and UPEP must be performed within 14 days prior to C1D1, and on C1D1. If Screening assessment performed within 3 days prior to C1D1, it is not necessary to repeat at C1D1. Subsequent on-treatment SPEP and UPEP are to be performed every 28 (±3) days on the scheduled assessment day. All responses based on biochemical investigations, including PD, require 2 consecutive assessments by local lab for confirmation. Once PD is confirmed, subsequent disease assessments are not required. Additional aliquots will be collected for IFE reflex testing, in case of potential interference of GEN3014 with interpretation of M-protein levels.

9. Perform serum FLC and serum/urine IFE when CR is suspected or maintained. To confirm CR (undetectable M-protein electrophoresis studies in both serum and urine will trigger central laboratory to perform IFE studies in both serum and urine, and FLC in serum. Perform serum FLC on Day 1 of every cycle for all subjects.
10. A skeletal survey, including cranium, is required during Screening. Results from skeletal survey performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Additional imaging will be performed as clinically indicated.
11. At baseline (Screening) only, non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy) up to 42 days prior to enrollment may be collected for MRD assessment if the fresh aspirate fails to calibrate during testing.
12. To confirm CR/sCR, assess MRD, and for other biomarker evaluations. Samples are to be collected at C4D1 ±7 days for all subjects. Also collect samples at time of suspected CR/sCR, and at 6, 12, 18, 24, and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. If 1 of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. The bone marrow tests at CR/sCR and beyond will only be required if subject's response is near CR or better by blood and urine evaluations. If clinically feasible, a bone marrow aspirate will also be performed at End of Treatment/PD.
13. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Results from radiologic plasmacytoma assessment performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Imaging methodology used for evaluation should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will only be monitored for PD.

Table 1-6 Schedule of Activities – Subjects With R/R AML – Expansion Part A (GEN3014 Single Cohorts)

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X												
Eligibility criteria	5.1, 5.2		X												
Demographics	8.1.1		X												
Medical history[4]	8.1.3		X[4]	X											
Disease status	8.1.2	Includes diagnosis and staging criteria	X												
Constitutional symptoms	8.3.7	At Screening and before GEN3014 dosing	X	X		X	X	X	X	X	X				
ECOG PS	8.3.5		X	X					X		X	X	X		
Prior anti-cancer therapy	6.7.1		X												
Prior/concomitant medications and therapies	6.7		X	X	X	X	X	X	X	X	X	X	X		
Height	8.3.2		X												
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X	X	X	X	X	X	X			
Vital signs	8.3.3	On GEN3014 dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	8.3.1	At Screening, perform complete physical exam. At subsequent visits, a	X	X					X		X		X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
		symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).													
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X	X	X	X		X	X	X		
Adverse Events[4,5]	8.4		X[4]	X	X	X	X	X	X	X	X	X	X	X[5]	
TRIAL DRUG ADMINISTRATION															
Post Infusion Monitoring[6]	4.1.1.2			X[6] (C1)	X[6]	X[6] (C1)	X[6] (C1)	X[6] (C1)							
Pre-infusion and post-infusion medication	6.2	Pre- and post-infusion medications required before all GEN3014 infusions.		X	X	X	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[7]	X[7]	X	X	X	X	X	X				
LOCAL LABORATORY ASSESSMENTS															
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	8.3.6	Also see Table 10-1. At Safety	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
		Follow-up visit as required per local health authorities (see Appendix 10.15).													
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X					X		X	X	X		
β2-microglobulin	8.3.6	Also see Table 10-1	X												
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X					X		X	X	X		
HBV and HCV serology	8.3.6	Also see Table 10-1	X												
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X												
CMV serology	8.3.6	Also see Table 10-1	X												
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X	X	X	X		X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X												
Cytogenetics	8.1.2.2, 8.3.6.1	Also see Table 10-1	X												
Molecular mutational status	8.1.2.2, 8.3.6.1	Also see Table 10-1	X												

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
CENTRAL LABORATORY															
PK	8.6		See Table 1-8												
ADA	8.9														
Biomarkers	8.8														
MRD	8.8		See Table 1-10												
AML DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS															
Immunoglobulins (IgA, IgG, IgM)	8.3.6.2	Also see Table 10-1	X												
Bone marrow aspirate[8,9] and bone marrow biopsy	8.2.2.2		X[8]	During treatment, collect at Cycle 2 Day 1 (+3 days), Cycle 3 Day 1 (±7 days), then every 3 cycles (±1 cycle).[9]								X	X[9]		
Peripheral blood assessment[10]	8.2.2.1		X	X[10]					X[10]		X[10]	X			
CT/MRI for extramedullary disease[11]	8.2.2.3	Subject with history of plasmacytomas or if clinically indicated at Screening.	X[11]	Measure every 8 weeks, and when clinically indicated[11]								X			
Response assessment	8.2.2	Response assessment to be performed on Day 1 of each cycle, starting with C2D1		X (C2)					X		X	X	X		
END OF TREATMENT															
New anti-cancer therapy	7.1.1													X	X
Survival Status	7.1.2														X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CBC=complete blood count; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FFPE=formalin-fixed, paraffin-embedded; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; Ig=immunoglobulin; IRR=infusion-related reaction; min=minute(s); MRD=minimal residual disease; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; R/R AML=relapsed or refractory acute myeloid leukemia; SAE=serious adverse event; TLS=tumor lysis syndrome; UNS=unscheduled.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 30 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.
2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
5. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
6. During Cycle 1, subject must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
7. During Cycle 1, C1D1 dose is split between C1D1 and C1D2; full dose is administered on C1D8, C1D15, C1D22.
8. At baseline (Screening) only, non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy) up to 42 days prior to enrollment may be collected for MRD assessment if the fresh aspirate fails to calibrate during testing.
9. Additional sampling may be performed at other times at the investigator's discretion. If clinically feasible, a bone marrow aspirate will also be performed at End of Treatment/PD.
10. Perform during Screening and at Day 1 of each cycle. Include AML blast cell count and CBC with differential including promyelocytes, myelocytes, and metamyelocytes.
11. Extramedullary disease should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening.

Table 1-7 Schedule of Activities – Subjects With R/R DLBCL – Expansion Part A (GEN3014 Single Cohorts)

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X												
Eligibility criteria	5.1, 5.2		X												
Demographics	8.1.1		X												
Medical history[4]	8.1.3		X[4]	X											
Disease status	8.1.2	Includes diagnosis and staging criteria	X												
Constitutional symptoms	8.3.7	At Screening and before GEN3014 dosing	X	X		X	X	X	X	X	X				
ECOG PS	8.3.5		X	X					X		X	X	X		
Prior anti-cancer therapy	6.7.1		X												
Prior/concomitant medications and therapies	6.7		X	X	X	X	X	X	X	X	X	X	X		
Height	8.3.2		X												
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X	X	X	X	X	X	X			
Vital signs	8.3.3	On GEN3014 dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Physical examination	8.3.1	At Screening, perform complete physical exam. At subsequent visits, a symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X					X		X		X	X	
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X	X	X	X		X	X	X		
Adverse Events[4,5]	8.4		X[4]	X	X	X	X	X	X	X	X	X	X	X[5]	
TRIAL DRUG ADMINISTRATION															
Post Infusion Monitoring[6]	4.1.1.2			X[6] (C1)	X[6]	X[6] (C1)	X[6] (C1)	X[6] (C1)							
Pre-medication and post-infusion medication	6.2	Pre- and post-infusion medications required before all GEN3014 infusions.		X	X	X	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[7]	X[7]	X	X	X	X	X	X				
LOCAL LABORATORY ASSESSMENTS															
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Biochemistry	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X					X		X	X	X		
β2-microglobulin	8.3.6	Also see Table 10-1	X												
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X					X		X	X	X		
HBV and HCV serology	8.3.6	Also see Table 10-1	X												
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X												
CMV serology	8.3.6	Also see Table 10-1	X												
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X	X	X (C3)			X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X												
Cytogenetics	8.1.2.3, 8.3.6.1	Also see Table 10-1	X												
Molecular mutational status	8.1.2.3, 8.3.6.1	Also see Table 10-1	X												

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
CENTRAL LABORATORY															
PK	8.6		See Table 1-8												
ADA	8.9														
Biomarkers	8.8.2.6														
MRD/ctDNA	8.8		See Table 1-11												
DLBCL DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS															
Immunoglobulins (IgA, IgG, IgM)	8.3.6.2	Also see Table 10-1	X												
Tumor biopsy	8.8.1	A portion of biopsy will be used for biomarker evaluations. Also see Table 1-11	X						X[8] (C3)				X[8]		
DLBCL with bone marrow involvement: bone marrow aspirate/biopsy	8.2.3.2	Biopsy obtained as routine standard of care may be used, if taken up to 42 days before C1D1. A portion of bone marrow aspirate/ biopsy will be used for biomarker evaluations. Also see Table 1-11.	X	Bone marrow biopsy plus aspirate is required for confirmation of an observed radiologic CR; should be done within 30 days of the initial documentation of radiologic CR								X			
FDG-PET-CT/ CT/MRI	8.2.3.1		X	Required at: C2 (W6), C3 (W12), C5 (W18), C6 (W24), then every 24 weeks thereafter (Cycle 12, 18, 24, etc.) until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first								X			
MRI or CT of the brain	8.2.3.1	Perform at Screening only if brain involvement is suspected	X	May be performed during the trial if clinically indicated.											

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycle 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Response assessment	8.2.3	Response required per efficacy assessment time points		Required at: C2 (W6), C3 (W12), C5 (W18), C6 (W24), then every 24 weeks thereafter (Cycle 12, 18, 24, etc.) until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first								X			
END OF TREATMENT															
New anti-cancer therapy	7.1.1													X	X
Survival Status	7.1.2														X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FDG=fluorodeoxyglucose; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; Ig=immunoglobulin; IRR=infusion-related reaction; min=minute(s); MRD=minimal residual disease; MRI=magnetic resonance imaging; PET-CT=positron emission tomography-computed tomography; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; SAE=serious adverse event; TLS=tumor lysis syndrome; UNS=unscheduled.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 60 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.
2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
5. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
6. During Cycle 1, subject must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
7. During Cycle 1, C1D1 dose is split between C1D1 and C1D2; full dose is administered on C1D8, C1D15, C1D22.
8. Unless otherwise agreed with sponsor's medical monitor or delegate, if clinically feasible, a fresh core biopsy is to be taken from subjects in Cycle 3 and at the End of Treatment visit.

Table 1-8 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – All Subjects – Expansion Part A (GEN3014 Single Cohorts)

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immu-nophe-notyping	Tumor Biopsy for IHC and DNA/ RNA seq (DLBCL)	Pro-teo-mics	Explor-atory PBMCs	DNA-seq control sample (saliva)	Bone Marrow for Target Engage-ment: Immuno-phenotyping and DNA/ RNA seq (MM and AML), and IHC (AML Only)
Screening	**Day -21 to Day -1**			X				X[7]			X	X
Cycle 1	**Day 1**	Predose (-30 min)	X		X	X	X		X	X		
		End of infusion (+5 min)	X[1]									
		End of infusion +4 h (±30 min)			X	X						
	Day 2	Predose (-30 min) Day 2	X		X	X	X					
		End of Day 2 infusion (+5 min)	X[1]									
		End of Day 2 infusion +4 h (±30 min)	X		X	X						
	Day 3	End of Day 2 infusion +24 h (±2 h)	X		X	X	X			X		
	Day 5	End of Day 2 infusion +72 h (±24 h)	X				X					
	Day 8	Predose (-30 min)	X		X	X	X		X			
		End of infusion (+5 min)	X[1]									
	Day 15	Predose (-30 min)	X			X	X		X			
		End of infusion (+5 min)	X[1]									
	Day 22	Predose (-30 min)	X	X		X	X		X			
		End of infusion (+5 min)	X[1]									

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immu-nophe-notyping	Tumor Biopsy for IHC and DNA/ RNA seq (DLBCL)	Pro-teo-mics	Explor-atory PBMCs	DNA-seq control sample (saliva)	Bone Marrow for Target Engage-ment: Immuno-phenotyping and DNA/ RNA seq (MM and AML), and IHC (AML Only)
Cycle 2 to Cycle 6	**Day 1**	Predose (-30 min)	X	X[2]			X	X[4]	X	X		X[5]
		End of infusion (+5 min)	X[1]									
	Day 8 (+2d)	Predose (-30min)	X									
	Day 15 (+2d)	Predose (-30min)	X				X					
	Day 22 (+2d)	Predose (-30min)	X									
		End of infusion (+5 min)	X[1,3]									
		End of infusion +4 h (±30 min)	X[3]									
	Day 23	End of infusion +24 h (±2 h)	X[3]									
	Day 25	End of infusion +72 h (±24 h)	X[3]									
Cycle 7 and Beyond	**Day 1 (+3d)**	Predose (-30 min)	X	X[2]			X[2]			X[2]		
End of Treatment			X	X				X[6]	X			X[6]
UNS			X	X	X	X	X			X		

ADA=anti-drug antibody; C=cycle; D/d=day; DNA=deoxyribonucleic acid; h=hour(s); IHC=immunohistochemistry; min=minutes; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic(s); RNA=ribonucleic acid; R/R AML=relapsed or refractory acute myeloid leukemia; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; RRMM=relapsed or refractory multiple myeloma; seq=sequencing; UNS=unscheduled.

1. After flush.
2. ADA and biomarker samples in even cycles only.
3. Cycle 2 only.
4. For R/R DLBCL: collect sample at C3D1 only.
5. For R/R AML: collect samples at C2D1 and C3D1. For RRMM: collect sample at C4D1 only. Testing at these time points is for immunophenotyping only.
6. Collect if clinically feasible.
7. Fresh tumor biopsy at Screening is required if clinically feasible. If fresh tissue cannot be obtained, then archived tumor tissue from a recent biopsy (≤24 months old) must be provided.

Table 1-9 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Expansion Part A (GEN3014 Single Cohorts)

Screening or Treatment Cycle (28 days per cycle)	**Screening**	**Post-treatment Collection**
Day (window)	**Day -21 to Day -1**	**±1 month**
Bone marrow aspirate for MRD	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial
Whole blood MRD and ctDNA	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial

C=cycle; D/d=day; CR=complete remission; ctDNA=circulating tumor deoxyribonucleic acid; MRD=minimal residual disease; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response.

Table 1-10 Minimal Residual Disease Evaluation Schedule – Subjects with R/R AML – Expansion Part A (GEN3014 Single Cohorts)

Screening or Treatment Cycle (28 days per cycle)	**Screening**	**Cycles 2, 3, 6, 9, and 12**	**Additional Post-treatment Collections**
Day (window)	**Day -21 to Day -1**	**Day 1 (±3d for C2, ±7d for C3; ±1 cycle for all others)**	**±1 month**
Bone marrow aspirate for MRD	X	X	At CR/CRi, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/CRi and remain on trial.

C=cycle; D/d=day; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; ctDNA=circulating tumor deoxyribonucleic acid; MRD=minimal residual disease; R/R AML=relapsed or refractory acute myeloid leukemia.

Table 1-11 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with R/R DLBCL – Expansion Part A (GEN3014 Single Cohorts)

Screening or Treatment Cycle (28 days per cycle)	Screening	Cycles 1, 3, 5, 7, and 10	Cycle 13 and onward
Day (window)	**Day -21 to Day -1**	**Day 1 (+2d)**	**Day 1 (+2d)**
Whole blood MRD and ctDNA[1,2]	X	X	A whole blood sample will be obtained every 6 months (±1 month) for up to 3 years.
DLBCL with bone marrow involvement: Bone marrow aspirate MRD[3]	X[3]	• If a subject is in CR, a portion of the aspirate collected to confirm CR will be used to assess MRD; a bone marrow aspirate is then mandatory to confirm MRD negativity. • If a subject is MRD positive in the bone marrow but maintains clinical response, an additional bone marrow aspirate will be collected after 3 months, if clinically feasible.	

CR=complete remission; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; MRD=minimal residual disease; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma.
1. 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 and ctDNA.
2. ctDNA samples will be collected up to 1 year from subjects enrolled in the Expansion Part A.
3. If bone marrow involvement was documented to be absent at Screening, MRD will not be assessed in post-treatment samples.

Table 1-12 Schedule of Activities – Subjects with RRMM – Expansion Part B (Randomized H2H)

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycles 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
Informed consent	10.1.5	Obtain prior to any trial-related activity	X												
Eligibility criteria	5.1, 5.2		X												
Demographics	8.1.1		X												
Medical history[4]	8.1.3		X[4]	X											
Disease status	8.1.2	Includes diagnosis and staging criteria	X												
Constitutional symptoms	8.3.7	At Screening and before trial drug dosing	X	X		X	X	X	X	X	X				
ECOG PS	8.3.5		X	X					X		X	X	X		
Prior anti-cancer therapy	6.7.1		X												
Prior/concomitant medications and therapies	6.7		X	X	X	X	X	X	X	X	X	X	X		
Height	8.3.2		X												
Body weight	8.3.2	Measure weight within 72 h before GEN3014 infusion	X	X		X	X	X	X	X	X	X			
Vital signs	8.3.3	On trial drug dosing days, as per Section 8.3.3. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Physical	8.3.1	At Screening,	X	X					X		X		X	X	

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycles 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
examination		perform complete physical exam. At subsequent visits, a symptom-directed/ clinically-indicated (brief) physical examination may be performed. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).													
12-Lead ECG	8.3.4	Perform in triplicate	X	X		X	X	X	X		X	X	X		
Adverse Events[4,5]	8.4		X[4]	X	X	X	X	X	X	X	X	X	X	X[5]	
TRIAL DRUG ADMINISTRATION															
Post Infusion Monitoring[6]	4.1.1.2			X[6] (C1)	X[6]	X[6] (C1)	X[6] (C1)	X[6] (C1)							
Pre-infusion and post-infusion medication	6.2	Pre-administration medications required before all GEN3014 and daratumumab SC doses		X	X	X	X	X	X	X	X				
GEN3014 administration	4.1.1, 4.1.1.1	C1D1 dose is split between 2 consecutive days (C1D1 and C1D2).		X[7] (C1)	X[7]	X	X	X	X	X	X				
Daratumumab SC administration	6.1.6.3			X		X	X	X	X	X	X				

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycles 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
LOCAL LABORATORY ASSESSMENTS															
Hematology	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	8.3.6	Also see Table 10-1. At Safety Follow-up visit as required per local health authorities (see Appendix 10.15).	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	8.3.6	Also see Table 10-1	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	8.3.6	Also see Table 10-1	X	X					X		X	X	X		
β2-microglobulin	8.3.6	Also see Table 10-1	X												
Pregnancy test (serum or urine)	8.3.6	Also see Table 10-1 Serum pregnancy test at Screening. Subsequent tests can be serum or urine. Confirm negative result before dosing.	X	X					X		X	X	X		

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycles 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
HBV and HCV serology	8.3.6	Also see Table 10-1	X												
HIV serology	8.3.6	Performed at Screening only if required per local health authorities or institutional standards.	X												
CMV serology	8.3.6	Also see Table 10-1	X												
TLS	8.3.6, 10.3.6	Also see Table 10-1. Use Cairo-Bishop Grading System.	X	X	X	X	X	X	X (C3)			X			
Blood type assessment	8.3.6.3	Also see Table 10-1	X												
Cytogenetics	8.1.2.1, 8.3.6.1	Also see Table 10-1	X												
Molecular mutational status	8.1.2.1, 8.3.6.1	Also see Table 10-1	X												
CENTRAL LABORATORY															
PK	8.6		see Table 1-8												
ADA	8.9														
Biomarkers	8.8.1														
MRD/ctDNA	8.8		see Table 1-9												
MM DISEASE: ASSESSMENTS INCLUDING CENTRAL AND LOCAL LABORATORY ASSESSMENTS															
Quantitative serum Ig panel	8.2.1.1, 8.3.6.2	All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Also see Table 10-1.	X												
SPEP and UPEP	8.2.1.1,	Perform Screening	X[8]	X[8]					X[8]		X[8]	X	X[8]		

Cycle(s)	Pro-tocol Section	Notes	Screen-ing	Q1W (Weekly)					Q2W		Q4W	UNS	End of Treat-ment	Safety Follow-up[1]	Survival Status/ contact[2]
				Cycles 1-2					Cycles 3-6		Cycle 7 onward				
Cycle Day			**D -21 to D -1**	**D1[3]**	**D2 (C1 only)**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		**ASAP after last dose**	**30d after last dose**	**Q3M**
Visit Window							**+3d**		**+3d**		**+3d**		**+7d**	**+7d**	**±7d**
(24-h urine sample) and interference assay sample[8]	8.3.6.4	SPEP and UPEP within 14 days prior to C1D1. Also see Table 10-1.													
Serum FLC and serum/urine IFE[9]	8.2.1.1, 8.3.6.4	Also see Table 10-1	X	X[9]					X[9]		X[9]	X	X[9]		
Serum calcium corrected for albumin	8.2.1.2, 10.7	Also see Table 10-1	X	X					X		X	X	X		
Skeletal survey[10]	8.2.1.5		X[10]	As clinically indicated[10]											
Bone marrow aspirate[11,12] and/or bone marrow biopsy	8.2.1.3	Needed to confirm CR/sCR, assess MRD, and for other biomarker evaluations (see Table 1-8)	X[11]	Collect at C4D1 ±7 days for all subjects, and at time of suspected CR/sCR. Also collect at 6, 12, 18, 24 and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. At investigator's discretion, may be repeated if clinically indicated.[12]								X	X[12]		
Assess extramedullary plasmacytomas[13]	8.2.1.4	Subject with history of plasmacytomas, or if clinically indicated at Screening.	X[13]	Measure every 4 weeks for physical examination (if applicable) and every 12 weeks for imaging assessment[13]								X			
Response Assessment	8.2.1	To be performed starting C2D1		X (C2)					X		X	X	X		
END OF TREATMENT															
New anti-cancer therapy	7.1.1													X	X
Survival Status	7.1.2														X

ADA=anti-drug antibody; AE=adverse event; ASAP=as soon as possible; C=cycle; CMV=cytomegalovirus; CR=complete remission; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FFPE=formalin-fixed, paraffin-embedded; FLC=free light chain; h=hour(s); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; Ig=immunoglobulin; IRR=infusion-

related reaction; min=minute(s); MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); Q3M=every 3 months; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; sCR=stringent complete response; SPEP=serum protein electrophoresis; TLS=tumor lysis syndrome; UNS=unscheduled; UPEP=urine protein electrophoresis.

1. Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of GEN3014. If the subject initiates new anti-cancer therapy within 60 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer therapy. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up.
2. 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.
3. Baseline is defined as the available data from the latest recorded measurement made before the first GEN3014 administration.
4. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first GEN3014 dose should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 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.
5. Only SAEs judged by the investigator as related to GEN3014 should be reported after the safety follow-up period.
6. During Cycle 1, subject must be observed after each GEN3014 infusion for at least 4 hours. Additional or longer monitoring is permissible per the investigator's discretion. If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion.
7. During Cycle 1, C1D1 dose is split between C1D1 and C1D2; full dose is administered on C1D8, C1D15, C1D22.
8. SPEP and UPEP must be performed within 14 days prior to C1D1, and on C1D1. If Screening assessment performed within 3 days prior to C1D1, it is not necessary to repeat at C1D1. Subsequent on-treatment SPEP and UPEP are to be performed every 28 (±3) days on the scheduled assessment day. All responses based on biochemical investigations, including PD, require 2 consecutive assessments by local lab for confirmation. Once PD is confirmed, subsequent disease assessments are not required. Additional aliquots will be collected for IFE reflex testing, in case of potential interference of GEN3014 with interpretation of M-protein levels.
9. Perform serum FLC and serum/urine IFE when CR is suspected or maintained. To confirm CR (undetectable M-protein electrophoresis studies in both serum and urine will trigger central laboratory to perform IFE studies in both serum and urine, and FLC in serum. Perform serum FLC on Day 1 of every cycle for all subjects.
10. A skeletal survey, including cranium, is required during Screening. Results from skeletal survey performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Additional imaging will be performed as clinically indicated.
11. At baseline (Screening) only, non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy) up to 42 days prior to enrollment may be collected for MRD assessment if the fresh aspirate fails to calibrate during testing.
12. To confirm CR/sCR, assess MRD, and for other biomarker evaluations. Samples are to be collected at C4D1 ±7 days for all subjects. Also collect samples at time of suspected CR/sCR, and at 6, 12, 18, 24, and 30 (±1) months post C1D1 for subjects who achieve CR/sCR and remain on trial. If 1 of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. The bone marrow tests at CR/sCR and beyond will only be required if subject's response is near CR or better by blood and urine evaluations. If clinically feasible, a bone marrow aspirate will also be performed at End of Treatment/PD.
13. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Results from radiologic plasmacytoma assessment performed within 42 days before C1D1 as routine follow up for subject's disease state may be used. Imaging methodology used for evaluation should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will only be monitored for PD.

Table 1-13 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – GEN3014 IV-Treated Subjects – Expansion Part B (Randomized H2H)

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immuno-pheno-typing	Pro-teomics	Explora-tory PBMCs	DNA-seq control sample (saliva)	Bone Marrow for Immuno-phenotyping and DNA/ RNA seq
Screening	**Day -21 to Day -1**			X						X	X
Cycle 1	**Day 1**	Predose (-30 min)	X		X	X	X	X	X		
		End of infusion (+5 min)	X[1]								
		End of infusion +4 h (±30 min)			X	X					
	Day 2	Predose (-30 min) Day 2	X		X	X	X				
		End of Day 2 infusion (+5 min)	X[1]								
		End of Day 2 infusion +4 h (±30 min)	X		X	X					
	Day 3	End of Day 2 infusion +24 h (±2 h)	X		X	X	X		X		
	Day 5	End of Day 2 infusion +72 h (±24 h)	X				X				
	Day 8	Predose (-30 min)	X		X	X	X	X			
		End of infusion (+5 min)	X[1]								
	Day 15	Predose (-30 min)	X			X	X	X			
		End of infusion (+5 min)	X[1]								
	Day 22	Predose (-30 min)	X	X		X	X	X			
		End of infusion (+5 min)	X[1]								
Cycle 2 to Cycle 6	**Day 1**	Predose (-30 min)	X	X[2]			X	X	X		X[4]
		End of infusion (+5 min)	X[1]								
	Day 8 (+2d)	Predose (-30min)	X								
	Day 15 (+2d)	Predose (-30min)	X				X				
	Day 22 (+2d)	Predose (-30min)	X								
		End of infusion (+5 min)	X[1,3]								
		End of infusion +4 h (±30 min)	X[3]								
	Day 23	End of infusion +24 h (±2 h)	X[3]								
	Day 25	End of infusion +72 h (±24 h)	X[3]								

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immuno-pheno-typing	Pro-teomics	Explora-tory PBMCs	DNA-seq control sample (saliva)	Bone Marrow for Immuno-phenotyping and DNA/ RNA seq
Cycle 7 and Beyond	**Day 1 (+3d)**	Predose (-30 min)	X	X[2]			X[2]		X[2]		
End of Treatment			X	X				X			X[5]
UNS			X	X	X	X	X		X		

ADA=anti-drug antibody; C=cycle; D/d=day; DNA=deoxyribonucleic acid; h=hour(s); H2H=head-to-head; min=minutes; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic(s); RNA=ribonucleic acid; seq=sequencing; UNS=unscheduled.

1. After flush.
2. ADA and biomarker samples in even cycles only.
3. Cycle 2 only.
4. For RRMM: collect sample at C4D1 only. Testing at these time points is for immunophenotyping only.
5. Collect if clinically feasible.

Table 1-14 Schedule for PK, Biomarker/Pharmacodynamic, and Immunogenicity Sampling – Daratumumab SC-Treated Subjects – Expansion Part B (Randomized H2H)

Cycle (28-day cycles)	Day (Window)	Time Point (Window)	PK	ADA	Cyto-kines	Comple-ment	Immuno-pheno-typing	Pro-teomics	Explora-tory PBMCs	DNA-seq control sample (saliva)	Bone Marrow for Immuno-phenotyping and DNA/ RNA seq
Screening	**Day -21 to Day -1**			X						X	X
Cycle 1	**Day 1**	Predose (-30 min)	X	X	X	X	X	X	X		
		End of infusion +4 h (±30 min)	X		X	X					
	Day 2	End of infusion +24 h (±2 h)	X		X	X	X				
	Day 4	End of infusion +72 h (±24 h)	X				X				
	Day 8	Predose (-30 min)	X		X	X	X	X			
	Day 15	Predose (-30 min)	X			X	X	X			
	Day 22	Predose (-30 min)	X	X		X	X	X			
Cycle 2 to Cycle 6	**Day 1**	Predose (-30 min)	X	X[1]			X	X	X		X[3]
	Day 8 (+2d)	Predose (-30 min)	X								
	Day 15 (+2d)	Predose (-30 min)	X				X				
	Day 22 (+2d)	Predose (-30 min)	X								
		End of infusion +4 h (±30 min)	X[2]								
	Day 23	End of infusion +24 h (±2 h)	X[2]								
	Day 25	End of infusion +72 h (±24 h)	X[2]								
Cycle 7 and Beyond	**Day 1 (+3d)**	Predose (-30 min)	X	X[1]			X[1]		X[1]		
End of Treatment			X	X				X			X[4]
UNS			X	X	X	X	X		X		

ADA=anti-drug antibody; C=cycle; D/d=day; DNA=deoxyribonucleic acid; h=hour(s); H2H=head-to-head; min=minutes; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic(s); RNA=ribonucleic acid; SC=subcutaneous; seq=sequencing; UNS=unscheduled.

1. ADA and biomarker samples in even cycles only.
2. Cycle 2 only.
3. Collect sample at C4D1 only. Testing at this time point is for immunophenotyping only.
4. Collect if clinically feasible.

Table 1-15 Minimal Residual Disease and ctDNA Evaluation Schedule – Subjects with RRMM – Expansion Part B (Randomized H2H)

Screening or Treatment Cycle (28 days per cycle)	**Screening**	**Post-treatment Collection**
Day (window)	**Day -21 to Day -1**	**±1 month**
Bone marrow aspirate for MRD	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial
Whole blood MRD and ctDNA	X	At CR/sCR, and at 6, 12, 18, 24, and 30 months post C1D1 for subjects who achieve CR/sCR and remain on trial

C=cycle; CR=complete remission; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day; H2H=head-to-head; MRD=minimal residual disease; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Diseases

2.1.1.1 Multiple Myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy characterized by clonal proliferation of abnormal plasma cells in the bone marrow. In the United States (US), an estimated 34,920 new cases of MM were diagnosed in 2021 with 12,410 deaths estimated (SEER-MM, 2021).

The clinical outcome and survival of MM has been dramatically improved over the last decade with the wide use of proteasome inhibitors (PIs; eg, bortezomib, carfilzomib) and immunomodulatory imide drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide) as standard of care (Brenner et al., 2009; Kumar et al., 2008; Thumallapally et al., 2016). However, the majority of MM patients will relapse after the initial treatment. Over the course of disease, after each line of therapy, the disease becomes more aggressive and the duration of remission becomes progressively shorter. The median overall survival in MM patients who were PI- and IMiD-refractory was only 8 months (Usmani et al., 2016).

Daratumumab is a first-in-class anti-cluster of differentiation (CD)38 antibody approved for RRMM, which has shown an encouraging response rate in RRMM both as a single agent or in combinations with a PI and/or an IMiD (Chari et al., 2017; Dimopoulos et al., 2018; Lonial et al., 2016; Moreau et al., 2019; Spencer et al., 2018). Another anti-CD38 antibody isatuximab showed similar activities (Attal et al., 2019; Martin et al., 2015; Richter et al., 2016) and was approved for RRMM in combinations with a PI or an IMiD. Although the clinical efficacy of daratumumab is well established, there are about 60% of patients not responding to the treatment, and eventually all patients progress.

In addition to antibody treatment, there are multiple B-cell maturation antigen (BCMA) chimeric antigen receptor T cell (CAR-T) therapies currently in development for MM (Gagelmann et al., 2020). Although anti-tumor activity is very promising, the toxicity of cytokine release syndrome (CRS) can potentially be life-threatening.

In summary, MM remains as an incurable disease after multi-modality therapies. There is a significant unmet medical need for subjects with RRMM who have exhausted standard-of-care or are resistant to prior therapies.

2.1.1.2 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common type of leukemia in adults, accounting for 36% of all leukemias with a median age of 68 years at diagnosis. In the US, the estimated new cases of AML in 2021 is 20,240 with estimated deaths of 11,400. The 5-year survival rate (2011 to 2017) remains low at 29.5% (SEER-AML, 2021).

AML is characterized by accumulation of abnormal myeloid blasts in the bone marrow leading to bone marrow failure and dysfunctional hematopoiesis (Lowenberg et al., 1999). Although the majority of AML patients will achieve a remission after the initial treatment with the conventional chemotherapy (ie, a “7+3” regimen), approximately two-thirds of patients will relapse and require

salvage therapies. If a patient fails to achieve remission (primary refractory) or relapses afterwards, the prognosis is dismal, with a median survival of 6 to 9 months (Heuser et al., 2020).

In recent years, our understanding of genetic and epigenetic signatures of AML has significantly advanced. Multiple targeted therapies including FLT3 inhibitors, IDH1/2 inhibitors, and BCL2 inhibitors have shown encouraging results when combining with cytotoxic or hypomethylating agents (Kayser and Levis, 2018). However, for the vast majority of relapsed or refractory AML (R/R AML) patients, therapeutic options are limited with an unsatisfactory clinical outcome. Allogeneic hematopoietic stem cell transplant (HSCT) remains as the only potential cure for patients with intermediate risk and adverse risk disease. Novel therapies are needed to control the disease progression, induce deep and sustained remission, and potentially bridge patients to transplantation.

2.1.1.3 Diffuse Large B-Cell Lymphoma

DLBCL is the most common aggressive lymphoma representing 30% to 35% of all non-Hodgkin lymphoma (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 disease. It is known that 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 relapsed or refractory DLBCL (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 HSCT and achieve long-term survival (Gisselbrecht et al., 2010; Sehn et al., 2012b). On the contrary, R/R DLBCL patients who do not respond to second-line immunochemotherapy only have a life expectancy of 4 months (Elstrom et al., 2010; Friedberg, 2011; Van Den Neste et al., 2016). Due to advanced age and/or comorbidities only about 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 CAR-T cell therapies (ie, KYMRIAH®, YESCARTA®, BREYANZI ®) have revolutionized the treatment of refractory B-cell lymphoid malignancies and demonstrated durable remissions in R/R large B-cell lymphomas including DLBCL, high grade B-cell lymphoma (HGBCL), and primary mediastinal large B-cell lymphoma (PMBCL), and follicular lymphoma (Abramson et al., 2020; Locke et al., 2019; Schuster et al., 2019). However, potentially life-threatening toxicities including CRS and neurotoxicity, extended production time precluding patients with rapidly progressing disease, and high-treatment expense have limited the access. Additional immunotherapies including ZYNLONTA® (Caimi et al., 2021), MONJUVI® (Duell et al., 2021; Salles et al., 2020), and POLIVY® (Sehn et al., 2020; Sehn et al., 2021) and a targeted agent XPOVIO® (Kalakonda et al., 2020) have demonstrated encouraging activity in R/R DLBCL either as monotherapy or in combinations although these are unlikely to be curative.

Taken together, most R/R DLBCL patients cannot expect to be cured with secondary therapies and a new investigational therapy with manageable toxicities is needed.

2.1.2 Introduction to GEN3014

GEN3014 (also referred to as HexaBody®-CD38 or IgG1-3003-028-E430G) is a human immunoglobulin (Ig)G1κ monoclonal antibody (mAb) that contains the hexamerization-enhancing mutation E430G (HexaBody technology, Genmab) and binds with high affinity to an epitope on human CD38.

HexaBody molecules are regular IgG1 antibodies that have an engineered fragment crystallizable (Fc)-region containing a single mutation, such as E430G, that enhances the formation of ordered hexameric structures upon binding to membrane-expressed antigens through Fc-Fc interactions between monomeric IgG molecules (de Jong et al., 2016). The hexameric antibody structures form the optimal docking site for the hexavalent complement component C1q, which is the first component of the classical pathway of complement activation (Diebolder et al., 2014; Ugurlar et al., 2018). Consequently, introduction of a hexamerization-enhancing mutation has been shown to result in enhanced complement-dependent cytotoxicity (CDC) activity for antibodies against different hematological cancer targets, such as CD20, CD52 and CD38. HexaBody molecules are monomeric in solution, and only upon cell surface antigen binding, antibody hexamerization occurs (de Jong et al., 2016).

HexaBody-CD38 is designed to induce strong anti-tumor activity in CD38-expressing tumors through highly potent CDC and other Fc-mediated effector functions, including antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In addition to these direct anti-tumor activities, by the depletion of CD38-expressing cells (and thereby CD38 enzyme activity) as well as direct inhibition of CD38 cyclase activity, GEN3014 might also cause a relief of immune suppression in the tumor microenvironment and result in potentiation of anti-tumor immune responses.

2.1.3 Summary of Nonclinical Studies

2.1.3.1 GEN3014

A nonclinical pharmacology package demonstrating the potency and mechanism of action (MOA) of GEN3014 in models representing MM, AML and B-cell non-Hodgkin lymphoma (B-NHL) malignancies is available. GEN3014 induced highly potent tumor cell killing in MM patient samples ex vivo and in a panel of MM, AML and B-NHL cell lines through CDC. GEN3014 was considerably more potent than daratumumab in preclinical studies at low target expression levels, while it did not induce significant lysis of normal human leukocytes in vitro. Furthermore, the compound demonstrated potent ADCC and ADCP activity, and induced direct cell killing after Fc-crosslinking of tumor cell lines in vitro. In addition, GEN3014 was found to potently inhibit the CD38 cyclase activity in vitro. In cell-line- and patient-derived models of B-NHL in nude mice, GEN3014 demonstrated promising anti-tumor activity in vivo. It is hypothesized that GEN3014 may relieve immune suppression in the tumor microenvironment by targeting CD38+ immune cells and inhibition of CD38 cyclase activity. Together, these preclinical data support further clinical investigation of GEN3014 in CD38-expressing hematologic malignancies, including MM, AML, and B-cell lymphomas.

A nonclinical safety package to support the phase 1/2 trial with GEN3014 is also available and consists of in vitro species cross-reactivity assessment and in vitro safety studies using human cells and tissues (ie, cytokine release assay, tissue cross-reactivity, hemolytic potential and plasma

compatibility assays). GEN3014 does not cross-react with CD38 of any laboratory animal species and consequently no in vivo animal toxicology studies have been performed.

In a tissue cross-reactivity (TCR) study (study CRL 20178631) with GEN3014 in a panel of normal human tissues using an immunohistochemistry (IHC) technique, staining with FITC-labelled GEN3014 was generally consistent with the reported expression of its target protein, CD38, in various cell types, including mononuclear cells (lymphocytes, macrophages), hematopoietic precursors, various epithelial cells, neurons and glial cells, striated (skeletal) muscle, endothelium, and cardiac interstitial cells. In a comparable TCR study with daratumumab using human tissues (study CRL 260571), a very similar staining pattern was observed.

In an in vitro hemocompatibility study with human whole blood (study CRL 361820), GEN3014 (using daratumumab as reference) in clinically relevant concentrations did not cause hemolysis of the red blood cells and did not precipitate or cause clumping in the plasma.

Three in vitro cytokine release assays (ProImmune 33871_1_v2, ProImmune 333871_2_v2 and ProImmune 34162) were conducted, in which GEN3014 was incubated with human whole blood (in solution or plate-bound, using daratumumab as reference) and cytokines in the plasma (ie, interleukin [IL]-2, IL-4, IL-6, IL-8, IL-10, interferon gamma [IFNγ], and tumor necrosis factor alpha [TNFα]) were measured. For GEN3014, elevated median levels for IL-6 and IFNγ were observed at the 4 highest concentrations, as well as slightly elevated median levels for IL-8. Elevated median levels for IL-6, IL-8 and IFNγ were also observed for daratumumab at the 4 highest concentrations, although to a less extent than GEN3014. A post-hoc analysis of the cytokine responses to GEN3014 and daratumumab suggested a positive correlation between the responses. The results indicate that elevated IL-6, IL-8 and IFNγ responses could potentially occur at higher doses of test article GEN3014.

Refer to the GEN3014 Investigator's Brochure (IB) for additional details on nonclinical studies.

2.1.3.2 Daratumumab

Daratumumab is a targeted immunotherapy that binds with high affinity to tumor cells that overexpress CD38, a transmembrane glycoprotein. Multiple mechanisms of action have been observed for daratumumab including complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, antibody dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor mediated crosslinking of tumor-bound monoclonal antibodies (Overdijk et al., 2016). Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells, CD38+ myeloid-derived suppressor cells, and CD38+ regulatory B cells (Krejcik et al., 2016). The elimination of these immunosuppressive cells and modulation of CD38 enzymatic activity leads to the increased clonal expansion of CD8+ and CD4+ T cells (Chiu et al., 2016). Together, daratumumab's cytotoxic and immunomodulatory mechanisms of action are hypothesized to synergistically result in deep anti-myeloma responses.

Refer to the daratumumab IB for additional details on nonclinical studies.

2.1.4 Summary of Clinical Trials

2.1.4.1 GEN3014

For information related to GEN3014 clinical trials, please refer to the IB.

Preliminary anti-tumor activity has been observed in RRMM subjects with GEN3014 monotherapy.

2.1.4.2 Daratumumab

Daratumumab is a human IgG1κ mAb that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including MM. Daratumumab induces lysis of CD38-expressing tumor cells, including MM tumor cells that were freshly isolated from patients, by a number of mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively.

Daratumumab is available in IV and SC formulations. The SC formulation (daratumumab and hyaluronidase-fihj), referred to as daratumumab SC hereafter, provides an improved administration profile and has demonstrated to be non-inferior to daratumumab IV (Mateos et al., 2020). Both formulations have approvals as monotherapy and in combination with standard backbone regimens in patients with newly diagnosed and RRMM.

Daratumumab administered intravenously (DARZALEX®; daratumumab IV) is well-tolerated with manageable side effects. The most common side effect associated with daratumumab is infusion-related reactions (IRRs) (48%), lymphopenia (72%), neutropenia (60%), thrombocytopenia (48%), and anemia (45%), with most (>90%) of IRRs occurring during the first infusion (DARZALEX, 2021).

The subcutaneous formulation (DARZALEX FASPRO®; daratumumab SC) contains 1800 mg daratumumab (120 mg/mL) and 30,000 U recombinant human hyaluronidase PH20 (rHuPH20; 2000 U/mL) in a single vial. The SC formulation is given as a flat dose. The most common side effect associated with daratumumab SC is systemic administration-related reactions (sARRs) (12.7%), leukopenia (65%), lymphopenia (59%), neutropenia (55%), thrombocytopenia (43%), and anemia (42%) (DARZALEX FASPRO, 2021).

2.2 Trial Rationale

The treatment landscape for RRMM has been dramatically changed with the approval of daratumumab first as monotherapy, followed by combinations with an IMiD or a PI. A second anti-CD38 antibody isatuximab in combination with pomalidomide or carfilzomib and dexamethasone was recently approved for RRMM. Although the clinical outcome in RRMM has been improved with anti-CD38 containing regimens, there are substantial number of patients who either relapse after or are refractory to these treatments. While endeavors are being made to understand the resistance mechanisms, it is an attractive approach to investigate a more potent agent such as GEN3014 which has a higher affinity for CD38, enhanced CDC activity and inhibition of the CD38 cyclase activity that can potentially reverse the immunosuppressive tumor microenvironment.

Preclinically, CD38-targeting GEN3014 has demonstrated more potent tumor cell killing than daratumumab across a wide panel of MM, AML, and DLBCL cell lines. In primary myeloma samples, GEN3014 showed more potent CDC activity in newly diagnosed MM. In addition, therapeutic activity of GEN3014 was observed in AML and DLBCL patient-derived xenografts (PDX) in mice in vivo.

The aim of this phase 1/2 trial is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary anti-tumor activity of GEN3014 in subjects with RRMM and other hematologic malignancies. In the Dose Escalation, dose-liming toxicities (DLTs) will be monitored to determine the recommended phase 2 dose (RP2D), and if reached, the maximum tolerated dose (MTD) for both RRMM and R/R AML. In the Dose Escalation, both anti-CD38 mAb-naive RRMM and anti-CD38 mAb-treated RRMM will be enrolled. It is expected the majority of the subjects with RRMM have received prior daratumumab or daratumumab-containing regimens; and as a consequence, the baseline CD38 expression on daratumumab-exposed myeloma cells may be relatively lower; therefore it is important to recruit anti-CD38 mAb-naive subjects with RRMM who have abundant CD38 expression at the clinically active dose levels (eg, 16 mg/kg, 24 mg/kg) so that the safety and efficacy profile of GEN3014 can be established.

Following the Dose Escalation, in the Expansion Part A (GEN3014 Single Cohorts), the clinical activity of GEN3014 at the RP2D in anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, R/R DLBCL, and R/R AML will be assessed, as well as safety, tolerability, PK, pharmacodynamics, and biomarkers. After an interim analysis of the efficacy and safety data among anti-CD38 mAb-naive subjects with RRMM treated with GEN3014 at 16 mg/kg and 24 mg/kg, the Expansion Part B (Randomized H2H) will be initiated and the clinical activity of GEN3014 at the RP2D will be evaluated in a head-to-head manner as compared to daratumumab subcutaneous (SC) in anti-CD38 mAb-naive RRMM subjects. It is hypothesized that the preclinical observation of stronger complement-mediated tumor cell killing by GEN3014 may be translated into the clinic; specifically, subjects with lower CD38 levels or higher expression of complement inhibitory proteins may benefit from the GEN3014 treatment.

2.3 Benefit-Risk Assessment

Limited clinical data on GEN3014 exist, and the safety profile for GEN3014 is yet to be established. The trial population is limited to subjects with relapsed or refractory hematologic malignancies who have exhausted standard therapies or are ineligible for standard therapies. The risk to subjects in this trial should be minimized by compliance with the eligibility criteria, trial procedures, close monitoring, and proper/prompt management of treatment-emergent adverse events (TEAEs).

CD38 is a valid therapeutic target in MM as demonstrated by daratumumab either as a monotherapy or in combination therapies (Chari et al., 2017; Costa et al., 2019; Dimopoulos et al., 2018; Lonial et al., 2016; Mateos et al., 2018; Moreau et al., 2019; Spencer et al., 2018; Voorhees et al., 2019). GEN3014 (HexaBody-CD38) is a CD38-targeting fully human IgG1 mAb with an E430G hexamerization-enhancing Fc mutation. The proposed MOA of GEN3014 includes enhanced CDC activity and inhibition of the CD38 cyclase activity together with ADCC, ADCP, direct tumor cell kill (after antibody crosslinking) and immunomodulatory activity.

In addition to daratumumab, currently there are several CD38-targeting biologics in clinical development: isatuximab (Attal et al., 2019; Martin et al., 2015; Richter et al., 2016), felzartamab (Raab et al., 2015), and mezagitamab (Krishnan et al., 2019). All of the above mentioned anti-CD38 antibodies have shown single agent activity in RRMM. Major safety findings include IRRs and hematological toxicities (ie, thrombocytopenia, neutropenia, anemia) that are clinically manageable. Collectively, these data warrant clinical development of CD38-targeting compounds for CD38-expressing hematologic malignancies.

GEN3014 does not cross-react with CD38 in any commonly used laboratory animal species, therefore, no animal toxicology study was conducted. A comprehensive package of in vitro pharmacology and toxicology studies have been conducted to assess the safety and efficacy of GEN3014. Major nonclinical findings include:

1. In vitro, GEN3014 has shown superior CDC activity compared to benchmark CD38 antibody daratumumab. GEN3014 induced efficient tumor cell lysis in 23 out of 27 tumor cell lines representing MM, AML and B-NHL cell lines, including lysis in cell lines that were not sensitive to daratumumab. The potency of GEN3014-induced CDC was ~7-fold higher than the potency of daratumumab, and the mean maximal percentage tumor cell lysis was also higher for GEN3014 compared to daratumumab (72 ± 29% vs 44 ± 38%, respectively).
2. Ex vivo, GEN3014 showed enhanced CDC activity compared to daratumumab against MM cells harvested from patients with newly diagnosed MM and daratumumab-naive RRMM.
3. In vivo, the anti-tumor activity of GEN3014 was observed in a Daudi cell line-derived xenograft model, a DLBCL PDX model, and 2 AML PDX models.
4. In the nonclinical in vitro safety studies with GEN3014 the following observations were made:
    - In a tissue cross-reactivity study using a human tissue panel, GEN3014 (similar to daratumumab) generally bound to tissues and cells in consistence with the reported expression of CD38.
    - In a hemocompatibility study with human whole blood, GEN3014 (similar to daratumumab) did not cause hemolysis of the red blood cells, nor clumping or precipitation in the plasma.
    - In cytokine release assays using whole blood from healthy human donors, elevated levels of IL-6, IL-8, and IFNγ were observed at the highest concentrations of GEN3014 used (>0.8 µg/mL). Elevated levels of the same cytokines were also observed for daratumumab although to a less extent. The results indicate that elevated IL-6, IL-8, and IFNγ responses could potentially occur with higher doses of GEN3014.

IRRs have been reported in treatment with anti-CD38 antibodies, mostly in the first treatment cycle, and IRRs are expected with GEN3014 treatment. Pre-infusion medication, post-infusion medication, and management for IRRs and sARRs are provided in Section 6.2 Tumor lysis syndrome (TLS) is a known risk in the treatment of hematologic malignancies and prophylaxis guidelines are provided in Section 6.7.3.1. Scheduled blood collections for immunogenicity are provided in Table 1-3 (Dose Escalation), Table 1-8 (Expansion Part A [GEN3014 Single Cohorts]), Table 1-13 (GEN3014 IV-treated subjects – Expansion Part B), and Table 1-14 (daratumumab SC-treated subjects – Expansion Part B).

In summary, this trial explores GEN3014 in subjects with R/R hematologic malignancies including MM, AML, and DLBCL who have limited treatment options. Based on nonclinical data of GEN3014 and clinical data from other CD38-targeting compounds, GEN3014 has the potential to address the highly unmet medical need in these patient populations. With safety precautions and close monitoring plan in place, the described risks are outweighed by the potential benefit subjects might receive from GEN3014. Preliminary safety and efficacy data from RRMM subjects treated with GEN3014 at doses up to 8 mg/kg support the continuous development of GEN3014.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints for the Dose Escalation, Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H) of the trial are described in Table 3-1, Table 3-2, and Table 3-3, respectively.

Table 3-1 Objectives and Endpoints – Dose Escalation

Objectives	Endpoints
Primary	
• Determine the RP2D and if reached, the MTD of GEN3014	• Incidence of DLTs
• Evaluate the safety and tolerability of GEN3014	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs • Tolerability: Dose interruptions, delay, and dose intensity
Secondary	
• Characterize the PK properties of GEN3014	• Noncompartmental PK parameters (if feasible): ○ C_{max} ○ t_{max} ○ C_{trough} ○ $AUC_{0\text{-}last}$ and $AUC_{0\text{-}168h}$ ○ $R_{A,Cmax}$ and $R_{A,AUC}$ • In addition, a population PK modeling approach may be employed
• Characterize the pharmacodynamic properties of GEN3014	• Pharmacodynamic markers in blood and tumor samples, including frequencies of NK cells and other leukocyte subsets and complement analyses
• Evaluate immunogenicity	• Anti-GEN3014 antibodies
• Assess the preliminary anti-tumor activity of GEN3014	• ORR • CBR • DOR • TTR
• Assess the clinical efficacy of GEN3014	• Progression-free survival (PFS) • Overall survival (OS)
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3014	• Expression of CD38 and other molecular markers on tumor cells at baseline and during treatment
• Assess minimal residual disease (MRD) status	• Rate of MRD-negative remission in RRMM
• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

AE=adverse event; $AUC_{0\text{-}last}$=area under the concentration-time curve from time zero to last quantifiable sample; $AUC_{0\text{-}168h}$=area under the concentration-time curve from time zero to 168 hours; CBR=clinical benefit rate; CD=cluster of differentiation; C_{max}=maximum concentration; C_{trough}=predose concentration; DLT=dose-limiting toxicity; DOR=duration of response; ECG=electrocardiogram; MTD=maximum tolerated dose; NK=natural killer; ORR=objective response rate; PK=pharmacokinetic(s); $R_{A,AUC}$=accumulation ratio in AUC: $R_{A,Cmax}$=accumulation ratio in C_{max}; RP2D=recommended phase 2 dose; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; t_{max}=time to maximum concentration; TTR=time-to-response.

Table 3-2 Objectives and Endpoints – Expansion Part A (GEN3014 Single Cohorts)

Objectives	Endpoints
Primary	
• Assess the preliminary anti-tumor activity of GEN3014	• ORR
Secondary	
• Evaluate anti-tumor activity and efficacy of GEN3014	• CBR • DOR • TTR • PFS • OS
• Evaluate safety of GEN3014	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs • Immunogenicity: Anti-GEN3014 antibodies
• Characterize the PK of GEN3014	• Noncompartmental PK parameters (if feasible): ○ C_{max} ○ t_{max} ○ C_{trough} ○ $AUC_{0\text{-}last}$ and $AUC_{0\text{-}168h}$ ○ $R_{A,Cmax}$, $R_{A,AUC}$, and $R_{A,Ctrough}$ • In addition, a population PK modeling approach may be employed
• Evaluate the pharmacodynamic profiles of GEN3014	• Pharmacodynamic markers in blood and tumor samples, including frequencies of NK cells and other leukocyte subsets, and complement analyses
Exploratory	
• Assess potential biomarkers predictive of clinical response to GEN3014 and evaluate potential surrogacy with PFS and OS	• Baseline CD38 expression • Immune cell profiling • DNA mutation status and gene profile (RNA-seq)
• Assess MRD status	• Rate and duration of MRD-negative remission in RRMM, R/R AML, R/R DLBCL
• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

AE=adverse event; $AUC_{0\text{-}last}$=area under the concentration-time curve from time zero to last quantifiable sample; $AUC_{0\text{-}168h}$=area under the concentration-time curve from time zero to 168 hours; CBR=clinical benefit rate; CD=cluster of differentiation; C_{max}=maximum concentration; C_{trough}=predose concentration; DNA=deoxyribonucleic acid; DOR=duration of response; ECG=electrocardiogram; MRD=minimal residual disease; MTD=maximum tolerated dose; NK=natural killer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s); $R_{A,AUC}$=accumulation ratio in AUC; $R_{A,Cmax}$=accumulation ratio in C_{max}; $R_{A,Ctrough}$=accumulation ratio in C_{trough}; RNA=ribonucleic acid; RP2D=recommended phase 2 dose; R/R AML=relapsed or refractory acute myeloid leukemia; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; RRMM=relapsed or refractory multiple myeloma; OS=overall survival; SAE=serious adverse event; seq=sequencing; t_{max}=time to maximum concentration; TTR=time-to-response.

Table 3-3 Objectives and Endpoints – Expansion Part B (Randomized H2H)

Objectives	Endpoints
Primary	
• Compare overall response of GEN3014 IV vs daratumumab SC in anti-CD38 mAb-naive RRMM subjects	• ORR
Secondary	
• Compare time dependency in PK between GEN3014 IV vs daratumumab SC	• C_{trough} levels of GEN3014 IV, or daratumumab SC, on Cycle 3 Day 1
• Assess the anti-tumor activity of GEN3014 IV vs daratumumab SC	• VGPR or better • CR or better • DOR • TTR • PFS • OS • Time to next therapy (TTNT)
• Assess safety of GEN3014 IV vs daratumumab SC	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs • Immunogenicity: Anti-GEN3014 antibodies, anti-daratumumab antibodies, anti- rHuPH20 antibody
Exploratory	
• Evaluate the pharmacodynamic profiles of GEN3014 and compare with those of daratumumab	• Pharmacodynamic markers in blood and tumor samples, including frequencies of NK cells and other leukocyte subsets, and complement analyses
• Assess potential biomarkers predictive of clinical response to GEN3014 and evaluate potential surrogacy with PFS and OS	• Baseline CD38 expression • Immune cell profiling • DNA mutation status and gene profile (RNA-seq)
• Assess MRD status	• Rate and duration of MRD-negative remission
• Explore PK/pharmacodynamic relationship (PK/anti-tumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

AE=adverse event; CR=complete remission; C_{trough}=predose concentration; DNA=deoxyribonucleic acid; DOR=duration of response; ECG=electrocardiogram; H2H=head-to-head; IV=intravenous(ly); mAb=monoclonal antibody; MRD=minimal residual disease; NK=natural killer; ORR=objective response rate; OS=overall survival; PK=pharmacokinetic(s); PFS=progression-free survival; RNA=ribonucleic acid; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; SC=subcutaneous; seq=sequencing; TTR=time-to-response; VGPR=very good partial response.

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a phase 1/2, open-label, multicenter, multinational trial to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3014 in subjects with RRMM and other hematologic malignancies including R/R AML and R/R DLBCL. The trial will be conducted in 3 parts: Dose Escalation (phase 1), Expansion Part A (GEN3014 Single Cohorts) (phase 2), and Expansion Part B (Randomized H2H) (phase 2). Each part will consist of a Screening period (up to 21 days prior to Cycle 1 Day 1), a Treatment period (Cycle 1 Day 1 until trial drug discontinuation), and a Follow-up period (ie, 30-day safety follow-up from the last dose of trial drug and survival follow-up).

In Dose Escalation, GEN3014 will be evaluated in RRMM and R/R AML using the modified Bayesian Optimal Interval (mBOIN) design. At each dose level (DL), DLTs will be assessed in the first treatment cycle, ie, a DLT evaluation period of 28 days from Cycle 1 Day 1.

The RRMM Cohort will be opened first. Preliminary data from the RRMM Cohort at DLs up to 16 mg/kg including PK, pharmacodynamic, receptor occupancy, and safety will be analyzed. After the DL of 16 mg/kg has been cleared for the RRMM Cohort, the R/R AML Cohort may be initiated. Predictive PK-pharmacodynamic modeling for R/R AML, together with the preliminary data of GEN3014 in RRMM, will be used to further guide modification of the proposed starting dose for the R/R AML Cohort. For both RRMM and R/R AML, population PK modeling may be explored to facilitate selection of the optimal dosing and dosing schedule. The RP2D and MTD (if reached) for the 2 disease indications will be determined based on the observed toxicity with each.

In Expansion Part A (GEN3014 Single Cohorts), GEN3014 will be further evaluated in 4 cohorts: anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, R/R DLBCL, and R/R AML at the RP2D identified from the Dose Escalation. The clinical activity of GEN3014 will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers. Specifically, for the anti-CD38 mAb-naive cohort, daratumumab-naive subjects who received GEN3014 at the 16 mg/kg or 24 mg/kg dose during the Dose Escalation phase of the trial will be counted toward the 10-subject lead-in analysis prior to starting the H2H arm.

In Expansion Part B (Randomized H2H), GEN3014 IV will be compared to daratumumab SC to evaluate whether GEN3014 IV may be more potent in anti-CD38 mAb-naive RRMM subjects. A total of 80 subjects will be randomized in a 1:1 ratio to receive either GEN3014 IV at the RP2D or daratumumab SC at 1800 mg. Subjects will be stratified by body weight (≤70 kg and >70 kg) and number of prior lines of therapy (≤4 prior lines and >4 prior lines).

In treatment Cycle 1, all subjects are required to remain at the clinic for monitoring after the GEN3014 administration as described in Section 4.1.1.2 (Dose Escalation) and Section 6.1.6.2 (Expansion Part A and Expansion Part B).

GEN3014 will be administered as an IV infusion and daratumumab will be administered as an SC injection in 4-week (ie, 28-day) cycles as follows: every week (Q1W) in Cycles 1 and 2, every 2 weeks (Q2W) in Cycles 3 through 6, and every 4 weeks (Q4W) from Cycle 7 until disease progression, unacceptable toxicity, or withdrawal of consent. Additional dosing and dosing schedules may be explored during the Dose Escalation based on emerging data (see Section 6, Trial Treatment).

Assessments will be performed as detailed in the Schedule of Activities, Section 1.3.

Treatment for a subject should continue until the subject fulfills 1 of the treatment discontinuation criteria (refer to Section 7.1).

During the Dose Escalation, a Dose Escalation Committee (DEC) will assess the available data (including safety) according to DEC Charter and make recommendations on the next DL and/or propose the RP2D/MTD to the Safety Committee. A Data Monitoring Committee (DMC) will assess the totality of safety information of the trial and identify additional safety signals according to a DMC charter. Refer to the Committees Structure in Appendix 10.1.7, Committees Structure for details.

A diagram of the trial design is provided in Section 1.2, Figure 1-1.

4.1.1 Dose Escalation

In the Dose Escalation of GEN3014, there are 2 disease cohorts:

- RRMM Cohort: (See Sections 5.1.1 and 5.2.1 for Inclusion and Exclusion criteria.) GEN3014 will be tested in RRMM subjects at 6 DLs. In addition to subjects whose prior lines of therapy included an anti-CD38 mAb (ie, daratumumab, isatuximab), anti-CD38 mAb-naive subjects with RRMM are allowed to be enrolled.
- R/R AML Cohort: (See Sections 5.1.1 and 5.2.1 for Inclusion and Exclusion criteria.) GEN3014 will be tested in R/R AML at 3 DLs. The R/R AML Cohort will be initiated after the trial has cleared the DL of 16 mg/kg in the RRMM Cohort with preliminary data on safety, PK, and pharmacodynamics in subjects with RRMM who have been treated with GEN3014 at DLs up to 16 mg/kg (see Section 4.3.1.2). Based on emerging data in subjects with R/R AML treated with GEN3014, DLs for R/R AML including intermediate doses may be adjusted accordingly during the course of the trial.

Rationales for the starting dose and dosing regimen for each disease indication are provided in Section 4.3.1.

Safety assessments will be performed as indicated in Table 1-1 (subjects with RRMM) and Table 1-2 (subjects with R/R AML).

At each DL, DLTs will be assessed in the first treatment cycle, ie, a DLT evaluation period of 28 days from Cycle 1 Day 1. The RP2D and MTD (if reached) for RRMM and R/R AML will be determined.

For all subjects, in Cycle 1 the first dose of GEN3014 will be split into 2 doses and administered on 2 consecutive days, ie, Cycle 1 Day 1 and Cycle 1 Day 2. All doses will be administered based on the subject's current weight.

Subjects with RRMM

Subjects with RRMM will be enrolled at the trial initiation and dosed according to the schedule shown in Table 4-1.

Table 4-1 GEN3014 Dose Administration – Subjects with RRMM (Dose Escalation)

Subjects with MM	Minimum Number of Subjects	Dose Level	Dose Administered in Cycle 1	Dose Administered Each Dosing Day, Cycle 2 and Beyond
MM-DL1	1	0.2 to 0.6 mg/kg (intrasubject dose escalation)	Days 1 and 2: 0.1 mg/kg/day	0.6 mg/kg
			Days 8 and 9: 0.3 mg/kg/day	
			Day 15: 0.6 mg/kg	
			Day 22: 0.6 mg/kg	
MM-DL2	1	2 mg/kg	Days 1 and 2: 1 mg/kg/day	2 mg/kg
			Day 8: 2 mg/kg	
			Day 15: 2 mg/kg	
			Day 22: 2 mg/kg	
MM-DL3	3	4 mg/kg	Days 1 and 2: 2 mg/kg/day	4 mg/kg
			Day 8: 4 mg/kg	
			Day 15: 4 mg/kg	
			Day 22: 4 mg/kg	
MM-DL4	3	8 mg/kg	Days 1 and 2: 4 mg/kg/day	8 mg/kg
			Day 8: 8 mg/kg	
			Day 15: 8 mg/kg	
			Day 22: 8 mg/kg	
MM-DL5	3	16 mg/kg	Days 1 and 2: 8 mg/kg/day	16 mg/kg
			Day 8: 16 mg/kg	
			Day 15: 16 mg/kg	
			Day 22: 16 mg/kg	
MM-DL 6	3	24 mg/kg	Days 1 and 2: 12 mg/kg/day	24 mg/kg
			Day 8: 24 mg/kg	
			Day 15: 24 mg/kg	
			Day 22: 24 mg/kg	

Note: For MM-DL1, split doses are administered on Days 1-2 and Days 8-9 of Cycle 1; full doses are administered on subsequent dosing days. For all other MM-DL cohorts, split doses are administered only on Days 1-2 of Cycle 1; full doses are administered on subsequent dosing days.
Additional DL such as 20 mg/kg or modified dosing schedule(s) may also be explored based upon emerging data.
DL=dose level; RRMM=relapsed or refractory multiple myeloma; MM=multiple myeloma.

For the intrasubject dose escalations at MM-DL1 during Cycle 1 (DLT period; see Section 4.3.1), in order to be escalated to a higher dose, the subject must have tolerated the lower dose and must not have experienced any GEN3014-related toxicity of CTCAE grade ≥2 excluding grade 2 IRR at the lower dose originally assigned.

In the RRMM Cohort, the initial 2 MM-DLs will enroll 1 subject each (ie, accelerated titration). The trigger point to expand a 1-subject DL into a 3-subject DL (eg, adding 2 subjects to a single-subject cohort) is the observation of any of the following events during the first 28 days of treatment (ie, Cycle 1):

- Any hematologic toxicity ≥ grade 2.
- Any non-hematologic toxicity but not classified as an IRR ≥ grade 2.
- Any IRR ≥ grade 3.
- A DLT (see Section 6.6.1) is observed at any time within the first 28 days (Cycle 1).

AEs of specified grades, regardless of relationship to GEN3014, should be considered relevant for transitioning from single subject into the standard 3 subjects at the initial 2 DLs (single-subject DLs), unless the event can clearly be determined to be unrelated to the drug. All of the AEs of specified grades should be classified as DLTs except those that are clearly and incontrovertibly due to the underlying disease or extraneous causes.

If not earlier, when initiating MM-DL3, the sample size will default to 3.

If any single-subject MM-DL is expanded to a total of 3 subjects (based on a trigger point above being reached), all subsequent MM-DL(s) will have 3 subjects. When all subjects at the first 3-subject DL have completed the DLT period, the mBOIN algorithm (see Section 4.1.2) will suggest the next DL.

If expanding from a single-subject to 3 subjects on MM-DL1, where intrasubject dose escalation is applied during Cycle 1, the same intrasubject dose escalation is applied to the additional subjects. The same principle applies if MM-DL1 would be revisited at a later stage (eg, if de-escalation from MM-DL2 to MM-DL1 would be recommended; see Section 4.1.2 for further details on escalation rules).

Additional DLs, including an intermediate dose(s) (eg, 20 mg/kg) or modified dosing schedule(s) may also be explored based upon emerging data.

Subjects with R/R AML

The R/R AML Cohort will be initiated after the trial has cleared the DL of 16 mg/kg in the RRMM Cohort with preliminary data on safety, PK, and pharmacodynamics in RRMM subjects who have been treated with GEN3014 at DLs up to 16 mg/kg (see Section 4.3.1.2). See Table 4-2 for further details on dosing schedule.

Table 4-2 GEN3014 Dose Administration – Subjects with R/R AML (Dose Escalation)

Subjects with AML	Minimum Number of Subjects	Dose Level	Dose Administered in Cycle 1	Dose Administered Each Dosing Day, Cycle 2 and Beyond
AML-DL1	3	4 mg/kg	Days 1 and 2: 2 mg/kg/day	4 mg/kg
			Day 8: 4 mg/kg	
			Day 15: 4 mg/kg	
			Day 22: 4 mg/kg	
AML-DL2	3	8 mg/kg	Days 1 and 2: 4 mg/kg/day	8 mg/kg
			Day 8: 8 mg/kg	
			Day 15:8 mg/kg	
			Day 22: 8 mg/kg	
AML-DL3	3	16 mg/kg	Days 1 and 2: 8 mg/kg/day	16 mg/kg
			Day 8: 16 mg/kg	
			Day 15: 16 mg/kg	
			Day 22: 16 mg/kg	

Note: For AML-DL cohorts, split doses are administered on Days 1-2 of Cycle 1; full doses are administered on subsequent dosing days.
Additional DLs or modified dosing schedule(s) may also be explored based upon emerging data.
AML=acute myeloid leukemia; DL=dose level; R/R AML=relapsed or refractory acute myeloid leukemia.

In the R/R AML Cohort, in the Dose Escalation, the default DL size will be 3 subjects, from the start. Based on emerging data in subjects with AML treated with GEN3014, DLs for AML including intermediate doses will be adjusted accordingly during the course of the trial.

All DL Cohorts (RRMM and R/R AML)

After all subjects within a DL have completed the DLT evaluation period, the DEC will evaluate all available data (including but not limited to safety, PK, pharmacodynamic, and immunogenicity data) and propose initiation of the next DL. The Safety Committee will have to endorse the proposal before the next DL can start enrolling subjects. To supplement the routine safety monitoring by the Safety Committee 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. Additional details regarding the DEC, Safety Committee, and the DMC can be found in Appendix 10.1.7.

The timeframe for administering the first dose to subjects at a specific DL 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 enrolled in the investigated, non-cleared DL should receive the first dose at least 1 day apart.
- For a DL cleared for safety as recommended by the DEC/Safety Committee, there is no specific time frame for receiving the first dose among subjects (ie, additional subjects may be treated in parallel at the respective DL that are considered safe).

4.1.1.1 GEN3014 Administration Schedule for Dose Escalation

GEN3014 will be administered as an IV infusion in cycles of 4 weeks, ie, 28 days, as follows:

- Cycle 1: Days 1, 2, 8, 15, and 22 (Q1W) – see Table 4-1 and Table 4-2. Note that for RRMM, MM-DL1 will also have dosing on Day 9.
- Cycle 2: Days 1, 8, 15, and 22 (Q1W)
- Cycle 3-6: Days 1 and 15 (Q2W)
- Cycle 7 and beyond: Day 1 (Q4W)
- Each infusion is estimated to last between 1 and 8 hours. Please refer to the investigational medicinal product (IMP) manual for GEN3014 infusion guidelines.

Pre-infusion medication (corticosteroids, antipyretics, antihistamines, a leukotriene receptor antagonist) and post-infusion medication (corticosteroids) will be given as described in Section 6.2 to reduce the risk of IRRs.

Note: Additional dosing schedules may be explored based on emerging data.

4.1.1.2 Post-infusion Monitoring After GEN3014 Administration

During treatment Cycle 1 in the Dose Escalation, subjects in the first 2 dose levels (MM-DL1 and MM-DL2) are required to remain in the clinic for at least 8 hours after each GEN3014 infusion so that they can be observed closely. During treatment Cycle 1, all other subjects are required to remain in the clinic after each GEN3014 infusion for at least 4 hours where they will be observed closely. Beyond observation for AEs, vital signs will be measured and blood sampling for laboratory parameters, cytokines, PK and pharmacodynamic measurements will be performed.

If clinically indicated, observation of up to 24 hours postdose during Cycle 1 is acceptable at the discretion of the investigator.

If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion. If a subject is hospitalized for prolonged monitoring post-infusion, the hospitalization should not be reported as serious adverse events (SAEs).

4.1.2 Escalation Model

An mBOIN design will be utilized to make optimal recommendations at end of each observed cohort (Liu and Yuan, 2015). The target DLT rate is set to $\phi = 30\%$ with the assumptions that $\phi_1 = 0.6\phi$ is the highest sub-therapeutic DLT rate and $\phi_2 = 1.4\phi$ is the lowest DLT rate that has excessive toxicity. Under these assumptions, the observed DLT rates that rule if the next DL should be an escalation or de-escalation from the current DL are 24% and 36%, respectively (Liu and Yuan, 2015).

The DLT rate for a DL is estimated as total number of DLTs/total number of subjects treated (at that level). Based on the accrued data (on each DL) the mBOIN decision rules are supplied in Table 4-3. Section 9.2.1 presents simulations of the number of dosed subjects under different DLT rates.

Table 4-3 Modified BOIN Decision Rules

	Total Number of Subjects Treated at a Dose Level	2	3	4	5	6	7	8	9
Decision Based on Total Number of DLTs at the Dose Level	Escalate	0	0	0	≤1	≤1	≤1	≤1	≤2
	Remain	-	1	1	-	2	2	2	3
	De-escalate	1	2	2	2	3	3	3	4
	Terminate a dose level	≥2	3	≥3	≥3	≥4	≥4	≥4	≥5

4.1.2.1 Stopping Rules

The modified BOIN algorithm has the following stopping rules:

i. The escalation in MM stops if there are 9 subjects already dosed on the next DL

ii. The escalation in AML stops if there are 6 subjects already dosed on the next DL

These rules, and the planned number of DLs (6 and 3 for MM and AML, respectively), can be translated into an overall stopping rule for the mBOIN escalation that limits the number of subjects:

iii. Escalation in MM stops if 54 subjects have already been dosed.

iv. Escalation in AML stops if 18 subjects have already been dosed.

Further details on expected sample sizes are provided in Section 9.2.1.

At any time point in advance of this, the DEC and Safety Committee may conclude (given the totality of the accumulated data so far) on a RP2D for the expansion cohorts.

4.1.2.2 Dose Level Termination

A potential drawback of the basic BOIN design is that, theoretically, a very toxic DL could be investigated in multiple DLs, if a neighboring DL is not toxic. To avoid this problem, a DL termination criterion is implemented as a modification to the basic BOIN: A certain DL can no longer be investigated if an additional DLT-free cohort would lead to de-escalation. All higher DLs should also be terminated.

4.1.2.3 Dose Escalation Cohort Size

In the standard titration with 3 subjects per cohort, a recommendation based on Table 4-3 may be made in the following scenario: if 1 out of the 3 initial subjects on a new DL is non-DLT evaluable and the remaining 2 are DLT-evaluable; provided that neither of the 2 subjects experienced any grade ≥2 non-hematologic toxicity excluding grade ≤2 IRRs, nor any DLT during the 28-day DLT period. (See Section 9.3 for a definition of DLT-evaluable.) In this example the BOIN would recommend an escalation. (It is not necessary to replace the non-DLT evaluable subject to proceed with the escalation.)

Also, over-recruitment by 1 subject is allowed, so that each 3-subject cohort may consist of 2 to 4 subjects who are evaluable for DLT.

In case a cohort had less than 3 DLT evaluable subjects, the next cohort on the same DL may be enlarged to bring the number of subjects on the DL up to a multiple of 3.

4.1.2.4 Parallel DL(s) for Clinical Confirmation

To better understand the safety, tolerability, PK, pharmacodynamics or anti-tumor activity, up to 7 additional subjects may be allocated in parallel to DLs that are considered safe for such allocation (DLs at or below the currently-investigated one).

Any DLTs observed in such subjects will not directly contribute to the mBOIN design evaluation. However, if the mBOIN algorithm later stipulates de-escalation to an over-recruited DL, all subjects on that dose will be included in the mBOIN algorithm.

4.1.2.5 Determination of RP2D and MTD

The principal objective of mBOIN is to optimize the move (de-escalate, remain, escalate), such that the (estimated) toxicity of the next DL is within the target toxicity range $[\phi_1, \phi_2]$. As data accumulate (towards the end of the dose escalation), the MTD, if reached, may be that next DL (no subjects are dosed at the next DL at this point).

The RP2D to be used for the Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H) will be determined at the end of the Dose Escalation part by the DEC and Safety Committee, based on a review of the totality of data, including but not limited to safety (including DLTs, AEs, safety laboratory values, and observations made after the end of the DLT evaluation period), efficacy, PK and biomarker data, and dosing information. The RP2D may be the MTD (if reached) or a lower dose. The DEC and Safety Committee will strive towards alignment of the RP2D in the indications.

4.1.3 Expansion Part A (GEN3014 Single Cohorts)

In the Expansion Part A (GEN3014 Single Cohorts), there are 4 disease cohorts.

- Three cohorts of subjects will be treated with GEN3014 at the RP2D identified for RRMM from the Dose Escalation:

  - Anti-CD38 mAb-naive RRMM (N=10 subjects). Data from the initial 10 response-evaluable subjects (defined in Section 9.3), inclusive of those anti-CD38 mAb-naive subjects with RRMM who received GEN3014 at 16 mg/kg or 24 mg/kg from the Dose Escalation and/or from the Expansion Part A, will be reviewed by the Safety Committee and DMC when they have completed ≥2 cycles of treatment. If 2 or more (out of the initial 10) subjects respond to GEN3014, an H2H comparison to daratumumab SC will be initiated; see Sections 4.1.4 and 9.5.1. (Assessment of disease response will be conducted by the investigator in accordance with the IMWG 2016 Response Criteria.) The lead-in part may consist of more than 10 subjects to ensure exposure to at least 2 cycles of GEN3014 treatment.

  - Anti-CD38 mAb-refractory RRMM (N=20 subjects).

  - R/R DLBCL (N=up to 40 subjects). This cohort will include at least 15 R/R DLBCL subjects with >50% CD38 expression. When the initial 20 response evaluable subjects have completed ≥2 cycles of GEN3014 treatment, an interim futility analysis will be conducted; see Section 9.5.2. Based upon the response at the interim futility analysis, an additional 20 subjects may be enrolled into this cohort for a total of 40 subjects.

  See Sections 5.1.2 and 5.2.1 for inclusion and exclusion criteria.

- A fourth cohort of subjects with R/R AML (N=20 subjects) will be treated with GEN3014 at the RP2D identified for AML from the Dose Escalation. See Sections 5.1.2 and 5.2.1 for inclusion and exclusion criteria.

The administration schedule in Expansion Part A will be the same as in Dose Escalation (see Section 6.1.6.1).

4.1.4 Expansion Part B (Randomized H2H)

If the preliminary efficacy and safety are judged to be favorable in the initial 10 anti-CD38 mAb-naive subjects with RRMM who received 16 mg/kg or 24 mg/kg (in the Dose Escalation or Expansion Part A), an additional 80 anti-CD38 mAb-naive subjects with RRMM will be randomized in a 1:1 ratio to receive:

- GEN3014 IV at the RP2D (N=40), or
- Daratumumab SC at the approved dose of 1800 mg (N=40)

The administration schedule will be the same as in the Dose Escalation (see Section 6.1), except that the first dose of daratumumab SC will not be split between Days 1 and 2.

Randomization will be stratified by body weight at baseline (≤70 kg vs >70 kg), and number of prior lines of therapy (≤4 prior lines vs >4 prior lines). See Sections 5.1.3 and 5.2.2 for inclusion and exclusion criteria.

4.2 Trial Design Rationale

This trial is being conducted in 3 parts. The Dose Escalation is being conducted to identify the RP2D and the MTD (if reached), and to evaluate safety, and obtain preliminary efficacy of GEN3014 in subjects with RRMM and R/R AML. The Expansion Part A (GEN3014 Single Cohorts) is being conducted to evaluate clinical activity of GEN3014 together with safety, tolerability, PK, pharmacodynamics, and biomarkers. The Expansion Part B (Randomized H2H) is being conducted to evaluate the efficacy of GEN3014 as compared to daratumumab SC. Since GEN3014 carries the E430G mutation and binds a different epitope than daratumumab, it may result in therapeutic potential in daratumumab-naive and daratumumab-refractory MM patients.

To this end, the sponsor will conduct a Dose Escalation followed by Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H). These data will be used to inform future clinical development of GEN3014 in hematologic indications.

Escalation and de-escalation in the Dose Escalation will be guided by the mBOIN approach.

To collect further data on the safety, tolerability, PK and anti-tumor activity, the selected RP2D from the Dose Escalation will be studied in Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H). The Expansion Part A (GEN3014 Single Cohorts) will include 4 cohorts (ie, RRMM-anti-CD38 mAb-naive, RRMM-anti-CD38 mAb-refractory, R/R DLBCL, and R/R AML) and Expansion Part B (Randomized H2H) will evaluate GEN3014 IV in comparison to daratumumab SC in RRMM. All data will inform further investigation.

4.2.1 Rationale For Not Preselecting Subjects With DLBCL Based on Level of CD38 Expression in Dose Expansion Part A (GEN3014 Single Cohorts)

CD38 is expressed in the majority of DLBCL patients with heterogeneous levels. From preclinical studies, it is known that especially the level of CD38 expression per tumor cell is a very important determinant for sensitivity of that tumor cell to HexaBody-CD38-induced tumor cell lysis. It is also important to note that the Salles study (Salles et al., 2019) referenced in Section 4.3.2 had a cutoff of >50% of tumor cells positive for CD38, whereas the biology of CDC and hexamerization indicates that density of the antigen is more important than the quantity of CD38-positive cells.

The minimum CD38 expression level required for HexaBody-CD38 to be effective in DLBCL patients is not yet known. This trial is intended to evaluate if HexaBody-CD38 may be effective in broader DLBCL population due to increased potency compared to other CD38 mAbs. Thus, the current trial will be enrolling patients with R/R DLBCL irrespective of their CD38 expression level.

At this early stage of understanding the clinical activity of HexaBody-CD38 in DLBCL, the protocol therefore requires prospective collection of DLBCL tumor tissues and retrospective testing of CD38 expression. CD38 expression will be assessed using a well characterized CD38 IHC assay. A potential decision to selectively enroll patients with DLBCL with a certain level of CD38 expression in future HexaBody-CD38 clinical trials will be based on results from this trial.

4.3 Dose and Schedule Rationale

4.3.1 Dose Escalation

4.3.1.1 Dose Escalation for RRMM

The starting dose for the phase 1/2 clinical trial GCT3014-01 was based on an integrated evaluation of nonclinical pharmacology, PK and safety data, including a comparison against daratumumab as a benchmark (see GEN3014 IB for additional details).

GEN3014 binds to the same target as daratumumab and was shown to elicit the same effector mechanisms: CDC, ADCC, ADCP, direct cell death through Fc crosslinking and inhibition of CD38 cyclase activity. Antibody therapeutics displaying 1 or more of these effector mechanisms, including rituximab, obinutuzumab, daratumumab, and isatuximab, are generally administered at high DLs without major safety concerns (Lokhorst et al., 2015; Maloney et al., 1994; Martin et al., 2019; Sehn et al., 2012a). In the phase 1 clinical trial in MM, daratumumab started to show signs of efficacy at 4 mg/kg (Lokhorst et al., 2015) while the optimal therapeutic dose was found to be 16 mg/kg (Lokhorst et al., 2015; Xu et al., 2017), at an estimated average receptor occupancy of 90% and 98%, respectively (Genmab data on file, LAP&P report 19022). No MTD was established with the dose ranging up to 24 mg/kg. Since its approval for RRMM in 2015 (US) and 2016 (EU), the main adversities associated with daratumumab at the therapeutic dose including sARRs and cytopenias have been well managed in the clinical setting. Given the similarity in effector mechanisms, GEN3014 is not expected to be associated with safety liabilities beyond those established for daratumumab.

Effective concentrations of GEN3014 were similar to daratumumab for the FcγR-mediated effector functions ADCC, ADCP, and direct cell killing through Fc crosslinking (see GEN3014 IB). GEN3014 showed higher cyclase inhibition than daratumumab, while both compounds showed a comparable effect on hydrolase activity (see GEN3014 IB). Reduction in CD38 enzyme activity is not considered to pose a specific risk, as anti-CD38 antibody treatment intrinsically leads to a loss of CD38 in the tumor microenvironment. This was not associated with major adversities for daratumumab nor for isatuximab (Martin et al., 2019), which showed considerably stronger inhibition of both cyclase and hydrolase activity (see GEN3014 IB).

GEN3014 was designed to induce highly potent CDC in CD38-expressing tumor cells. GEN3014 induced dose-dependent CDC in 23 out of 27 tumor cell lines of MM, AML and B-NHL origin, with an EC_{50} that was a factor of 7 higher compared to daratumumab (see GEN3014 IB). A high degree of similarity was observed in concentration-response between cell lines and MM patient primary cells (see GEN3014 IB). The EC_{50} value depended on cell surface density of CD38,

with higher concentrations required for effective CDC in cell lines with lower CD38 expression. The maximum cell lysis was also highly correlated with CD38 expression. GEN3014 and daratumumab showed similarly low activity in cell lines with low CD38 density and near-complete lysis in cells with high CD38, while at intermediate CD38 density GEN3014 outperformed daratumumab. In line with these findings, GEN3014 did not induce specific lysis of non-malignant cells expressing low levels of CD38 including leukocytes and erythrocytes from 4 out of 5 healthy donors, while some lysis of monocytes, T cells, and NK cells was observed in the fifth donor. The slight reduction in NK cells that was observed was comparable between GEN3014 and daratumumab (see GEN3014 IB). Thus, GEN3014 showed improved CDC activity in malignant cells compared to daratumumab while the activity in healthy cell populations with lower CD38 density remained largely unchanged. In the context of phase 1/2 starting dose setting, enhanced CDC was the only critical difference between GEN3014 and daratumumab identified across the range of in vitro and ex vivo pharmacology and safety studies.

Given the mild safety profile and manageable adversities associated with daratumumab up to high DLs, CDC in itself is not considered a major liability. Yet, the enhanced potency of GEN3014 to induce CDC warrants some level of precaution. Therefore, the starting dose for GCT3014-01 was defined as the dose giving rise to 1-week average plasma exposure equal to the EC_{50} for CDC in MM cell lines. The observed EC_{50} was divided by a factor 1.5 to account for the higher potency of the pilot batch P3759152 (that is representative of the current GMP manufacturing process) to induce CDC (see GEN3014 IB). The associated dose was derived by a PK model for GEN3014 that was scaled from a published population PK model for daratumumab (Xu et al., 2017) as described in the IB.

The relative contribution of the various effector mechanisms to the overall efficacy of GEN3014 is currently unknown. It is therefore unclear how the superior CDC will influence the relationship between dose and efficacy relative to daratumumab. Given that antibody therapeutics with the same mechanisms are generally administered at high DLs without major safety concerns, the escalation in MM after the first cohort will cover the same steps as shown in the daratumumab phase 1 trial GEN501.

The PK of GEN3014 is anticipated to be time dependent. The lysis of malignant cells over the course of treatment is expected to reduce the impact of target-mediated clearance, so that sufficient target saturation can be maintained with decreasing dosing frequency. Whether the superior CDC translates to a faster depletion of tumor cells compared to daratumumab is currently unknown. Therefore, a regimen is used similar to that for daratumumab monotherapy: weekly for two 28-day cycles (QW×8), biweekly for four 28-day cycles (Q2W×8), then monthly (Q4W). Intrasubject dose escalation applies to the MM-DL1 (ie, a lower starting dose escalating to a higher dose in 1 subject). The first dose at each DL will be split equally between 2 consecutive days to accommodate long infusion durations and to control anticipated infusion reactions (ie, 50%/50% on D1/D2 and on D8/D9 for cohort MM-DL1; 50%/50% on D1/D2 for cohort MM-DL2 and beyond).

4.3.1.2 Dose Escalation for R/R AML

In the Dose Escalation, the R/R AML Cohort will be initiated after the DL of 16 mg/kg in the RRMM Cohort has been cleared by the Safety Committee. Preliminary safety, PK, and pharmacodynamic data of GEN3014 at DLs up to 16 mg/kg in RRMM subjects will be reviewed, supported by PK/pharmacodynamic modeling and exposure-safety analyses. The rationale to treat AML with a higher starting dose is based on the following:

(1) R/R AML is an aggressive disease, progressing fast with a narrow treatment window;

(2) The preliminary safety profile of GEN3014 in RRMM subjects will guide implementing additional safety measures in subjects with R/R AML as needed; and

(3) To avoid the sub-therapeutic dose for R/R AML where there is no or minimal receptor occupancy, it is more meaningful to test GEN3014 at a higher starting dose to quickly reduce the tumor burden and efficiently control the disease without compromising the safety of trial subjects.

CD38 expression in AML may be lower than MM. The cell surface density of CD38 in vitro was shown to correlate with potency of GEN3014 to induce CDC. Tumor burden is typically higher in AML, so that the total amount of CD38 present may be larger compared to MM. Therefore, equivalent DLs in AML both in terms of plasma concentrations and target occupancy may be at least as high as in MM.

Three DLs for AML are planned, starting at 4 mg/kg after the DL of 16 mg/kg in the RRMM Cohort has been cleared, and escalating to 8 and 16 mg/kg. The potential differences in dosimetry between RRMM and R/R AML will be studied further by PK/pharmacodynamic modeling, making use of emerging data from the RRMM subjects, and further quantification of CD38 expression in primary AML blasts. DLs and the dosing schedule for the R/R AML Cohorts may be adjusted based on these PK/pharmacodynamic analyses in conjunction with safety observations in both RRMM and R/R AML subjects.

4.3.2 Expansion Part A (GEN3014 Single Cohorts)

The GEN3014 dose for Expansion Part A (GEN3014 Single Cohorts) subjects with anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, and R/R DLBCL will be the RP2D which is based on assessment of all available data from the Dose Escalation part of this trial. The rationale to use the same RP2D for R/R DLBCL is based on the observation that the PK and safety profiles of daratumumab in B-NHL subjects including DLBCL are similar to MM subjects (Salles et al., 2019). Subjects with R/R AML will be treated with GEN3014 at the RP2D identified for R/R AML from the Dose Escalation. The GEN3014 administration schedule is based upon the primary results of the daratumumab GEN501 and SIRIUS studies, and similar mechanism of action between GEN3014 and daratumumab (Usmani et al., 2020).

4.3.3 Expansion Part B (Randomized H2H)

The GEN3014 dose for Expansion Part B (Randomized H2H) for subjects with anti-CD38 mAb-naive RRMM will be the RP2D from the Dose Escalation part of this study. The GEN3014 administration schedule is based upon the primary results of the daratumumab GEN501 and SIRIUS studies (Usmani et al., 2020). The first administration is split 50%/50% between 2 consecutive days (Cycle 1 Days 1 and 2) to accommodate long infusion durations and to control anticipated IRRs. The daratumumab SC dose will be at the approved dose of 1800 mg. The approved administration schedule for daratumumab SC monotherapy will be used. The schedule is the same as for GEN3014 except for the Cycle 1 Day 1/Day 2 split of the first administration, which is not warranted for SC dosing.

4.4 End of Trial Definition – Dose Escalation, Expansion Part A (GEN3014 Single Cohorts), and Expansion Part B (Randomized H2H)

The end of trial is defined as 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.

5 TRIAL POPULATION

The inclusion and exclusion criteria for enrolling subjects are described in Sections 5.1 and 5.2, respectively. Screening for eligible subjects will be performed during a 21-day period prior to the first dose of GEN3014 (Dose Escalation of GEN3014; Expansion Part A of GEN3014 in anti-CD38 mAb-naive RRMM Cohort, anti-CD38 mAb-refractory RRMM Cohort, R/R DLBCL Cohort, and R/R AML Cohort) or Expansion Part B (Randomized H2H). For the Expansion Part B, the eligibility information will be submitted to the sponsor's medical monitor for review prior to randomization. If the sponsor agrees that the eligibility criteria have been met, then the investigator will receive confirmation that the subject may be randomized into the study. If the sponsor considers that the eligibility criteria have not been met, then the sponsor will contact the investigator to discuss the subject. If there is a question about the inclusion or exclusion criteria, the investigator must consult with the sponsor's medical monitor and resolve any issues before enrolling a subject in the study.

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria – Dose Escalation

Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Dose Escalation part of the trial:

1. Must be at least 18 years of age.
2. Must sign an informed consent form (ICF) prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (deoxyribonucleic acid [DNA] and ribonucleic acid [RNA]).
3. Must have fresh bone marrow samples collected at Screening.
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0, 1, or 2.
5. Criterion modified per Amendment 2.

   5.1 Has acceptable laboratory test results during the Screening period, as follows:

Parameter		Result
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥50 mL/min estimated by Cockcroft-Gault (see Appendix 10.5) or serum creatinine ≤1.5 × upper limit of normal (ULN)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN *Note: A subject with Gilbert's syndrome may be included if total bilirubin is ≤3 × ULN and direct bilirubin is ≤1.5×ULN*
e.	Hemoglobin	≥8 g/dL (≥80 g/L or ≥5 mmol/L) *Note: Red blood cell transfusion may be administered during Screening to meet this requirement*

f.	Absolute neutrophil count	$>1.0 \times 10^9$/L (>1,000/μL) *Note: G-CSF may be administered during Screening to meet this requirement*
g.	Platelet count	$>50 \times 10^9$/L (>50,000/μL) *Note: Platelet transfusion may be administered during Screening to meet this requirement*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

6. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 10.4 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
7. A woman of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) at Screening
8. 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 GEN3014.
9. 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014.

Specific Inclusion Criteria for RRMM:

10. Criterion modified per Amendment 1.

    a. 10.1 Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

    - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

    and

    - Measurable disease at baseline as defined by any of the following:
        - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

        Or

        - Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

Note: Subjects with RRMM must have exhausted standard therapies, at the investigator's discretion.

11. Criterion modified per Amendment 2.

    11.1 Criterion modified per Amendment 1.

    11.2 Criterion modified per Amendment 1_SE-1.

    11.3 Criterion modified per Protocol Amendment_FR-1.

    11.4 For anti-CD38 mAb-naive RRMM subjects: Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or is double refractory to a PI and an IMiD; or subject received ≥2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody. Anti-CD38 mAb-naive RRMM subjects may be recruited from Sweden, France, Spain, Netherlands, and Australia, and from countries where anti-CD38 therapies are not available.

12. Criterion modified per Amendment 2.

    12.1 Criterion modified per Protocol Amendment_FR-1.

    12.2 For anti-CD38 mAb-treated RRMM subjects: Subject has received at least 2 prior lines of therapy and must have discontinued daratumumab or isatuximab for at least 4 weeks prior to the first dose of GEN3014. Note: Subjects should not have received any other anti-CD38 antibody except daratumumab or isatuximab.

13. Criterion modified per Amendment 2.

    13.1 Criterion modified per Amendment 3.

    13.2 Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see formula for corrected serum calcium in Appendix 10.7).

Specific Inclusion Criteria for R/R AML:

14. Criterion modified per Amendment 1.

    14.1 Relapsed or refractory AML, both de novo or secondary; must have failed all conventional therapy. Acute promyelocytic leukemia (APL) is excluded from this trial. Note: Relapse is defined by BM blasts ≥5% in patients who have been in complete remission (CR) previously, or reappearance of blasts in the blood, or development of extramedullary AML. Refractory is defined as not being able to achieve a CR after the initial therapy.

15. Subject with relapsed AML who received at least 2 prior therapies for AML with the exception of hydroxyurea.

16. Subject with refractory AML who received at least 1 prior line of therapy for AML with the exception of hydroxyurea.

17. Subject's life expectancy at Screening is judged to be at least 3 months.

5.1.2 Inclusion Criteria – Expansion Part A (GEN3014 Single Cohorts)

Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part A of the trial:

1. Must be at least 18 years of age.
2. Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA).
3. ECOG PS score 0, 1, or 2 for MM and AML; ECOG PS 0 or 1 for DLBCL.
4. Must have fresh bone marrow samples collected at Screening.
5. Criterion modified per Amendment 2.

   5.1 Has acceptable laboratory test results during the Screening period, as follows:

Parameter		Result
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥50 mL/min estimated by Cockcroft-Gault (see Appendix 10.5) or serum creatinine ≤1.5 × upper limit of normal (ULN)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN *Note: A subject with Gilbert's syndrome may be included if total bilirubin is ≤3×ULN and direct bilirubin is ≤1.5 × ULN*
e.	Hemoglobin	≥8 g/dL (≥80 g/L or ≥5 mmol/L) *Note: Red blood cell transfusion may be administered during Screening to meet this requirement*
f.	Absolute neutrophil count	>1.0 × 10^9/L (>1,000/µL) *Note: G-CSF may be administered during Screening to meet this requirement*
g.	Platelet count	>50 × 10^9/L (>50,000/µL) *Note: Platelet transfusion may be administered during Screening to meet this requirement*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

6. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 10.4 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.

7. A woman of childbearing potential must have a negative serum β-hCG at Screening.
8. 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 GEN3014.
9. 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014.

Specific Inclusion Criteria for RRMM:

10. Criterion modified per Amendment 1.

    10.1 Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

    - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

    and

    - Measurable disease at baseline as defined by any of the following:
        - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

        or

        - Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

    Note: Subjects with RRMM must have exhausted standard therapies, at the investigator's discretion.

11. Criterion modified per Amendment 3.

    11.1 For anti-CD38 mAb-naive RRMM Cohort: Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD; or subject received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).

12. Criterion modified per Amendment 2.

    12.1 Criterion modified per Amendment 3.

    12.2 For anti-CD38 mAb-refractory RRMM Cohort: Prior to trial entry, subject received daratumumab or a daratumumab-containing regimen or an isatuximab-containing regimen and had evidence of progressive disease (PD) during the treatment or within 90 days of treatment cessation.

13. Criterion modified per Amendment 2.

    13.1 Criterion modified per Amendment 3.

13.2 Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see formula for corrected serum calcium in Appendix 10.7).

Specific Inclusion Criteria for R/R DLBCL:

14. Criterion modified per Amendment 1.

14.1 Relapsed or refractory DLBCL, both de novo or histologically transformed. Note: Relapsed disease is defined as the reappearance or growth of lymphoma after at least 6 months duration of response (DOR). Refractory disease is defined as failure to achieve response after at least 2 cycles of therapy or reappearance after a DOR of <6 months. Subjects with R/R DLBCL must have exhausted standard therapies, at the investigator's discretion.

15. Received at least 2 prior lines of systemic therapy, with 1 being a CD20-containing chemoimmunotherapy.

16. Have at least 1 measurable site of disease:

- 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

- A CT scan (or 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.

17. Must have available archival or fresh tumor tissue or both to submit to a central laboratory for CD38 assay.

Specific Inclusion Criteria for R/R AML:

18. Criterion modified per Amendment 1.

18.1 Relapsed or refractory AML, both de novo or secondary; must have failed all conventional therapy. Acute promyelocytic leukemia (APL) is excluded from this trial. Note: Relapse is defined by BM blasts ≥5% in patients who have been in complete remission (CR) previously, or reappearance of blasts in the blood, or development of extramedullary AML. Refractory is defined as not being able to achieve a CR after the initial therapy.

19. Subject with relapsed AML who received at least 2 prior therapies for AML with the exception of hydroxyurea.

20. Subject with refractory AML who received at least 1 prior line of therapy for AML with the exception of hydroxyurea.

21. Subject's life expectancy at Screening is judged to be at least 3 months.

5.1.3 Inclusion Criteria – Expansion Part B (Randomized H2H)

Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part B of the trial:

1. Must be at least 18 years of age.
2. Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA).
3. ECOG PS score 0, 1, or 2.
4. Must have fresh bone marrow samples collected at Screening.
5. Has acceptable laboratory test results during the Screening period, as follows:

Parameter		**Result**
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥20 mL/min (Cockcroft-Gault formula [see Appendix 10.5] or EGFR [MDRD] or CKD-epi)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 × ULN)
e.	Hemoglobin	≥7.5 g/dL (≥4.65 mmol/L) *Note: Red blood cell transfusions are not permitted within 7 days before the laboratory test for eligibility review; recombinant human erythropoietin use is permitted*
f.	Absolute neutrophil count	>1.0 × 10^9/L (>1,000/μL) *Note: (Granulocyte colony stimulating factor [G-CSF] use is permitted)*
g.	Platelet count	>50 × 10^9/L (>50,000/μL) if bone marrow is >50% involved in myeloma. Otherwise ≥75 × 10^9/L *Note: Platelet transfusions are not permitted within 7 days before the laboratory test for eligibility review*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

6. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 or daratumumab SC administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 10.4 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
7. A woman of childbearing potential must have a negative serum β-hCG at Screening and within 72 hours of the first dose of study treatment prior to dosing.
8. 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 GEN3014 or daratumumab SC.

9. 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, either condom with spermicidal foam/gel/film/cream/suppository or 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 GEN3014 or daratumumab SC.
10. Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:
    - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

      and

    - Measurable disease at baseline as defined by any of the following:
      - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

      or

      - Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
11. Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD; or subject received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).
12. Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see formula for corrected serum calcium in Appendix 10.7).

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria – Dose Escalation and Expansion Part A (GEN3014 Single Cohorts)

Any potential subject who meets any of the following criteria will be excluded from being treated in the Dose Escalation and/or Expansion Part A (GEN3014 Single Cohorts) of the trial.

1. Criterion modified per Amendment 3.

   1.1 Prior treatment with any CD38-directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) in anti-CD38 mAb-naive RRMM Cohort. Note: Prior daratumumab or isatuximab exposure is allowed for anti-CD38 mAb-treated RRMM subjects in the Dose Escalation and anti-CD38 mAb-refractory RRMM Cohort in the Expansion Part A.
2. Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to the first dose of GEN3014.

   2CZ. Czech Republic: See Appendix 10.15 for requirements as per local health authorities.

3. Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3014.
4. Cumulative dose of corticosteroids more than the equivalent of ≥140 mg of prednisone within 2-week period before the first dose of GEN3014.
5. Criterion modified per Amendment 3

   5.1 Has clinically significant cardiac disease, including:

   - Myocardial infarction within 1 year prior to the first dose of GEN3014, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV [see Appendix 10.6]) uncontrolled cardiac arrhythmia (CTCAE v5.0 grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec.
6. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
7. Primary central nervous system (CNS) tumor or known CNS involvement at Screening.
8. Criterion modified per Amendment 3

   - 8.1 Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig 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).
9. Known medical history or ongoing hepatitis C infection that has not been cured.
10. Known history of seropositivity of human immunodeficiency virus (HIV).
11. Currently receiving any other investigational agents.
12. 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 GEN3014.
13. A man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3014.

Specific Exclusion Criteria for RRMM:

14. Prior allogeneic HSCT.
15. Autologous HSCT within 3 months of the first dose of GEN3014.

Specific Exclusion Criteria for R/R AML:

16. <5% blasts in blood or bone marrow at Screening.
17. Prior autologous HSCT.
18. Allogenic HSCT within 3 months of the first dose of GEN3014.
19. Criterion modified per Amendment 1.

19.1 Active graft-versus-host-disease requiring immunosuppressive treatment. Any immunosuppressive medication (eg, calcineurin inhibitors) must be stopped ≥4 weeks prior to the first dose of GEN3014.

Additional Exclusion Criteria for All Subjects:

20. Criterion modified per Amendment 2.

    20.1 Criterion modified per Amendment 1_DK-1.

    20.2 Criterion modified per Protocol Amendment ES-1.

    20.3 Criterion modified per Protocol Amendment FR-1.

    20.4 History of allergic reactions attributed to compounds of similar active substance or excipients.

21. Criterion added per Amendment 2.

    21.1 Criterion modified per Amendment 3

    21.2 Has known past (within 3 years) 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.

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

23. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the trial procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this trial.

Additional Exclusion Criterion for RRMM:

24. Known allergies, hypersensitivity, or intolerance to mAbs, human proteins, hyaluronidase, or excipients (refer to GEN3014 IB and daratumumab IB).

5.2.2 Exclusion Criteria – Expansion Part B (Randomized H2H)

Any potential subject who meets any of the following criteria will be excluded from being treated in the Expansion Part B (Randomized H2H) of the trial.

1. Prior or concurrent treatment with any CD38-directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) for RRMM.
2. Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to randomization.

2CZ. Czech Republic: See Appendix 10.15 for requirements as per local health authorities.

3. Treatment with an investigational drug (including anti-cancer investigational vaccines) within 4 weeks or 5 half-lives, whichever is longer, prior to the randomization.
4. Radiation therapy for treatment of plasmacytoma within 14 days of randomization (palliative radiation for pain control secondary to lytic lesion is allowed).
5. A maximum cumulative dose of dexamethasone 160 mg within 28 days of randomization.
6. Has clinically significant cardiac disease, including:
   - Myocardial infarction within 6 months before the date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV [see Appendix 10.6]) uncontrolled cardiac arrhythmia (CTCAE v5.0 grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities.
   - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec.
7. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
8. Primary central nervous system (CNS) tumor, current or history of CNS involvement by the disease under investigation.
9. Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig 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).
10. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
11. Known to be positive for human immunodeficiency virus (HIV), with 1 or more of the following:
    a. Not receiving highly active antiretroviral therapy (ART)
    b. Had a change in ART within 6 months of the start of Screening
    c. Receiving ART that may interfere with trial treatment (consult sponsor for review of medication prior to enrollment)
    d. CD4 count <350 cells/mm^3 at Screening
    e. Acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of start of Screening
    f. Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled).
12. Pulmonary

a. COPD with a FEV1 <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.

b. Moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the trial.

13. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products.

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

15. Major surgery within 2 weeks before randomization, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the trial. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question about whether a procedure is considered a major surgical procedure, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the trial.

16. Plasmapheresis within 28 days before randomization.

17. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the trial procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this trial.

18. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject 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. Subject is taking any prohibited medications as per Section 6.7.3.3.

19. Currently receiving any other investigational agents.

20. 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 GEN3014 or daratumumab SC.

21. A man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3014 or daratumumab SC.

22. Prior allogeneic HSCT.

23. Autologous HSCT within 3 months prior to randomization.

24. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any trial treatment or its excipients, or any of its metabolites (refer to GEN3014 and daratumumab IBs).

25. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:
    a. non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
    b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
    c. non-muscle invasive bladder cancer (NMIBC).
    d. localized prostate cancer (N0M0):
        - with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,
        - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
        - or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence
    e. Breast cancer:
        - adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
        - or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence
    f. Malignancy that is considered cured with minimal risk of recurrence.

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after Screening but before the first dose of trial treatment is given such that subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the trial.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (refer to Sections 5.1 and 5.2). 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 AE related to a trial assessment.

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

Some of the Screening assessments such as cytogenetics may be used for rescreening if performed within the required window schedule defined in Schedule of Assessments prior to Cycle 1 Day 1, or if approved by sponsor.

Rescreened subjects are required to sign a new ICF if updates have been made since signing the most recent ICF.

6 TRIAL TREATMENT

GEN3014 and daratumumab combined with hyaluronidase-fihj are the IMP intended to be administered to a trial subject according to the trial protocol.

6.1 Trial Treatment(s) Administered

6.1.1 GEN3014

GEN3014 will be administered as an IV infusion, by qualified site personnel. Refer to Section 6.2 for pre-infusion medication and post-infusion medication requirements. Detailed dose modification guidance is provided in Section 6.6. Refer to Section 6.7 for information regarding concomitant therapy. GEN3014 treatment should be continued until 1 or more of the discontinuation criteria in Section 7 are met.

Each infusion is estimated to last between 1 and 8 hours.

The first dose of GEN3014 should be split into 2 consecutive days (ie, C1D1 and C1D2).

Please refer to the GEN3014 IMP Manual for detailed instructions.

6.1.2 Daratumumab SC

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 to 5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. The dose of daratumumab will remain constant throughout the trial.

Detailed dose modification guidance is provided in Section 6.6. Refer to Section 6.7 for information regarding concomitant therapy. Daratumumab SC treatment should be continued until 1 or more of the discontinuation criteria in Section 7 are met.

Detailed instructions will be provided in the daratumumab IMP Manual.

6.1.3 Physical Description of Trial Drugs

6.1.3.1 GEN3014

GEN3014 is formulated as a liquid, 20 mg/mL, clear to slight opalescent, colorless to slight yellow solution. It will be manufactured and provided under the responsibility of the sponsor.

Refer to the GEN3014 IB for a list of excipients.

6.1.3.2 Daratumumab SC

Daratumumab SC (daratumumab and hyaluronidase-fihj) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution for subcutaneous use supplied as individually packaged single-dose vials providing 1800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL.

Refer to the daratumumab IB for a list of excipients.

6.1.4 Packaging of Trial Drugs

6.1.4.1 GEN3014

GEN3014 will be packaged with 1 vial per box, with an aluminum cap on the vial.

6.1.4.2 Daratumumab SC

Daratumumab SC will be packed with 1 vial per box.

6.1.5 Labeling

Trial drug labels will contain information to meet the applicable regulatory requirements. For further details see the GEN3014 IMP Manual and daratumumab IMP Manual.

6.1.6 Treatment Schedule

6.1.6.1 GEN3014 Administration Schedule for Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H)

GEN3014 will be administered as an IV infusion at the RP2D in cycles of 4 weeks, ie, 28 days, as follows:

- Cycle 1 (Q1W) on Days 1, 2*, 8, 15, and 22. Note: *The first dose of GEN3014 will be split into 2 consecutive days (ie, C1D1 and C1D2).
- Cycle 2 (Q1W) on Days 1, 8, 15, and 22
- Cycle 3-6 (Q2W) on Days 1 and 15
- Cycle 7 and beyond (Q4W) on Day 1

Dosing days may be adjusted to accommodate the schedule of the site or the subject. Tight visit windows (±1 day) are required for Day 1 in the first 3 treatment cycles. Changes to within-cycle dosing should not affect Day 1 of the next cycle.

6.1.6.2 Post-infusion Monitoring After GEN3014 Administration for Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H)

- During treatment Cycle 1 in the Expansion Part A (GEN3014 Single Cohorts) and Expansion Part B (Randomized H2H), all subjects are required to remain in the clinic after each GEN3014 infusion for at least 4 hours where they will be observed closely. Vital signs need to be monitored as per Section 8.3.3.
- Beyond observation for AEs, vital signs will be measured and blood sampling for laboratory parameters, cytokines, PK and pharmacodynamic measurements will be performed.
- If clinically indicated, observation of up to 24 hours postdose during Cycle 1 is acceptable at the discretion of the investigator.
- If a subject has an IRR of ≥ grade 3 during any infusion, the subject will be required to stay overnight following the infusion. If a subject is hospitalized for prolonged monitoring post-infusion, the hospitalization should not be reported as SAEs.

6.1.6.3 Daratumumab SC Administration Schedule for Expansion Part B (Randomized H2H)

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 to 5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. The dose of daratumumab will remain constant throughout the study. Refer to the IMP Manual for additional guidance on administration of daratumumab SC.

Table 6-1: Daratumumab SC Dosing Schedule, 4-Week Cycle Dosing Regimens

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every 2 weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	every 4 weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9.
[b] First dose of the every-4-week dosing schedule is given at Week 25.

6.1.7 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. Refer to the GEN3014 and daratumumab IMP Manuals for additional details.

6.1.7.1 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 SAE, the trial-site personnel must report the technical complaint to the sponsor according to the SAE reporting timelines (refer to Section 8.4.3.1, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.1.7.2 Contacting Sponsor Regarding Technical Complaints

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the Sponsor Contact page (provided separately from the protocol).

6.2 Pre-administration and Post-administration Prophylaxis

6.2.1 Premedication Prior to GEN3014 and Daratumumab SC Administration

The purpose of premedication is to reduce the risk of IRRs and sARRs. It is mandatory to premedicate subjects with corticosteroids, antihistamines, and antipyretics, before each GEN3014 and daratumumab SC administration (Table 6-2). It is mandatory to use a leukotriene receptor antagonist before each administration of GEN3014 and daratumumab SC during the first cycle (Table 6-2). Premedication specified should be administered 1 to 3 hours prior to GEN3014 and daratumumab SC administration:

- Methylprednisolone 100 mg, or equivalent, administered IV. Only intermediate-acting and long-acting steroids are allowed (please refer to Table 6-3 for conversion table).
- Antipyretics (paracetamol [acetaminophen]) 650 to 1000 mg PO.
- An antihistamine: Diphenhydramine 25 to 50 mg IV or PO, or equivalent.
- A leukotriene receptor antagonist: Montelukast, 10 mg PO.
- If there is no IRR during the first treatment cycle, the dose of corticosteroid may be reduced for subsequent cycles, ie, methylprednisolone at 60 mg IV or PO.

Table 6-2 Premedication Schedule

Pre-Infusion Medication	First Cycle	Subsequent Infusions
Methylprednisolone[1]	100 mg IV	60 mg IV or PO
Paracetamol (acetaminophen)	650 to 1000 mg PO	650 to 1000 mg PO
Diphenhydramine[2]	25 to 50 mg IV or PO	25 to 50 mg IV or PO
Montelukast	10 mg PO	Optional at investigator's discretion

IV=intravenous; PO=per os (oral).
1. Or equivalent dose of an intermediate-acting or long-acting corticosteroid.
2. Or alternative antihistamine at a proper dose.

Table 6-3 Corticosteroid Dose Equivalents

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

6.2.2 Post-GEN3014 Infusion Medication

For the prevention of delayed IRRs, all subjects are required to receive intermediate or long-acting corticosteroid orally (ie, 20 mg methylprednisolone or equivalent) in accordance with local standards on each of the 2 days following all GEN3014 infusions (beginning the day after the infusion).

In addition, for subjects with a higher risk of respiratory complications (eg, subjects who have a percent predicted forced expiratory volume in 1 second [FEV1%PRED] <75%), the investigator should consider prescribing the following medications after completion of the GEN3014 infusion:

- Antihistamine (diphenhydramine or equivalent) on the 2 days following all GEN 3014 infusions (beginning the day after the infusion).
- Short-acting β2-adrenergic receptor agonist, such as salbutamol aerosol.
- Control medications for lung disease (eg, inhaled corticosteroids with or without long-acting β2-adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol with or without inhaled corticosteroids for subjects with COPD.
- These at-risk subjects may be hospitalized for close monitoring at the investigator's discretion.

6.2.3 Post-Daratumumab SC Medication

This applies to subjects randomized to daratumumab SC in the Expansion Part B only. Administer post-administration medication to reduce the risk of delayed sARRs as follows:

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at Screening or developed FEV1 <80% during the study without any medical history), the following post-administration medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If subjects are hospitalized, then an improvement in FEV1 should be performed and documented prior to discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all administrations. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major sARRs, then these post-administration medications may be waived after 4 doses at the investigator's discretion.

Any post-administration medication will be administered after the administration has completed.

6.2.4 Management of GEN3014 Infusion-Related Reactions

Subjects should be carefully observed during GEN3014 infusions. Trained trial staff should be prepared to intervene in case of any infusion related reactions occurring, with resources necessary for resuscitation. Interrupt GEN3014 infusion for IRRs of any severity and institute medical management/supportive treatment as needed:

- For grade 1 or 2 IRRs, stop the infusion immediately and treat the subject; 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.
- For grade 3 IRRs, stop the infusion immediately and treat the subject; 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 GEN3014 and manage the IRR symptoms accordingly.
- For a grade 4 (life-threatening) IRR, permanently discontinue administration of GEN3014 and institute appropriate emergency care.

6.2.5 Management of sARRs and Local Injection Site Reactions of Daratumumab SC

6.2.5.1 Systemic Administration-Related Reactions

Systemic administration-related reactions are systemic reactions related to daratumumab administration. Subjects should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any sARRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an sARR develops during daratumumab SC administration, then the administration should be temporarily interrupted. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening sARR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be permanently discontinued.

6.2.5.2 Systemic Administration-Related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 sARR to be related to administration of trial drug, then the daratumumab administration should be interrupted. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion (DARZALEX FASPRO, 2021). Refer to the daratumumab IMP Manual for further details regarding continuation of daratumumab administration.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.

6.2.5.3 Systemic Administration-Related Reactions of Grade 3 or Higher

For sARR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped, and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. Refer to the daratumumab IMP Manual for further details regarding continuation of daratumumab administration.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the subject must be permanently discontinued from daratumumab treatment.

For sARR AEs that are Grade 4, the daratumumab administration must be stopped, and the subject permanently discontinued from daratumumab treatment.

6.2.5.4 Recurrent Systemic Administration-Related Reactions

If a Grade 3 sARR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

6.2.5.5 Injection Site Reactions

Skin reactions at or near the injection site (local), including injection site reactions, can happen with daratumumab. Symptoms at the site of injection may include itching, swelling, bruising, pain, rash, bleeding, or redness of the skin. These reactions sometimes happen more than 24 hours after an injection of daratumumab. Monitor for local reactions and consider symptomatic management.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Preparation, Handling, and Storage

The preparation, handling, and storage of GEN3014 and daratumumab SC are described in the IMP Manuals.

6.3.1.1 GEN3014

GEN3014 must be stored at controlled temperature ranging from 2 to 8 °C (36 to 46 °F).

6.3.1.2 Daratumumab SC

Daratumumab SC must be stored at controlled temperature ranging from 2 to 8 °C (36 to 46 °F) in the original carton to protect from light (DARZALEX FASPRO, 2021).

6.3.2 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of trial treatment in a drug accountability log. Drug accountability will be verified by the field monitor during site visits and at the completion of the trial.

For trials using Interactive Response Technology (IRT), the drug accountability will be documented within the system.

When drug accountability has been verified and a copy of the completed drug accountability log has been received by sponsor, the investigator will dispose all used and unused trial treatment and packaging in accordance with the guidance in the trial-specific preparation and administration guideline and local regulations per the trial drug IMP Manual.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Subject Numbering

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

6.4.2 Treatment Assignment

This is an open-label trial; blinding does not apply. Randomization only applies to Expansion Part B (Randomized H2H).

6.4.2.1 Dose Escalation

In the Dose Escalation, site personnel must contact the contract research organization (CRO) when a potential subject has been identified. Subjects will be designated by their disease type of either RRMM or R/R AML.

If there is an available enrollment slot in any currently enrolling DL, 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.

6.4.2.2 Expansion Part A (GEN3014 Single Cohorts) and Part B (Randomized H2H)

In the Expansion Part A (GEN3014 Single Cohorts), subjects will be assigned to 1 of the 4 cohorts: anti-CD38 mAb-naive RRMM, anti-CD38 mAb-refractory RRMM, R/R AML, or R/R DLBCL.

In the Expansion Part B (Randomized H2H), anti-CD38 mAb-naive subjects with RRMM will be randomized in a 1:1 ratio to receive either GEN3014 or daratumumab SC. Subjects will be assigned randomly to 1 of the 2 treatment groups based on a computer-generated randomization schedule prepared before the trial by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by body weight at baseline (≤70 kg; >70 kg) and number of prior lines of therapy (≤4 prior lines vs >4 prior lines). The IRT will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use their own user identification and personal identification number when contacting the IRT, and will then give the relevant subject details to uniquely identify the subject.

6.5 Compliance

GEN3014 and daratumumab SC will be administered by qualified site personnel to assure compliance with trial requirements. The date and time of each trial drug administration will be documented.

Intervention start and stop dates/time, including trial drug administration start/stop time for managing IRRs/sARRs, and dates for trial drug delays will also be documented.

6.6 Dose Modifications

6.6.1 Dose-Limiting Toxicity (Dose Escalation)

The DLT Evaluation Period is defined as the first 28 days of GEN3014 treatment (ie, Cycle 1). Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0, with the exception of TLS (see Appendix 10.3.6).

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

- All Grade 5 toxicities
- Hematological toxicities listed below:
  - Grade 4 thrombocytopenia (platelet count <25.0 $\times 10^9$/L [<25,000/µL]) lasting >7 consecutive days not attributable to the underlying disease.
  - Grade 4 neutropenia (neutrophil count <0.5 $\times 10^9$ cells/L [<500/µL]) lasting >7 consecutive days not attributable to the underlying disease.
  - Grade 3 and grade 4 febrile neutropenia (neutrophil count <1.0 $\times 10^9$ cells/L with a single temperature of >38.3 °C [100.9 °F] or with a sustained temperature of ≥38 °C [≥100.4 °F] for more than 1 hour) lasting >2 days.
  - Grade 3 and grade 4 hemorrhage associated with thrombocytopenia of ≥ grade 3 requiring platelet transfusion.
  - Grade 4 anemia
- Note: Since bone marrow aplasia is an expected consequence of AML therapies, only persistent pancytopenia lasting ≥14 days and not related to leukemia infiltration will be considered as a DLT for the R/R AML Cohort. Bone marrow evaluation may be required to determine if marrow aplasia is due to leukemia.
- Non-hematological toxicities:
  - All non-hematological toxicities of grade ≥3 (severe or life-threatening), **excluding** the following:
    a. Grade 3 fever (>40.0 °C [>104.0 °F]) for ≤24 hours
    b. Grade 3 hypotension (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. Grade 3 AST and/or grade 3 ALT returning to grade 1 or baseline in ≤7 days
    e. Grade 3 nausea that responds to adequate antiemetic treatment in ≤3 days
    f. Grade 3 vomiting that responds to adequate antiemetic treatment in ≤3 days

g. Grade 3 diarrhea that responds to adequate antidiarrheal treatment in ≤3 days

h. Grade 3 fatigue/asthenia when fatigue/asthenia was present at baseline or that lasts for <14 days

i. Alopecia (all grades)

- Grade 4 TLS (see Appendix 10.3.6 for additional information)
- Grade 4 IRR
- Any liver toxicity of elevated ALT or AST ≥ 3 times or greater above the upper limit of normal (ULN) with serum total bilirubin of ≥ 2 times the upper limit of normal, without findings of cholestasis and in the absence of alternative etiologies

Note: AEs of specified grades, regardless of relationship to GEN3014, should be considered relevant for dose escalation decisions, unless the event can clearly be determined to be unrelated to the drug. All of the AEs of specified grades should be classified as DLTs except those that are clearly and incontrovertibly due to the underlying disease or extraneous causes.

The investigator must notify the sponsor immediately of a DLT. Frequent laboratory monitoring of complete blood count (CBC) 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 GEN3014-related AEs will be monitored and included in the evaluation of the toxicity profile of GEN3014 unless the event is clearly determined to be unrelated to GEN3014 (eg, disease progression).

6.6.2 GEN3014 Dose Modification Guidance and Stopping Criteria

- No dose modification (increase or decrease) of GEN3014 will be permitted for this trial.
- If a subject experiences a DLT, the subject may continue treatment with GEN3014, if the toxicity recovers to ≤ grade 2 or baseline within 4 weeks from occurrence of the DLT. Continued administration of GEN3014 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 GEN3014, the treatment will be permanently discontinued. Treatment with GEN3014 will be discontinued in the event the DLT is not resolved within 4 weeks.
- If a subject experiences toxicity that would have qualified as a DLT but the event occurs after the DLT evaluation period, the subject's benefit-risk must be thoroughly assessed. Continued treatment with GEN3014 must be agreed between the sponsor and the investigator.
- For the subject who receives treatment beyond the DLT evaluation period, all corresponding AEs that would have met the DLT criteria will be considered for the purpose of determining the RP2D and/or MTD (if reached). For the declaration of the RP2D from the Dose Escalation for further development of GEN3014 in the Expansion, the totality of the data including safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated.
- During the trial, a planned dose of GEN3014 can be postponed for up to 4 weeks due to an AE whether it is considered drug-related or not.

- In case of dose delay of more than 4 weeks from the last trial drug administration due to toxicity, GEN3014 should be discontinued, unless resuming administration of GEN3014 is agreed between the sponsor and the investigator.
- During the trial, the GEN3014 dose can be held for the following laboratory results:
  a. If platelet count is $<50 \times 10^9$/L, hold dose until platelet count is $\geq 50 \times 10^9$/L.
  b. If febrile neutropenia is $<0.5 \times 10^9$/L, hold dose until neutrophil count is $\geq 0.5 \times 10^9$/L.
  c. If hemoglobin is <8 g/dL (<8 g/L or <5 mmol/L), hold dose until hemoglobin is ≥8 g/mL (≥8 g/L or ≥5 mmol/L).

Note: If the investigator deems any of the above cytopenia as bone marrow involvement due to the disease, continuation of GEN3014 treatment can be discussed with the sponsor's medical monitor. Transfusion with blood products and/or administration with granulocyte colony-stimulating factor (G-CSF) is permitted if needed (refer to Section 6.7.3.2).

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

Refer to Section 9.6 for safety stopping criteria for the Expansion cohorts.

6.6.3 Daratumumab SC Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

Daratumumab SC administration must be captured in the source documents and the electronic case report form (eCRF).

6.6.3.1 Daratumumab SC Dose Modifications

Dose modification of 1800 mg daratumumab SC (increase or decrease) is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

6.6.3.1.1 Daratumumab SC Dose Delays

If any of the following criteria are met and the toxicity is more than expected for the underlying MM, the daratumumab injection must be held to allow for recovery from toxicity as noted below. If attribution is unclear, then daratumumab should be held until recovery from toxicity as noted below:

The criteria for a delay are:

- Grade 4 hematologic toxicity, except for grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days

- Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

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

6.6.3.1.2 Daratumumab SC Skipped Doses

Other than on Day 1 of a cycle, if any "within-cycle" daratumumab administration does not commence within the prespecified window (Table 6-4) of the scheduled administration date, then the dose will be considered a skipped dose. Administration may resume at the next planned dosing date. A minimum of 4 days between daratumumab doses must be observed. A skipped dose will not be made up.

Table 6-4 Daratumumab SC Administration Schedule for Dose Delays

Cycles	Frequency	Dose Held	Dosing Restart
1 and 2	Weekly (q1wk)	>3 days	Next planned weekly dosing date
3 to 6	Every 2 weeks (q2wks)	>7 days	Next planned every 2 weeks dosing date
7+	Every 4 weeks (q4wks)	>14 days	Next planned every 4 weeks dosing date

6.6.3.1.3 Treatment Continuation Following Daratumumab SC Delay

If the treatment is interrupted for >28 days due to toxicity, but the event has resolved to grade 2 or baseline, consult with the Sponsor to discuss continuation on study. If not approved, subject should be discontinued from study treatment and proceed to End of Treatment visit. Subjects missing ≥3 consecutive planned doses of trial drug for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Systemic administration-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment.

6.7 Prior and Concomitant Therapies

6.7.1 Prior Anti-Cancer Therapies

Prior anti-cancer therapies received from the time of initial diagnosis and until 14 days before administration of the first dose of GEN3014 should be reported. These include chemotherapy, radiation therapy, surgery, antibody, CAR-T cell therapy, transplantation, investigational drug, etc.

The best response, reason for discontinuation, dates of treatment, and date of progression should be reported for prior anti-cancer therapies.

6.7.2 Other Prior Therapies

Any other medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) received within 21 days before administration of the first dose of GEN3014 must be documented.

6.7.3 Concomitant Therapies

The subject must be told to notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) he/she takes after the start of GEN3014 or daratumumab SC treatment. All medications (other than GEN3014 or daratumumab SC) and therapies (eg, physical therapy, herbal/natural medications and blood transfusions) administered during the trial (ie, beginning with administration of the first dose of GEN3014 or daratumumab SC until 30 days after the last dose of GEN3014 or daratumumab SC) must be documented.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.7.3.3).

Concomitant therapies should also be documented beyond 30 days only in conjunction with SAEs that meet the criteria in Appendix 10.3.

6.7.3.1 Recommended Therapies

The following therapies are recommended as prophylaxis during the trial.

Drugs affecting bone structure and mineralization
All patients receiving primary myeloma therapy should be given bisphosphonates or denosumab per NCCN guidelines 2022 (NCCN, 2022). Commercially available bisphosphonates or denosumab, should be used according to the manufacturer's recommendations, as described in the prescribing information and per institutional guidelines (Anderson et al., 2018). The initiation and changing of the bisphosphonate or denosumab therapy during the trial should be discussed with the sponsor to avoid interference with the evaluation of the bone disease progression.

Therapy for Tumor Lysis Syndrome
It is recommended that high-risk subjects (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg, rehydration, diuretics, allopurinol 300 mg daily, and medication to increase urate excretion).

All subjects should be monitored for symptoms of TLS (see Appendix 10.3.6). Management of TLS, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended.

Prophylaxis for IRRs
All subjects will receive prophylactic therapy to prevent IRRs during the Treatment period, as described in Section 6.2.

Therapy for *Pneumocystis carinii*
Pneumocystis carinii pneumonia prophylaxis should be considered, as per institutional guidelines.

Prophylaxis for Herpes Zoster Reactivation
Prophylaxis for herpes zoster reactivation should be initiated within 1 week after starting GEN3014 or daratumumab SC and continue for 3 months following treatment. Acceptable antiviral therapy includes acyclovir (eg 400 mg given orally 3 times a day, or 800 mg given orally

2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards).

Prevention of steroid induced gastritis
Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).

Infection Prophylaxis
Prophylactic use of antibiotics is highly recommended due to the susceptibility of patients with MM to infections. Prophylactic administration of antibiotics should be considered and dependent on institutional guidelines.

6.7.3.2 Permitted Concomitant Medications and Therapies

In addition to recommended therapies (see Section 6.7.3.1), the following concomitant medication and therapies are permitted during the trial:

- 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. Note: SARS-CoV-2 vaccine should not be administered during the DLT period.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and ≥ grade 3 neutropenia, when clinically indicated or at the investigator's discretion. In case of ≥ grade 3 neutropenia, use of growth factors is mandated
- Erythropoietin
- Red blood cell and platelet transfusions, if clinically indicated
- Multivitamins, vitamin D, calcium and supplements, for prevention of weight loss
- Prescribed medicinal cannabinoids as palliative therapy
- Stool softeners if needed, high fiber diet and adequate hydration to prevent constipation
- Adequate hydration is recommended for prevention of myeloma-related kidney disease
- Local palliative radiotherapy for bone fracture/pain associated with MM and that is refractory to narcotic analgesics (because pathologic bone fractures do not by themselves fulfill a criterion for disease progression)
- Typically, IV contrast is not used in CT scanning of subjects with secretory MM due to risk to the kidney. If administration of IV contrast is necessary, adequate precautions including hydration are recommended.

The trial site will supply supportive medication, eg, pre-infusion medication, post-infusion medication, anti-viral medication.

6.7.3.3 Prohibited Concomitant Therapy

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

The following medications are prohibited during the trial (from the first dose of GEN3014 or daratumumab SC):

- Any systemic anti-cancer therapy, eg, chemotherapy, immunotherapy, radiotherapy or experimental therapy, other than GEN3014 or daratumumab SC, including medication that targets CD38, is prohibited.
- Medications used for other indications that have anti-myeloma properties (for example, interferon and clarithromycin (Ghosh et al., 2013; Niesvizky et al., 2008; Rossi et al., 2013))
- Continuation of trial drug during or after emergency orthopedic surgery or radiotherapy, because subjects' benefit may only occur in the absence of disease progression, and after consultation with and approval of the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject for whom delay of systemic therapy is not appropriate.
- Corticosteroid that exceeds a total daily dose of 10 mg of prednisolone or equivalent administered for more than 10 days unless for the management of AEs (excluding corticosteroids given as GEN3014 pre-infusion and post-infusion medication as prophylaxis for IRRs, as described in Section 6.2.1).
- IV contrast is not used in CT scanning of subjects with secretory MM because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.
- Emergency orthopedic surgery or radiotherapy. Continuation of trial drug during or after emergency orthopedic surgery or radiotherapy because of subject benefit may only occur in the absence of disease progression and after consultation with and approval by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 6 to 8 weeks of treatment and the absence of evidence of disease progression is to be reviewed and approved by the sponsor. If emergency radiotherapy during trial drug administration is required, eg, for bone pain or risk of fracture, this is allowed when there is no evidence of disease progression and approved by sponsor.
- Refer to Appendix 10.15 for local health authority requirements.

6.7.4 Rescue Medicine

Rescue medication to reverse the action of GEN3014 or daratumumab SC is not available.

6.8 Treatment after the End of the Trial

6.8.1 Subject Contact and Trial Treatment After the End of the Trial

Investigators may contact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 10.1.5, Informed Consent Process).

7 DISCONTINUATION OF TRIAL TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Trial Treatment

A subject's trial drug must be discontinued if:

- Unacceptable AE requiring treatment discontinuation*
- Subject non-compliance
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for MM, AML, or DLBCL.
- Sponsor decision
- Subject request to discontinue trial treatment*
- Pregnancy
- Clinical progression*
- Disease progression (according to response criteria, Section 8.2)
- Other

*Every effort should be made to continue evaluations according to the trial protocol. When a subject discontinues trial drug, the subject remains in the trial and is followed until meeting 1 of the reasons listed in Section 7.2.

If a subject's trial drug must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the trial. The End of Treatment assessments should be performed. In addition, the subject will still be followed for the safety follow-up visit (see Section 7.1.1) and for survival status (see Section 7.1.2) through the end of the trial.

Subjects should be examined regularly according to the Schedule of Activities (Section 1.3), or more frequently, as needed. If the decision to discontinue trial drug occurs around the time of the next planned treatment administration visit, the assessment schedule for the End of Treatment Visit should be followed. Subjects should be followed for safety as detailed in Section 7.1.1 and Appendix 10.3.

After treatment discontinuation, the subject should receive suitable treatment as decided by the investigator (see Section 6.8).

Trial treatment assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will be entered to ensure the protocol-specified number of subjects complete the trial.

7.1.1 Safety Follow up Evaluation

Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (±7 days) after the subject receives the last dose of GEN3014. If the subject initiates new anti-cancer treatment within 30 days of the last dose of GEN3014, the safety follow-up visit should be performed prior to starting new anti-cancer treatment. Once new anti-cancer treatment is initiated, the subject will move into survival status follow-up (see Section 7.1.2).

7.1.2 Survival Status

Survival status will be assessed every 3 months (±7 days), beginning from the day of last GEN3014 or daratumumab SC dose and continuing until the subject dies or withdraws from the trial. Subjects may be contacted by telephone, email, or visit. Survival status may be requested more frequently around the time of a database lock. Subjects who are not available, or whose designated family members are not available, for this assessment should be entered as "lost to follow-up" (see Section 7.3 and Section 6.8.1).

7.2 Subject Discontinuation/Withdrawal from the Trial

A subject will be withdrawn from the trial for any of the following reasons:

- Death
- Lost to follow-up
- Sponsor decision
- Subject withdraws consent
- Pregnancy

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

7.3 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 (as a minimum of 3 documented attempts). Subjects lost to follow-up should be documented.

8 TRIAL ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (see Section 1.3) summarizes the frequency and timing of measurements applicable to this trial. At each visit, trial assessments should be completed before trial drug administration.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the trial.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

8.1 Demography and Baseline Assessments

8.1.1 Demographics

Demographic details will be assessed at Screening.

8.1.2 Diagnosis and Disease Status

The following should be recorded at Screening:

- A subject's history relating to the underlying disease, including primary diagnosis, date of diagnosis, as well as disease status at trial entry, staging, and risk category.
- Cytogenetics and molecular mutational status.
- Transfusion dependency.

Transfusion dependency will be assessed at Screening, every 8 weeks (RRMM and R/R DLBCL) or every 4 weeks (R/R AML) during treatment, and at the end of treatment visit, according to local institution guidelines. The number of units for red blood cells and platelets transfusions must be recorded.

8.1.2.1 RRMM

The primary diagnosis of MM, and the status and staging criteria at Screening, will be determined by the IMWG International Staging System (see Appendix 10.8). The cytogenetic panel for MM used should include, but are not limited to the following common chromosome abnormalities: del(17p), t(14;20), t(4; 14) (p16; q32) or t(14; 16) (q32; q23) t (6;14), t(11;14), Gain 1q, TP53 mutation (Dispenzieri et al., 2007; Kumar et al., 2009; Mayo-Clinic, 2018; Mikhael et al., 2013).

8.1.2.2 R/R AML

The diagnosis of AML subtype at Screening will be reported according to the WHO 2016 Classification for AML and related neoplasm and risk categorization (Appendix 10.10).

Molecular mutational status will be done at Screening. The molecular mutation panels for AML include but are not limited to the following: IDH1/2, TP53, TET2, RUNX1, DNMT3A, ASXL1, K/NRAS, FLT3, CEBPA, JAK2, NPM1, and IKZF2.

8.1.2.3 R/R DLBCL

The primary diagnosis of DLBCL, and the status and staging criteria at Screening, will be determined by the Ann Arbor staging criteria, including constitutional symptoms (B symptoms), (see Appendix 10.13).

For DLBCL, major biologically distinct molecular subtypes (germinal center B-cell [GCB]) and activated B-cell (ABC), MYC positivity, chromosomal rearrangements of MYC plus BCL-2, MYC plus BCL-2 and BCL-6 will be collected at Screening.

8.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to the first dose of GEN3014 or daratumumab SC should be documented in the source documents as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN3014 or daratumumab SC dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy and/or CT scan).

Any medical history/current medical condition that worsens after the first dose of GEN3014 or daratumumab SC will be documented as an AE. See additional reporting details in Section 8.4 and Appendix 10.3.

8.2 Efficacy Assessments

Efficacy assessments will be conducted as specified in the Schedules of Activities (Section 1.3). In the Dose Escalation, Expansion Part A (GEN3014 Single Cohorts), and Expansion Part B (Randomized H2H), response to the trial treatment will be reported per the investigator's assessment.

8.2.1 Efficacy Assessments for RRMM

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG Response Criteria (Kumar et al., 2016). Disease evaluations will include measurements of myeloma proteins, bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of β2-microglobulin, albumin, and serum calcium corrected for albumin. Disease evaluations must be performed every 28 days (±3 days) as defined in Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), and Table 1-12 (Expansion Part B [Randomized H2H]) until disease progression according to IMWG Response Criteria (see Appendix 10.9). All response categories require 2 consecutive assessments made at any time, prior to initiating a new therapy. As minimal residual disease (MRD) will also be evaluated, these criteria will be included per IMWG Response Criteria (Appendix 10.9); see Section 8.8.3 for more information on assay and methodology.

8.2.1.1 Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. The investigator will use results provided by the central laboratory for disease assessment. Only 1 serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests.

- Serum quantitative Ig panel: IgG, IgA, IgM, IgE, and IgD at Screening as indicated on Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), and Table 1-12 (Expansion Part B [Randomized H2H]). These analyses will be performed by the local laboratory.
- Serum M-protein quantitation by electrophoresis (SPEP).
- Serum immunofixation (IFE) at Screening and thereafter when M-protein is non-quantifiable.
- Serum FLC assay.
- 24-hour urine M-protein quantitation by electrophoresis (UPEP).
- Urine IFE at Screening and thereafter when a M-protein is non-quantifiable.

Blood and 24-hour urine samples will be collected as specified in Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), or Table 1-12 (Expansion Part B [Randomized H2H]) until disease progression. Disease progression based on 1 of the laboratory tests alone must be confirmed by a repeat sample testing 1 to 4 weeks later. Serum and urine IFE will be performed at Screening and at the time when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or non-quantifiable). For subjects with light chain MM, serum IFE test, urine IFE test, and serum FLC assay will be performed routinely.

For subjects who have achieved a very good partial response (VGPR) or better with suspected GEN3014 interference on serum IFE, a reflex assay using the anti-idiotype mAb may be used to confirm GEN3014 migration on the IFE. Subjects who meet all other IMWG criteria for CR/stringent complete response (sCR) (see Appendix 10.9), and whose positive IFE is confirmed to be GEN3014, will be considered complete responders.

8.2.1.2 Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed locally, as specified in Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), or Table 1-12 (Expansion Part B [Randomized H2H]) until disease progression. Development of hypercalcemia (corrected serum calcium >11 mg/dL [>2.75 mmol/L]) can indicate disease progression or relapse if it is not attributable to any other cause (see IMWG disease response criteria in Appendix 10.9). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels (“corrected serum calcium”). The formula for adjustment is presented in Appendix 10.7. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the ULN are considered to be hypercalcemic for this trial.

8.2.1.3 Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed for clinical assessments and biomarker evaluations.

At Screening, clinical characterization of the myeloma (morphology, cytogenetics, and IHC or immunofluorescence or flow cytometry) may be done by a local laboratory and a portion of the bone marrow aspirate is required to be sent to the central laboratory to establish baseline MM clonality to monitor MRD and to perform biomarker analyses as described in Section 8.8.1 and Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), and Table 1-12 (Expansion Part B [Randomized H2H]). In addition, non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or formalin-fixed paraffin-embedded (FFPE) block (clot section only, no bone marrow biopsy) up to 42 days prior to enrollment may be collected for MRD assessment.

Additional bone marrow aspirate collections will be performed during GEN3014 treatment to confirm CR/sCR or relapse from CR/sCR, as clinically indicated. In addition, MRD may be evaluated for subjects who achieve CR at time points as detailed in Section 8.8.3 and Table 1-4 (Dose Escalation), Table 1-9 (Expansion Part A [GEN3014 Single Cohorts]) and Table 1-15 (Expansion Part B [Randomized H2H]). For sCR IHC immunofluorescence requires kappa/lambda ratio analysis of ≥100 cells or 2- to 4-color flow cytometry.

First or second pulls for all collections are strongly preferred.

Additional biomarker evaluations are described in Section 8.8.1.

8.2.1.4 Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening period. MRI or clinical examination can be used to document extramedullary sites of disease. CT scan evaluation is acceptable alternative (if no contraindication to use of IV contrast). PET scans and ultrasound are not acceptable methods for documentation of size of extramedullary plasmacytomas.

For all subjects with a history of plasmacytomas or if clinically indicated, an assessment of extramedullary plasmacytomas must be performed at Screening by clinical examination or radiologic imaging. Assessments of plasmactyomas, done locally every 4 weeks for physical examination. For subjects with a history or subjects, as clinically indicated during treatment, assessments of plasmacytomas are performed until development of confirmed CR or confirmed PD.

If assessment can be done radiologically, then evaluations may be done every 12 weeks. Methodology of assessments must be consistent throughout all visits. Irradiated or excised lesions will be considered not measurable, and will only be monitored for PD.

To qualify for PR or MR, in addition to meeting the criteria set for M protein or FLC levels or percent of plasma cells, if present at baseline, a ≥50% reduction in the sum of the products of the maximal perpendicular diameters (sum of the product of the diameters [SPD]) of soft tissue plasmacytomas is also required. PD per plasmacytomas includes the appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or a ≥50% increase in the longest diameter of a previous lesion in >1 cm short axis. (See IMWG 2016 disease progression criteria in Appendix 10.9).

8.2.1.5 Skeletal Survey

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by CT scan or X-ray during the Screening period.

If results of skeletal survey have been performed up to 6 weeks (42 days) before Cycle 1 Day 1 as routine follow-up for the subject's disease, then the skeletal survey can be used and there is no need to repeat for Screening. During the Treatment period and before disease progression is confirmed, CT scans or X-rays should be performed whenever clinically indicated based on symptoms, to document response or progression. MRI is an acceptable method for evaluation of bone disease, and may be included at the discretion of the investigator; however, it does not replace the skeletal survey (see the IMWG disease response criteria in Appendix 10.9). If a radionuclide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionuclide bone scan does not replace a complete skeletal survey.

Sometimes subjects present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory CT scans or X-rays are necessary. In instances where changes may be more subtle, a repeat CT scan or X-ray may be needed in 1 to 3 weeks.

8.2.2 Efficacy Assessments for R/R AML

For AML, the revised IWG 2003 criteria (Cheson et al., 2003) will be used for efficacy assessment. Evaluation of response during trial treatment will be based on blood and bone marrow assessment as well as presence or absence of extramedullary disease. Disease evaluations must be performed in every cycle as defined in Table 1-2 (Dose Escalation) and Table 1-6 (Expansion Part A [GEN3014 Single Cohorts]), until disease progression according to AML treatment response criteria. Refer to Appendix 10.11 for detailed response criteria. Response assessment will be conducted locally by the trial investigator(s).

8.2.2.1 Peripheral Blood Assessment

Peripheral blood assessments must be performed at Screening (within 14 days prior to the first dose of GEN3014 or daratumumab SC) and on day 1 of each cycle. During treatment, if a peripheral blood assessment is consistent with a possible PR, CR, complete remission with incomplete hematologic recovery (CRi), then a bone marrow aspiration or biopsy sample must be performed within 5 days to confirm the PR, CR or CRi.

Assessments include:

- Complete blood cell count including WBC
- Differential including promyelocyte, myelocyte, and metamyelocyte
- Blast cell count
- Platelet count

8.2.2.2 Bone Marrow Assessment

Bone marrow aspirate and biopsy will be performed for clinical assessments and biomarker evaluations.

Bone marrow aspiration and core biopsy sample must be obtained at Screening. During trial treatment, bone marrow aspiration should be taken at these time points per Table 1-2 (Dose Escalation) and Table 1-6 (Expansion Part A [GEN3014 Single Cohorts]): Cycle 2 Day 1 (+3 days), Cycle 3 Day 1 (±7 days), then every 3 cycles (±1 cycle). If a peripheral blood assessment is consistent with a possible PR, CR, CRi, then a bone marrow aspiration and biopsy must be performed within 5 days. Bone marrow aspirate and biopsy should also be performed at 1 month after achievement of the first CR to confirm the response and every 3 cycles (±1 cycle) thereafter.

During Expansion Part A (GEN3014 Single Cohorts), if a fresh bone marrow aspirate cannot be obtained at Screening, or if a baseline clone fails to calibrate during MRD testing, then non-decalcified diagnostic slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy) should be collected for MRD assessments.

Bone marrow assessment for diagnosis and response will be performed at a local laboratory.

Bone marrow assessment for MRD and biomarkers will be conducted at a central laboratory designated by the sponsor. A portion of the bone marrow aspirate will be used for MRD evaluation (see Section 8.8.3) in the Expansion Part A (GEN3014 Single Cohorts) (Table 1-10) as well for biomarker evaluations (see Section 8.8.1) in both the Dose Escalation (Table 1-2), Expansion Part A (GEN3014 Single Cohorts) (Table 1-6).

First or second pulls for all collections are strongly preferred.

8.2.2.3 Extramedullary Disease Assessment

CT/MRI scans may be acquired to evaluate extramedullary disease. CT scans are required for subjects at Screening if clinical suspicion of extramedullary disease exists or the subject has a clinical history. If clinically indicated, post baseline scans should only be performed in these anatomical regions that demonstrate possible disease and performed every 8 weeks. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated. If a subject is known to have a medical contraindication to CT IV contrast agent or develops a contraindication during the trial, a CT scan without contrast should be acquired. Chest CT scans should include both axillae in their entirety. MRI should only be used to image anatomical regions that cannot be adequately imaged by CT and if a subject is intolerant of IV CT contrast.

8.2.3 Efficacy Assessments for R/R DLBCL

Assessment of response and disease progression will be conducted in accordance with the Lugano response criteria for lymphoma (Cheson et al., 2014) (see Appendix 10.14). Disease evaluations will include imaging assessments, physical exam including constitutional symptoms (see Section 8.3.7), ECOG performance status, MRD status, and other procedures as necessary (see Table 1-7). Response assessment will be conducted locally by trial investigators.

8.2.3.1 Imaging Assessment

For the imaging assessments, the same radiographic modality used at Screening for disease evaluation should be used throughout the trial for the response evaluations.

An ^{18F}-FDG PET-CT scan (or CT/MRI and FDG PET when combined PET-CT scan not available) must be performed at Screening (ie, ≤21 days prior to the first dose of GEN3014) and at the time points indicated on Table 1-7.

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) (see Table 10-6 in Appendix 10.14). That is, at each time point, the most metabolically active lesion is assessed using the 5-point scale (Van Heertum et al., 2017), and this will determine the overall time point response per Table 10-6 in Appendix 10.14.

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 stand-alone 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 as to not compromise PET results. The PET-CT acquisition methodology (eg, administration of IV contrast) should remain consistent between Screening and subsequent assessments for any given subjects. In subjects with low or variable FDG avidity the response will be derived per Table 10-5 in Appendix 10.14.

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

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

An MRI scan or CT scan of the brain should be performed at Screening only if brain involvement is suspected, and may be performed during the trial if clinically indicated.

8.2.3.2 Bone Marrow Assessment

DLBCL subjects with bone marrow involvement, fresh bone marrow aspirate and biopsy must be obtained at Screening (ie, within 3 weeks prior to the first dose of GEN3014) and at the time of CR or as clinically indicated. A bone marrow biopsy obtained as routine standard of care may be used instead, if taken up to 42 days before first dose of GEN3014. If bone marrow aspirate is obtained, determination of bone marrow involvement may be confirmed by flow cytometry.

- A bone marrow biopsy plus aspirate (performed at local laboratory) is required for confirmation of an observed radiologic CR and should be done preferably within 30 days of the initial documentation of radiologic CR (Cheson et al., 2014). Bone marrow evaluation must include morphological examination and either flow cytometry or IHC, if warranted, to confirm the presence or absence (CR) of lymphoma. If bone marrow involvement can be confirmed with morphology, flow cytometry/IHC need not be done if this is not part of a trial-site standard practice.
- For subjects having bone marrow involvement documented at Screening, a portion of the aspirate collected to confirm radiologic CR will be used for MRD assessments (see Section 8.8.3 and Table 1-11).

- For subjects having no bone marrow involvement at Screening, no further bone marrow examination for MRD is required.

8.3 Clinical Safety Assessments

Details regarding the DEC, Safety Committee, and DMC are provided in Committees Structure in Appendix 10.1, Regulatory, Ethical, and Trial Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events and Serious Adverse Events and Appendix 10.3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the trial must be documented. Any clinically significant abnormalities persisting at the end of the trial/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

8.3.1 Physical Examination

A complete (full) physical exam should be performed during Screening period. At subsequent visits, a symptom-directed/clinically-indicated (brief) physical examination may be performed.

Full Physical Exam:

The investigator or qualified designee will perform a full physical examination according to standard of care at Screening, 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, new or worsening findings should be reported as AEs.

Brief Physical Exam:

For visits that do not require a full physical examination (as specified in the Schedule of Activities), the investigator or qualified designee will perform a symptom-directed physical examination as clinically indicated prior to trial treatment administration. After the first dose of trial treatment, new or worsening findings since the last assessment should be documented as AEs.

8.3.2 Body Measurements

8.3.2.1 Height

Height (without shoes) must be measured at Screening and rounded to nearest centimeter or inch.

8.3.2.2 Weight

Body weight (without overcoat and shoes) will be measured as indicated in the Schedule of Activities (Section 1.3) and rounded to nearest kilogram.

Body weight should be assessed within 72 hours prior to each dose of GEN3014. This weight will be used for calculation of the dose and should be documented.

8.3.3 Vital Signs

Vital signs including temperature (°C or °F), respiratory rate, oxygen saturation, blood pressure (mm Hg) and pulse/heart rate (beats/min) will be measured as indicated in the Schedule of Activities (Section 1.3).

Within each visit, preferably the same equipment shall be used for vital sign measurements.

As indicated in the Schedule of Activities (Section 1.3), vital signs should be assessed during Cycle 1 at the following timepoints:

- right before the trial drug administration
- at the end of administration, 30 min, 1 hour and 3 hours after the end of administration

From Cycle 2 and onward, vital signs should be assessed right before the trial drug administration and at the end of administrations.

8.3.4 Electrocardiograms

The ECGs will be recorded digitally at the sites by using the standard 12-leads as indicated in the Schedule of Activities tables (Section 1.3). ECGs will be performed in accordance with the ECG manual issued by the ECG vendor. The digital ECGs will be electronically transmitted from the sites to a central laboratory for a measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

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

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

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the printout. 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 in a supine or reclined position for at least 10 minutes. ECGs should be performed in triplicate, 5 minutes apart (±2 minutes). In case any irregularity (eg, vomiting or cough) occurs during the recording of the ECG, the ECG should be repeated.

8.3.5 ECOG Performance Status

The ECOG PS will be assessed by the investigator as indicated in the Schedule of Activities. Performance status will be scored using the ECOG PS scale index (Table 8-1).

Table 8-1 ECOG Performance Status

Score	Performance Status
0	Fully active, able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

8.3.6 Clinical Laboratory Assessments

Blood and urine samples for: will be collected as indicated in the Schedule of Activities (see Section 1.3) and further described in Appendix 10.2, Clinical Laboratory Tests: serum chemistry; hematology; coagulation testing; β2-microglobulin; HBV, HCV, and cytomegalovirus (CMV) serology; urinalysis; pregnancy testing (if applicable); and HIV serology at Screening (only if required per local health authorities or institutional standards).

Additional clinical laboratory tests to be performed are listed in Section 8.3.6.1 (all subjects), Section 8.3.6.2 (all subjects), Section 8.3.6.3 (all subjects), Section 8.3.6.4 (subjects with RRMM), and Section 8.3.6.5 (subjects with R/R AML).

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF.

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

Both local and central laboratory test results should be assessed for abnormalities (see Appendix 10.3.3 for additional information on reporting of laboratory abnormalities that are considered AEs). Please be aware that when an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

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

8.3.6.1 Cytogenetics and Molecular Mutational Status (All Subjects)

Blood samples will be collected at Screening for cytogenetics and molecular mutational status for subjects with RRMM (see Section 8.1.2.1), R/R AML (see Section 8.1.2.2), and R/R DLBCL (see Section 8.1.2.3).

8.3.6.2 Immunoglobulin Analyses (All Subjects)

- For subjects with R/R AML, and R/R DLBCL, blood samples will be collected for analysis of IgA, IgG, and IgM at Screening (using the local laboratory).
- For subjects with RRMM, blood samples will be collected for analysis of IgA, IgG, IgM, IgE, and IgD at Screening (using the local laboratory).
- For subjects with RRMM, blood samples will be also collected for analysis of the quantitative serum Ig panel (IgG, IgA, IgM, IgE, and IgD) at Screening and at the time points indicated on Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A [GEN3014 Single Cohorts]), and Table 1-12 (Expansion Part B [Randomized H2H]). These analyses will be performed by the central laboratory.

8.3.6.3 Blood Type Assessment (All Subjects)

A blood sample will be collected at Screening. Blood type, Rh, and indirect antiglobulin test (IAT) should be done before the first dose of GEN3014 or daratumumab SC. Subject red blood cell phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first GEN3014 or daratumumab SC administration.

CD38 is expressed at very low levels on erythrocytes. It is known that daratumumab binds to the CD38 on erythrocytes, which results in a positive Indirect Coombs test. This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. The determination of a subject's ABO and Rh blood type is not expected to be affected. It is expected GEN3014 and daratumumab SC will interfere with the Indirect Coombs testing and thus making complete blood typing difficult while subjects are receiving the trial treatment and for at least 6 months after treatment ends.

To be cautious and in case of urgent need for blood transfusions, follow the instruction as below:

- Type and screen subjects prior to the first dose of GEN3014 or daratumumab SC.
- Notify blood transfusion centers of this interference with serological testing and inform blood banks that a subject has received GEN3014 or daratumumab SC.
- Request subjects to carry a card with the blood type at all times during this trial.
- Blood banks can eliminate the daratumumab interference with IAT by treating reagent red blood cells with dithiothreitol (DTT) (Chapuy et al., 2016; Chapuy et al., 2015).

8.3.6.4 SPEP, UPEP, Interference Assay, FLC and IFE (Subjects With RRMM)

Blood and urine samples will be collected for subjects with RRMM, at the time points indicated on Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A), and Table 1-12 (Expansion Part B).

8.3.6.5 Peripheral Blood Assessment (Subjects with R/R AML)

At the time points indicated on Table 1-2 (Dose Escalation) and Table 1-6 (Expansion Part A), blood samples will be collected to assess the AML blast count and CBC with differential including promyelocytes, myelocytes, and metamyelocytes, as described in Section 8.2.2.1.

8.3.7 Constitutional Symptoms (All Subjects)

Constitutional symptoms will be evaluated for all subjects at Screening and before GEN3014 and daratumumab SC administration as indicated by the Schedule of Activities (Section 1.3). Constitutional symptoms include night sweats, weight loss >10% over 6 months, extreme fatigue and/or fever without infection (see Appendix 10.13, B symptoms).

8.4 Adverse Events and Serious Adverse Events

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

Information in this section should be used in conjunction with the additional details provided in Appendix 10.3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.4.1 Definition of Adverse Events and Serious Adverse Events

The definitions of adverse events (AEs), SAEs, adverse events of special interest (AESIs), as well as attribution definitions, severity criteria, special reporting situations, and procedures, are provided in Appendix 10.3.

8.4.1.1 Adverse Events of Special Interest for GEN3014

IRRs will be considered AESIs for GEN3014 (see Appendix 10.3).

8.4.2 Adverse Event Reporting

All AEs, whether serious or non-serious (see definitions in Appendix 10.3), will be documented from the first dose of GEN3014 or daratumumab SC until 30 days after the last dose of GEN3014 or daratumumab SC, subject withdrew consent, subject started new anti-cancer treatment, or the subject died, whichever comes first, as documented in the Schedule of Activities, Section 1.3.

As noted in Section 8.1.3, medical conditions (signs, symptoms, and diagnosis) that occur after the ICF is signed and prior to the first 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).

For details regarding follow-up of AEs and SAEs, see Section 8.4.6, Follow-up of Adverse Events and Serious Adverse Events.

8.4.3 Events Requiring Immediate Reporting

The events that require immediate reporting are detailed in the subsections below.

8.4.3.1 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.
- A grade 3 or grade 4 laboratory abnormality as per CTCAE does not automatically indicate an SAE unless it meets the criteria of an SAE as defined in Appendix 10.3.1. Grade 3 or grade 4 laboratory abnormality if deemed serious per Appendix 10.3.1 must be reported as an SAE when these are assessed as clinically significant by the reporting investigator.

8.4.3.2 Overdose/Medication Errors

GEN3014 overdose is defined as a subject receiving a dose of the trial drug in excess of 10% of that specified in this protocol. All cases of overdose must be reported to the Sponsor within 24 hours of knowledge of the event (see additional details in Section 8.5, Treatment of Overdose). In

case of daratumumab SC overdose, please refer to the daratumumab IB for information. 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 within 24 hours of knowledge of the event.

8.4.3.3 Pregnancy

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

All reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor within 24 hours of knowledge of the event. In the case of pregnancy in the partner of a male subject, a separate ICF will be obtained from the female partner for collection of information regarding the pregnancy.

The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to GEN3014 or daratumumab SC must be promptly reported to the sponsor or designee.

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

8.4.3.4 Adverse Events of Special Interest or Other Events of Interest

8.4.3.4.1 Adverse Events of Special Interest

IRRs will be considered as AESIs for GEN3014; IRRs that are SAEs or of Grade 3 and higher must be reported within 24 hours of the occurrence.

8.4.3.4.2 Other Events of Interest

For daratumumab SC, systemic administration-related reactions (sARR) that are SAEs or of Grade 3 and higher should be reported within 24 hours of the occurrence.

8.4.4 Regulatory Reporting Requirements for Suspected Unexpected Serious Adverse Events (SUSARS)

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met (see Section 8.4.3.1).

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is documented and reported as soon as possible, but within a maximum of 15 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 independent Ethics

Committee (IEC)/Institutional Review Board (IRB) according to the applicable local regulatory requirements. Relevant follow–up information of fatal or life-threatening SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods according to local regulations.

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

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

8.4.5.1 Disease Progression or Death

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be reported as AEs or SAEs.

1. That is, the terms “disease progression,” “progression of disease,” or “malignant disease progression” and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
    - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
    - Clinical symptoms of progression that cannot be determined as reasonably due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study should be reported as an AE or SAE.
2. Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Appendix 10.3.1, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

8.4.5.2 Unrelated Procedures

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

8.4.6 Follow-up of Adverse Events and Serious Adverse Events

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

All SAEs that are ongoing at the safety follow-up visit(s) should continue to be followed on a regular basis until the event has been resolved, until the investigator assesses it as chronic and all queries have been resolved, or until the start of new anti-cancer treatment, whichever comes first.

Only SAEs judged by the investigator as related to trial drug should be reported after the safety follow-up period.

8.4.7 Warnings and Precautions

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

8.5 Treatment of Overdose

Rescue medication to reverse the action of GEN3014 is not available. In case of overdose, medication errors, misuse and/or abuse of the trial drug subjects should receive supportive care according to local guidelines and potential side effects of GEN3014 should be treated symptomatically.

In case of daratumumab SC, please refer to the daratumumab IB for information.

In the event of an overdose, the investigator should:

- Contact the Sponsor's Medical Monitor immediately (see Section 8.4.3, Events Requiring Immediate Reporting).
- Obtain a sample for PK analysis if requested by the sponsor's Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

8.6 Pharmacokinetics

Blood samples will be collected to evaluate the PK of GEN3014 or daratumumab SC at the time points specified in the Schedule of Activities (Section 1.3).

Serum samples will be analyzed to determine concentrations of GEN3014 or daratumumab SC using a validated, specific, and sensitive immunoassay methods under the supervision of the sponsor.

Additional information about the collection, handling, and shipment of samples is included in the laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic assessments/samples will be performed/collected as per the time points specified in the Schedule of Activities (Section 1.3).

8.8 Biomarkers

Samples for biomarker analyses will be collected as specified in the Schedule of Activities (Section 1.3). Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

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

8.8.1 Biomarker Assessments in Bone Marrow and/or Tumor Samples

Bone marrow samples will be collected as described in:

- Table 1-1 (Dose Escalation), Table 1-5 (Expansion Part A), Table 1-13 and Table 1-14 (Expansion Part B) for subjects with RRMM (also see Section 8.2.1.3),
- Table 1-2 (Dose Escalation) and Table 1-6 (Expansion Part A) for subjects with R/R AML (also see Section 8.2.2.2), and
- Table 1-7 (Expansion Part A) for subjects with R/R DLBCL (also see Section 8.2.3.2).

As results for the following assessments rely heavily on having non-hemolyzed bone marrow aspirate provided from subjects, sample collection from the first or second pull of the procedure is highly preferred.

For subjects with R/R DLBCL, an archival tumor biopsy, which is a recently collected tumor biopsy taken prior to enrollment (≤24 months old), or preferably 2 fresh core tumor biopsies collected before treatment with trial drug (ie, during the Screening period) are mandatory for all subjects with accessible tumors, unless medically unfeasible and reviewed and approved by the sponsor. A subject must have either an archival tumor sample OR fresh tumor sample for enrollment unless approval is given by the sponsor. The biopsy can be a whole lymph node or core biopsy. A fine needle aspirate will not be sufficient. All tumor biopsies should be FFPE.

During the trial, if any additional bone marrow aspirates or tumor biopsies are collected that are part of normal clinical practice, these will be examined as described below.

Biomarker analyses in bone marrow aspirates or tumor samples at baseline and during treatment with GEN3014 may help confirm GEN3014's mode of action and enable the identification of biomarkers predictive of response to GEN3014. Bone marrow aspirates or tumor biopsies will be evaluated for target expression (protein or RNA), as well as molecular profiling to identify potential mechanisms of tumor response and/or treatment-induced changes in the immune microenvironment. In the Expansion Part B (Randomized H2H), biomarker observations of subjects treated with GEN3014 may be compared to those of daratumumab-treated subjects in order to understand differences and/or similarities between both mAbs.

8.8.1.1 Immunophenotyping/Protein Expression Analyses

Expression of proteins related to MM or AML biology or GEN3014's mode of action will be evaluated by immunophenotyping bone marrow aspirates at baseline as well as during GEN3014 treatment using multicolor flow cytometry.

Expression of proteins related to MM, AML and/or DLBCL biology or GEN3014's mode of action may also be evaluated in bone marrow and/or tumor biopsies by IHC 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.

CD38 expression as well as expression of membrane-expressed complement regulatory proteins on tumor cells may be determined. Also, frequencies of various immune cell subsets, including NK cells and T cells, in bone marrow aspirates may be determined. Correlation analyses of this protein expression data with pharmacodynamics and efficacy assessments may be performed.

8.8.1.2 DNA/RNA Analyses

RNA sequencing may be performed on bone marrow aspirates or tumor biopsies to determine CD38 RNA expression levels, as well as to evaluate other potential genes associated with CD38 biology, with immune effector cell activation, or with cancer biology in general.

Bone marrow and/or tumor samples may also be analyzed using Next Generation Sequencing (NGS) for analyses of DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements or polymorphisms in genes associated with CD38 expression or function, trial drug's proposed mode of action, or cancer biology.

In addition, to assess MRD status NGS may be used to detect expression of malignant clone Ig gene rearrangements (such as clonoSEQ®) in bone marrow aspirate, tumor/bone marrow biopsy or peripheral blood/plasma as is outlined in Section 8.8.3.

8.8.2 Biomarker Assessments in Blood Samples

Biomarker assessments will also be performed using whole blood samples to investigate potential pharmacodynamic markers and explore the relationship to the efficacy and/or mode of action of GEN3014. In the Expansion Part B (Randomized H2H), biomarker observations of anti-CD38 mAb-naive RRMM subjects treated with GEN3014 may also be compared to those of daratumumab-treated subjects in order to understand differences and/or similarities between both mAbs. Assessments will be performed at baseline (before infusion at Cycle 1 Day 1) and at later cycles during treatment in order to enable correlation analyses with response to treatment or disease biology.

8.8.2.1 Immunophenotyping Analyses

Immunophenotyping will be performed (eg, measurement of NK cells, T cells, B cells, monocytes) at baseline and during treatment at planned visits so changes associated with the mode of action of GEN3014, subject response to GEN3014, and disease biology can be evaluated. CD38 expression in relation to expression of complement regulatory proteins CD46, CD55, and CD59, may be monitored to enable correlation analysis of expression level of these proteins with pharmacodynamic and efficacy assessments.

8.8.2.2 Cytokine Analyses

Pathophysiological biomarkers of infusion reactions, including cytokines IL-1, IL-6, IL-8, IL-10, TNFα, and IFNγ, will be measured to determine whether reported infusion reactions are related to cytokine release events.

8.8.2.3 Complement Analyses

As complement-mediated cytotoxicity is an anticipated key MOA of GEN3014, activation of the complement pathway will be assessed as pharmacodynamics marker potentially predictive of clinical responses. Complement pathway activity will be monitored by CH50 measurements in serum, and individual complement pathway components such as C2 may be monitored in plasma for depletion following complement activation.

8.8.2.4 Proteomics Analyses

The levels of specific proteins (eg, BCMA, granzyme B) in blood samples may be determined at baseline and during treatment at planned visits so changes associated with the mode of action of GEN3014, subject response to GEN3014, and/or disease biology can be evaluated.

8.8.2.5 Exploratory PBMC Analyses

Peripheral blood mononuclear cells (PBMCs) will be collected to perform additional exploratory analyses that could increase our understanding of the MOA of GEN3014, subject response to GEN3014 and disease biology.

If an increase in total T-cell number is observed following treatment with GEN3014, T-cells within the exploratory PBMC sample may be assessed for changes in T-cell receptor clonality. Increased T cell clonality may indicate induction of an adaptive immune response by GEN3014. Correlation analyses of T cell clonality with response may be performed.

Also, CD38 occupancy by GEN3014 in PBMCs may be monitored to enable correlation analysis of GEN3014 binding with pharmacodynamic and efficacy assessments.

8.8.2.6 DNA/RNA Analyses

DNA/RNA samples will be collected and analyzed as part of exploratory research to help identify markers of response or resistance to treatment. They may be analyzed for DNA/RNA aberrations such as DNA mutations, gene expression levels, copy number variations, microsatellite instability, indels, gene polymorphisms and/or rearrangements in genes. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

On circulating tumor-derived DNA (ctDNA) samples, the ctDNA may be quantified as well as analyses such as DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements in genes may be performed to evaluate the association of such biomarkers with GEN3014's mode of action, subject response, or disease biology.

A genomic DNA control (saliva) sample (see Table 1-3 [Dose Escalation], Table 1-8 [Expansion Part A], Table 1-13 [GEN3014-treated subjects – Expansion Part B], and Table 1-14 [daratumumab SC-treated subjects – Expansion Part B]) is requested at Screening to confirm the tumor specificity of any genomic alterations that are identified.

In addition, to assess MRD status NGS will be used to detect expression of malignant clone-specific DNA sequences (such as clonoSEQ®) in peripheral blood/plasma as is outlined in Section 8.8.3.

Where required by local law, a separate ICF will be used for DNA/RNA research. If DNA/RNA research evaluations are performed, the results may be reported in a separate report.

8.8.3 Minimal Residual Disease Analysis

MRD will be assessed by tracking the presence of tumor-cell specific DNA. For RRMM and R/R DLBCL subjects, DNA will be tracked that encodes the B-cell receptor (BCR) that is expressed specifically by the cancer cells. For subjects with R/R AML, DNA will be tracked that contains a combination of mutations and/or other DNA aberrations that is specific to the cancer cells.

The cancer-cell specific DNA will be identified in the bone marrow (BM) aspirate (RRMM, R/R AML) or tumor biopsy (R/R DLBCL) that is requested at Screening using NGS. After start of

treatment, bone marrow aspirate (RRMM, R/R AML) and/or blood (RRMM, R/R AML, R/R DLBCL) samples are requested at fixed time points 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. These samples are requested at the fixed time points and at time of CR (refer to Appendix 10.9), as outlined in Table 1-4 (Dose Escalation), Table 1-9 (Expansion Part A), and Table 1-15 (Expansion Part B) for subjects with RRMM; Table 1-10 (Expansion Part A) for subjects with R/R AML; and Table 1-11 **(**Expansion Part A) for subjects with R/R DLBCL.

As an exploratory analysis, when a subject reaches a CR, a portion of the samples collected to confirm CR will be used to assess MRD. Additionally, DLBCL subjects having bone marrow involvement documented at Screening will have a portion of the aspirate collected to confirm CR used to assess MRD. DLBCL subjects having no bone marrow involvement at Screening, will not require further bone marrow examination for MRD.

8.9 Immunogenicity

Venous blood samples will be drawn for analysis of anti-drug antibodies (ADAs) as per the time points specified in the Schedule of Activities (Section 1.3). Serum samples will be screened for ADAs binding to trial drug and the titer of confirmed positive samples will be reported. Neutralization characterization of ADAs may also be performed using appropriate methods.

9 STATISTICAL CONSIDERATIONS

The statistical analysis of the data collected in this trial is the responsibility of the sponsor. The objectives and endpoints for the 3 trial parts are tabulated in Table 3-1 (Dose Escalation), Table 3-2 (Expansion Part A [GEN3014 Single Cohorts]), and Table 3-3 (Expansion Part B [Randomized H2H]). This section will (without particular reference to trial part) outline the planned analysis for each endpoint. The analyses will be detailed further in the Statistical Analysis Plan (SAP) to be finalized before database lock.

All presentations will be done separately for the different trial parts. Subjects in the Dose Escalation part will be analyzed according to the DL received. Subjects in Expansion Part A (GEN3014 Single Cohorts) will be analyzed according to their assigned expansion cohort. Subjects in Expansion Part B (Randomized H2H) will be analyzed according to their assigned treatment.

Statistical deliveries (tables, listings and figures) may be produced for the following milestones:

- Periodic DMC reviews
- **Dose Escalation**: Primary safety and efficacy analyses will be conducted on all subject data at the end of the escalation, at latest 6 months after last patient first dose. Separate deliveries may be planned for the RRMM and R/R AML disease cohorts as feasible.
- **Expansion Part A (GEN3014 Single Cohorts)** consists of 4 parallel cohorts:
    - Anti-CD38 mAb-naive RRMM cohort
    - Anti-CD38 mAb-refractory RRMM cohort
    - R/R DLBCL cohort
    - R/R AML cohort

  Each cohort will assess the disease-specific anti-tumor activity of GEN3014. No comparisons between cohorts are planned. Each cohort may report its individual primary analysis. The primary analyses will be conducted on all subject data, at latest 6 months after last patient first dose in respective expansion cohort. Timing of futility analyses in DLBCL cohort is described below.

- **Expansion Part B (Randomized H2H)** in anti-CD38 mAb-naive RRMM subjects: Primary safety and efficacy analyses will be conducted on all subject data, at latest 6 months after last patient first dose.
- The final analyses will be reported as an addendum to the primary analyses, based on the accumulated data up to 5 years after study start.

9.1 Statistical Hypotheses

Objectives and endpoints of the trial are stated in Section 3. There are no pre-defined hypotheses for this trial. The escalation part is designed to determine the RP2D and MTD (if reached), and the Expansion Part A to assess the anti-tumor activity of GEN3014.

In the Expansion Part B (Randomized H2H), the response ratio and the geometric mean ratio of C_{trough} on Cycle 3 Day 1 will be derived to describe the proportion of effect of daratumumab SC

retained by GEN3014 IV as compared to daratumumab SC. The comparison serves as a preliminary estimation of the relative effect of the 2 anti-CD38 mAb molecules.

9.2 Sample Size Determination

9.2.1 Dose Escalation

9.2.1.1 RRMM Escalation Cohort

The escalation algorithm is described in Section 4.1.2. The planned sample size in the escalation part will be up to 54 subjects: up to 9 subjects can (in theory) be dosed at each of the 6 planned DLs before the mBOIN algorithm stops. The actual number of subjects who will be dosed depends primarily on the true underlying rate of DLT, as well as potential administrative decisions taken by the DEC and SC during the escalation.

To gain insight in how different underlying DLT rates affects the number of subjects dosed, 6 different toxicity scenarios have been used to simulate DLTs and then following the algorithm laid out in Section 4.1.2. The mean number of subjects dosed at each DL, the total mean and the 95% quartile of number of subjects across 100,000 simulations are tabulated in Table 9-1. The sample size does not account for additional subjects in parallel cohorts.

Table 9-1 Modified BOIN Characteristics for RRMM Dose Escalation Cohort

Simulation Scenario		DL1	DL2	DL3	DL4	DL5	DL6	Total mean	N_{95}
1	Prob(DLT)	0%	1%	2%	3%	4%	5%	-	-
	Prob(explored)	100%	100%	100%	100%	100%	100%	-	-
	n* (when explored)	1.0	1.1	3.2	3.3	3.4	9.0	20.9	25
2	Prob(DLT)	1%	2%	3%	4.5%	6%	10%	-	-
	Prob(explored)	100%	100%	100%	100%	99%	98%	-	-
	n* (when explored)	1.1	1.1	3.3	3.5	3.8	9.0	21.6	26
3	Prob(DLT)	1%	5%	7.5%	12.5%	17.5%	20%	-	-
	Prob(explored)	100%	100%	100%	98%	92%	78%	-	-
	n* (when explored)	1.1	1.4	4.0	4.8	5.4	8.8	23	31
4	Prob(DLT)	5%	15%	20%	25%	30%	40%	-	-
	Prob(explored)	100%	99%	94%	76%	53%	31%	-	-
	n* (when explored)	1.6	3.0	5.9	6.5	7.2	7.6	21.3	32
5	Prob(DLT)	1%	5%	15%	25%	30%	45%	-	-
	Prob(explored)	100%	100%	100%	90%	63%	36%	-	-
	n* (when explored)	1.1	1.8	5.6	6.6	7.5	7.2	21.6	32
6	Prob(DLT)	15%	27.5%	32.5%	40%	50%	60%	-	-
	Prob(explored)	100%	94%	75%	39%	14%	3%	-	-
	n* (when explored)	3.3	5.3	7.0	7.2	6.4	5.5	17.4	27

n*=average number of subjects; BOIN=Bayesian Optimal Interval; DLT=Dose-Limiting Toxicity; N_{95}=95% quantile of number subjects dosed across 100,000 simulations; Prob=probability; RRMM=relapsed or refractory multiple myeloma.

For the safer toxicity profiles (Scenario 1 and 2) the escalation is expected to escalate with 1 cohort per DL: approximately 1 subject each at the 2 lowest DLs, and 3 on the remaining, except for the highest where (the maximum) 9 are dosed. The probability to explore each DL is close to 100%. As the toxicity increases the probability to explore a more toxic levels decreases, as expected from the mBOIN rules in Section 4.1.2.

In the 100,000 simulations the average total number of subjects across the different simulation scenarios lies between approximately 18 and 23 subjects. The largest N_{95} quantile across the scenarios is observed for Scenario 4. The likelihood that the number of subjects in this scenario would exceed 32 is 5%.

9.2.1.2 R/R AML Escalation Cohort

Summary statistics based on 100,000 simulations given 5 different toxicity profiles for the (minimum) 3 planned DLs to be tested in R/R AML are presented in Table 9-2. As observed for the RRMM escalation cohorts, the more toxic a DL is assumed to be, the less the likelihood is to dose subjects at that DL. There is no accelerated titration planned, the initial cohort size is 3.

The mean total number of subjects is approximately 10 to 13 subjects depending on the underlying toxicity profile, with the largest N_{95} quantile at 18 (eg, the maximum number of R/R AML subjects for escalation, excluding potentially parallel cohorts).

Table 9-2 Modified BOIN Characteristics for R/R AML Dose Escalation Cohort

Simulation Scenario		DL1	DL2	DL3	Total mean	N_{95}
1	Prob(DLT)	0%	7.5%	15%	-	-
	Prob(explored)	100%	100%	94%	-	-
	n* (when explored)	3.1	3.8	6.0	12.5	15
2	Prob(DLT)	5%	10%	20%	-	-
	Prob(explored)	100%	97%	88%	-	-
	n* (when explored)	3.5	4.1	5.9	12.7	15
3	Prob(DLT)	15%	25%	33%	-	-
	Prob(explored)	100%	81%	49%	-	-
	n* (when explored)	4.4	5.0	5.6	11.2	18
4	Prob(DLT)	20%	30%	40%	-	-
	Prob(explored)	100%	71%	35%	-	-
	n* (when explored)	4.6	5.2	5.4	10.2	15
5	Prob(DLT)	20%	35%	55%	-	-
	Prob(explored)	100%	71%	28%	-	-
	n* (when explored)	4.8	5.4	4.9	10.0	15

n*=average number of subjects; BOIN=Bayesian Optimal Interval; DLT=dose-limiting toxicity; N_{95}=95% quantile of number subjects dosed across 100,000 simulations; Prob=probability; R/R AML=relapsed or refractory acute myeloid leukemia.

9.2.2 Expansion Part A (GEN3014 Single Cohorts)

The cohorts in Expansion Part A are hypothesis generating, used to further explore the safety and disease-specific anti-tumor activity of GEN3014. Sample sizes are limited to 10 to 20 subjects. This is true for all cohorts, except for the R/R DLBCL cohort, wherein a Simon's 2-stage design is used (see Section 9.5.2) at a sample size of 40 subjects.

9.2.3 Expansion Part B (Randomized H2H): Comparison of GEN3014 IV vs Daratumumab SC in Anti-CD38 mAb-naive RRMM Subjects

The comparison of the 2 anti-CD38 mAb molecules will be based on 40 subjects randomized to GEN3014 IV vs 40 subjects randomized to daratumumab SC. The ratio in the response rates between the 2 arms will described using the Miettinen-Nurminen method (Newcombe, 1998).

9.3 Populations for Analyses

Full Analysis Set (FAS): The FAS and safety set are defined in the same way and will comprise all enrolled subjects who receive at least 1 dose of trial drug (GEN3014 or daratumumab SC). In case of any deviations from planned dosing, subjects will be treated as per actual dosing.

The FAS will be used to summarize efficacy and safety analyses.

Response Evaluable Set (RES): Compromises all subjects in the FAS that at the timing of data cutoff date (for any interim reporting of the ongoing data):

- have measurable disease at baseline;
- had ≥1 on-treatment disease assessment;
- have died within 60 days of first trial treatment without post-baseline disease assessment (these are included as non-responders)

Safety Set: See definition for FAS.

Per-Protocol Set: Not applicable

Dose-Determining Analysis Set (DDS): The DDS will include all FAS subjects in the Dose Escalation part who meet the minimum exposure criterion and have sufficient safety evaluations, or experience a DLT during the first 28 days of dosing (ie, in Cycle 1).

A subject will meet the minimum exposure criterion if the subject receives 4 out of the 4 preplanned doses during the DLT period. (The 2 initial split doses in Day 1 and Day 2 account for 1 preplanned dose.)

Pharmacokinetic Analysis Set 1 (PAS1): The PAS1 will include all enrolled subjects who receive at least 1 dose of trial drug (GEN3014 or daratumumab SC) and who provide at least 1 evaluable PK sample.

Pharmacokinetic Analysis Set 2 (PAS2): The PAS2 will include all enrolled subjects who received all 8 weekly GEN3014 or daratumumab SC doses in Cycles 1 and 2 with the cumulative dose administered amounting to 80% to 125% of the planned dose, and provided a predose PK blood sample on Cycle 3 Day 1.

Immunogenicity Analysis Set (IAS): The IAS will include all enrolled subjects who receive at least 1 dose of trial drug (GEN3014 or daratumumab SC) and have a baseline and at least 1 evaluable on-treatment ADA sample.

Biomarker Analysis Set (BAS): The BAS will include all enrolled subjects who receive at least 1 dose of trial drug (GEN3014 or daratumumab SC) and have at least 1 evaluable biomarker sample.

9.4 Statistical Analyses

9.4.1 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 history and current medical history at baseline will be summarized by system organ class and preferred term, by cohort or expansion cohort, depending on part.

9.4.2 Exposure to Trial Drug and Concomitant Medications

The duration of exposure in months to GEN3014 or daratumumab SC 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 and significant non-drug therapies prior to and after the start of the trial treatment will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system.

9.4.3 Efficacy Analyses

The response assessment, eg, for the primary endpoint of ORR in expansion, is disease specific:

- The response in RRMM Cohorts will be assessed following The International Myeloma Working Group consensus criteria (IMWG) 2016 (Kumar et al., 2016)
- The response in the R/R DLBCL Cohort will be assessed following the revised response criteria for Hodgkin and non-Hodgkin lymphoma (Lugano classification) (Cheson et al., 2014)
- The response in the R/R AML Cohort will be assessed following The International Working Group (IWG) response criteria for AML (Cheson et al., 2003)

9.4.3.1 Objective Response Rate and Clinical Benefit Rate

ORR is defined as the proportion of subjects with a partial response, or better. Summaries of eg, VGPR and CBR will be provided with ORR as appropriate.

Disease-specific best overall response (BOR) will be summarized in conjunction with the ORR. The estimated rates and the exact 2-sided 95% confidence intervals (CI) (using the Clopper-Pearson method) will be summarized. Individual subject data listings will be provided.

The ORR for subjects treated with GEN3014, as compared to the ORR in subjects treated with daratumumab SC in the Expansion Part B with anti-CD38 mAb-naive RRMM subjects, will be presented by the response ratio and the corresponding 2-sided 95% confidence interval based on the Miettinen-Nurminen method (Newcombe, 1998). P values will not be presented.

9.4.3.2 Duration of Response

DOR is defined as time from first response (PR or better) to timing of disease progression or death (due to any cause), whichever comes first. The analysis only applies to those with a response (PR or better).

Date of progression will be censored as planned for progression-free survival (PFS).

DOR distribution will be estimated using the Kaplan-Meier method, and the survival curve, median and 95% CI of the median will be presented. If there are too few responders, this analysis may be omitted. Individual subject data listings will be provided.

9.4.3.3 Time-to-Response

Time-to-response (TTR) is defined as the time from date of first dose, or date of randomization for subjects in the Expansion Part B, to time of response (PR or better). TTR will be summarized and presented descriptively for those with a response (PR or better).

9.4.3.4 Progression-Free Survival

PFS is defined as the time from the date of first dose, or date of randomization for subjects in the Expansion Part B, to the date of progression or death (due to any cause), whichever comes first. PFS will be censored similar to Table C1 in Appendix C in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-small Cell Lung Cancer Drugs and Biologics (FDA-Guidance, 2015), with further details to be provided in the SAP.

The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented. 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.

9.4.3.5 Overall Survival

Overall survival (OS) is defined as the time from the date of first dose, or date of randomization for subjects in the Expansion Part B, to the date of death due to any cause. Subjects who withdrew consent to study or are lost to follow up will be censored at the latest date the subject was known to be alive (on or before the cutoff date).

The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, first and third quartiles and 95% CIs of the medians will be presented. 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.

9.4.3.6 Time to Next Therapy

Time to next therapy (TTNT) for subjects in the Expansion Part B is defined as the time from randomization to the start of subsequent anti-cancer therapy. Death due to PD without start of subsequent therapy will be considered as an event. Subjects who withdrew consent to study or are lost to follow up or die due to causes other than disease progression will be censored at their last disease assessment.

TTNT will be summarized similarly to OS.

9.4.4 Exploratory Analysis

9.4.4.1 Rate and Duration of MRD-Negative Remission

The rate of MRD-negative remission is defined as the proportion of subjects with at least 1 MRD-negative sample. MRD-negative remission applies to RRMM in both the Dose Escalation and the Expansion, but only applies to R/R AML and R/R DLBCL in the Expansion.

Duration of MRD-negative remission is defined as the number of days from the date of the first documented MRD-negative sample to the date of MRD status change (not MRD-negative). This will be censored and analyzed using the same statistical methodology as for PFS.

9.4.5 Safety Analyses

9.4.5.1 Adverse Events

Summary tables for AEs will include only AEs that started, or pre-existing AEs that worsened, during the on-treatment period, ie, TEAEs.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term; intensity based on grades of NCI-CTCAE v5.0 for all AEs (except for clinical TLS which is graded by the Cairo-Bishop classification); type of AE; and relationship to trial treatment.

Treatment-emergent SAEs 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 pretreatment and post-treatment period will be flagged.

Further summaries of AEs will be specified in the SAP.

Adverse Events of Special Interest

Adverse events of special interest constitute the IRRs. These will be summarized as part of the other TEAEs. Symptoms of IRRs as collected in the eCRF may be provided in listings.

9.4.5.2 Clinical Laboratory Tests

Grading of laboratory values will be assigned programmatically as per NCI-CTCAE v5.0. 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.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the 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 grade.

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.

9.4.5.3 Vital Signs

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

9.4.5.4 ECG Parameters

Triplicates of 12-lead ECGs including PR, QRS, QT, heart-rate-corrected QT intervals using Fridericia's correction (QTcF), and RR intervals will be obtained for each subject. 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 (by cohort).

9.4.6 Pharmacokinetic Analyses

The PAS1 will be used for the analyses presented in this section.

Individual curves of concentration of trial drug vs time, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. The following PK parameters may be calculated based on the availability of data using non-compartmental methods:

- Maximum (peak) observed serum drug concentration (C_{max});
- Time to reach maximum (peak) serum drug concentration (t_{max});
- Area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to 168 h ($AUC_{0\text{-}168h}$);
- Predose concentrations (C_{trough}); and
- Subject-wise accumulation ratios in C_{max} ($R_{A,Cmax}$), AUC ($R_{A,AUC}$) and C_{trough} ($R_{A,Ctrough}$) between Cycle 1 and Cycle 2 and in C_{trough} between Cycle 1 Day 8 and Cycle 3 Day 1.

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

If deemed applicable, compartmental (population) PK modeling approaches will be applied. The results of the compartmental modeling will be documented outside the scope of the Clinical Study Report (CSR).

9.4.6.1 Cycle 3 Day 1 Trough Concentration

The PAS2 will be used for the analyses presented in this section.

The C_{trough} on Cycle 3 Day 1 is defined as a secondary endpoint in Expansion Part B, as part of the comparison of the 2 anti-CD38 mAb molecules. The C_{trough} levels in the 2 arms will be compared by calculating the geometric mean ratio and the corresponding 90% CI.

9.4.7 Pharmacodynamic Analyses

Pharmacodynamic analyses are designed to identify DLs at which GEN3014 is biologically active and to confirm the expected MOA of the drug (based on nonclinical studies) in human subjects. In the anti-CD38 mAb-naive RRMM Expansion Part B, similar analyses may be performed on subjects treated with daratumumab SC in order to compare these with GEN3014 IV observations and identify differences and/or similarities in pharmacodynamic activity of both compounds.

Pharmacodynamic studies will include immunophenotyping analyses of the frequencies of NK cells and other leukocyte subsets as well as cytokine and complement analyses in peripheral blood. Curves of concentration of a pharmacodynamic marker vs time will be presented.

9.4.8 Biomarker Analyses

The BAS will be used for the analyses presented in this section.

The biomarker studies are designed to identify markers predictive of response (or resistance) to GEN3014. Correlation of baseline expression levels, or on-treatment changes in expression levels, with response, may identify responsive (or resistant) subgroups in addition to genes and pathways of which activity is altered following treatment with GEN3014. In the anti-CD38 mAb-naive RRMM Expansion Part B, biomarker observations of subjects treated with GEN3014 IV may be compared to those of daratumumab SC-treated subjects in order to understand differences and/or similarities between both mAbs.

Any biomarker measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose.

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

9.4.9 Immunogenicity Analyses

The IAS will be used for the immunogenicity analysis.

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 (C_{max}, AUC, C_{trough}) and the association between positive/non-positive ADA and major safety signals (CTCAE $\geq$ grade 3) will be explored. The association with clinical response will be explored in Expansion cohorts only.

9.4.10 Multiplicity

As the trial does not address a hypothesis per se, there is no multiplicity to correct for.

9.5 Interim Analyses

9.5.1 Expansion Part A – Anti-CD38 mAb-Naive RRMM Cohort

As outlined in Section 4.1.3, data from the initial 10 anti-CD38 mAb-naive RRMM subjects belonging to the RES who received GEN3014 (at 16 mg/kg or 24 mg/kg) from the Dose Escalation and/or from the Expansion Part A, will be reviewed by the Safety Committee and DMC when they have completed ≥2 cycles of treatment. If 2 or more out of the initial 10 subjects respond to GEN3014, the comparison vs daratumumab SC will be initiated.

Should the true underlying response rate be 40%, the probability to have 2 or more responders in 10 subjects is 95%. That is, it would be very unlikely to have 0 or 1 responders (in 10 evaluated) under the assumption of a response rate of 40%.

9.5.2 Expansion Part A – R/R DLBCL Cohort

The maximum sample size in the R/R DLBCL expansion cohort is set to 40 subjects. In order not to expose R/R DLBCL subjects to a potentially non-efficacious GEN3014 RP2D dose, an ongoing and non-binding interim futility analysis will be conducted based on the response data from the initial 20 subjects belonging to the RES. The timing of the interim analysis is when the initial 20 subjects have completed ≥2 cycles of GEN3014 treatment. The totality of the data (including efficacy, safety, and PK) will be evaluated by the sponsor Safety Committee, which decides if enrollment should be stopped or continued.

The SADAL trial reported an ORR of 28% (36/127; 95% CI 20.7-37.0)(Kalakonda et al., 2020) which led to approval of XPOVIO in R/R DLBCL subjects. For the purpose of signal finding in heavily pre-treated DLBCL patients the undesirable response rate for GEN3014 is set to 20% and the desirable response rate is set to 40%. With a Simon's 2-stage design (with type I error rate of 4.04% and power of 85.39%) at least 5/20 responders are needed to pass the futility bar. At least 13/40 responders are needed to consider GEN3014 having a potential in DLBCL who have exhausted SOC.

9.6 Safety Stopping Guidance for Expansion Cohorts

Pocock's flexible alpha-spending method will be used as a stopping guidance for each expansion cohort (Ivanova et al., 2005). For each individual cohort, the overall significance level to stop further treatment due to safety concern is set to 5%. Table 9-3 through Table 9-6 provide stopping guidance for the different disease cohorts treated with GEN3014 in expansion (does not include subjects treated with daratumumab SC). (The nominal P values will be adjusted if the information rates deviate from the planned.)

For the grade 4 treatment-related AEs, the same acceptable rate of 10% is adopted for all expansion cohorts. Treatment-related deaths may occur with a slightly higher rate in the AML cohort as compared to the MM and DLBCL cohorts. For AML, if data indicate a treatment-related death rate exceeding 5%, stopping the expansion cohort will be considered. For MM and DLBCL, if data indicate a treatment-related death rate exceeding 1%, stopping the expansion cohort will be considered.

Table 9-3 Stopping Guidance for RRMM anti-CD38 mAb-naive

	n=5	n=10	n=20	n=35	n=50
Grade ≥4 Treatment-Related AE	4	4	6	8	10
Treatment-Related Death	3	3	4	6	7

AE=adverse event; CD=cluster of differentiation; mAb=monoclonal antibody; RRMM=relapsed or refractory multiple myeloma.

Table 9-4 Stopping Guidance for RRMM anti-CD38 mAb-refractory

	n=5	n=10	n=20
Grade ≥4 Treatment-Related AE	3	4	6
Treatment-Related Death	3	3	4

AE=adverse event; CD=cluster of differentiation; mAb=monoclonal antibody; RRMM=relapsed or refractory multiple myeloma.

Table 9-5 Stopping Guidance for R/R DLBCL

	n=5	n=10	n=20	n=40
Grade ≥4 Treatment-Related AE	3	4	6	9
Treatment-Related Death	2	2	2	3

AE=adverse event; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma.

Table 9-6 Stopping Guidance for R/R AML

	n=5	n=10	n=20
Grade ≥4 Treatment-Related AE	3	4	6
Treatment-Related Death	2	3	4

AE=adverse event; R/R AML=relapsed or refractory acute myeloid leukemia.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

The principles of the Declaration of Helsinki, the consolidated ICH-GCP, and applicable regulations and national law(s) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

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

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

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

10.1.1 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6(R2), and applicable regulatory and country-specific requirements. This includes supervision of the trial and staff. Delegation of responsibilities should be to only qualified staff and should be documented. In case the investigator is unavailable (eg, on vacation), the investigator should assure that a qualified, trained deputy physician is available for medical care of the subjects. Handover of information must be ensured and documented. The investigator shall notify the sponsor of any serious breach of ICH GCP E6(R2), the protocol or any regulation where required immediately.

10.1.2 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given written approval of the final protocol, amendments to the protocol (if applicable), the ICF, applicable recruiting materials, 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.

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

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

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

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

10.1.3 Financial Disclosure

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

10.1.4 Administrative Procedures

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in the Sponsor's Medical Monitor or contact information). Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

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

Regulatory Documentation

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

Subject Identification, Enrollment, and Screening Logs

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

The subject identification log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the sponsor or any third parties. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by their subject number (or Screening number if not enrolled).

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

10.1.5 Informed Consent Process

The ICF(s) that is/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 ICF should be in accordance with principles that originated in the Declaration of Helsinki, ICH GCP E6(R2), applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects (or his/her legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail.

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

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

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

Subjects (or his/her legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) and EU General Data Protection Regulation (GDPR) requirements, where applicable, and the IRB/IEC or trial center. The investigator or authorized person obtaining the informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the subject.

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

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.

Subjects who are rescreened are required to sign a new ICF if updates have been made since signing the most recent ICF.

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

10.1.6 Data Protection

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

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

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

Additional technical security measures implemented include that:

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

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

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

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

The subject has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including any other relevant

agreement and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

10.1.7 Committees Structure

Dose Escalation Committee and Safety Committee:

The DEC will be chaired by the sponsor's Responsible Medical Officer (or delegate) and membership will include investigator(s), a sponsor clinical scientist, a safety physician, a statistician, a clinical pharmacologist, and other sponsor staff, as appropriate. The DEC will meet at regular frequency throughout the Dose Escalation part.

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

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

Documentation of meeting outcomes will be maintained by the sponsor. Decisions will be communicated to investigators and decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities, as required.

Sponsor/the Safety Committee will consider the recommendation made by the DEC and make the final decision regarding dose escalation (or de-escalation). The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in subject benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

Data Monitoring Committee:

A DMC will be established to ensure the continuing safety of the subjects enrolled in this trial. This committee will consist of medical experts in the relevant therapeutic area; committee membership responsibilities, authorities, and procedures will be documented in its charter.

The committee will review the totality of safety information on an ongoing and periodic basis, and make recommendations accordingly.

10.1.8 Dissemination of Clinical Trial Data

The results of the trial will be reported in a CSR generated by the sponsor and will contain data from all trial sites that participated in the trial as per protocol. Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Exploratory DNA, pharmacodynamic, biomarker, PK, and immunogenicity 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.

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

Data Quality Management

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

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

Record Retention

In compliance with ICH GCP E6(R2), the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH GCP guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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.

Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial-site visit log that will be kept at the trial-site. The first post-initiation visit will be made as soon as possible after enrollment (ie, the first subject has signed the ICF) has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with

local regulations, eg, in the event of a national emergency, and in agreement with the investigator, remote source data verification or source data review may be performed.

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

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

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 principal investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designees.

Similar procedures for inspections may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection. Regulatory Inspectors must be allowed direct access to original medical records (source data/documents).

10.1.10 Source Documents and Case Report Form Completion

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, as described in the monitoring guidelines (or equivalent) and captured in a source data verification log at the site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. Signed and dated ICFs will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each subject:

- Subject’s name and date of birth.
- Screening/randomization number.

- Trial identification.
- Confirmation of eligibility for participation in the trial, including diagnosis.
- Medical history.
- Date of each visit.
- Any assessment performed eg, results of safety and efficacy evaluations.
- Concomitant medications.
- Occurrence of any AEs/SAEs (including description and duration).
- Receipt, preparation, 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.

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

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

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

Case Report Form Completion

Case report form (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 eCRF as soon as possible after the data are available. Source data and the eCRFs 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.

10.1.11 Trial and Site Start and Closure

The first act of recruitment is the first subject Screening visit and will be the trial start date.

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given to the sponsor in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's guidance documents/trial plans, ICH GCP E6(R2), and applicable regulatory requirements.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further trial drug development. The sponsor may, based on available data, discontinue further development of GEN3014. Following trial termination, the sponsor will make their best effort to provision post-trial access to GEN3014 for those ongoing trial subjects with a potential treatment benefit, in accordance with local laws and requirements.

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

10.1.12 Liabilities and Insurance

The sponsor is responsible for taking out relevant clinical trial insurance in accordance with local law and regulations.

10.1.13 Publication Policy

All information, including but not limited to information regarding GEN3014 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory 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. CROs involved in the trial are not permitted to publish without the sponsor’s prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN3014, 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 CSR generated by the sponsor and will contain data from all trial sites that participated in the trial. 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 for the CSR (eg, when a signature by a coordinating investigator is required). Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2010; ICMJE, 2019), the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the pre-specified and approved publication plan. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the current version of 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' (ICMJE Recommendations) http://www.icmje.org/recommendations/, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work.

Registration of Clinical Trials and Disclosure of Results

It is the responsibility of Genmab to register the trial in an appropriate public registry according to applicable regulations (eg, www.ClinicalTrials.gov; a website maintained by the National Library of Medicine at the US National Institutes of Health; trial registration may occur in other registries in accordance with local regulatory requirements). A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed. The laboratory reports must be filed with the source documents.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5. Evaluation of subject eligibility must be evaluated based on central laboratory data.

Furthermore, local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions. The tests to be performed at central and local laboratories are detailed in Table 10-1. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Local laboratory values for biochemistry, hematology, and coagulation must be obtained within 3 days prior to the first dose of each subject and reviewed prior to the first dose to ensure that the subject is still eligible. For subsequent doses, these laboratory values must be obtained the day before or on the day of each trial drug administration and reviewed by the investigator prior to each trial drug administration, to ensure the subject can be dosed according to the dosing instructions defined in the protocol.

For AE reporting of laboratory test abnormalities refer to Appendix 10.3.3.

Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-Required Laboratory Assessments

Test Category	Notes
All Subjects - Local Laboratory	
Hematology	Hemoglobin, hematocrit, CBC including WBC differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes [absolute values for differential are preferred]) reticulocytes and platelets
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, bicarbonate, LDH, calcium, chloride, magnesium, inorganic phosphorus (phosphate), sodium, potassium, creatinine, total and direct bilirubin, BUN or urea, uric acid, glucose (non-fasting), total protein
Coagulation	INR, aPTT, PT, fibrinogen
Urinalysis	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, specific gravity.
β2-microglobulin	At Screening only.
Pregnancy test (serum or urine)	For female subjects with reproductive potential, a serum pregnancy test (β-hCG) should be performed at Screening, and a urine or serum test at the start of each cycle and at the end of treatment visit.
Serology	• At Screening only. • HBV: HbsAg, anti-HBs, and anti-HBc. • HCV: HCV antibody. If positive serology PCR for HCV-RNA to be performed. • CMV serology (IgG and IgM) at Screening. If positive, further surveillance, ie, PCR for CMV-DNA to be performed at the investigator's discretion. • HIV: Performed at Screening only if required per local health authorities or institutional standards.
Tumor lysis (TLS) sample	Uric acid, potassium, inorganic phosphorus (phosphate), calcium, and serum creatinine.
Bone marrow biopsy and/or aspirate	For subject response assessments, perform locally, a portion will be sent to central laboratory (see below).
Blood type assessment	At Screening only. See Section 8.3.6.3.
Cytogenetics	At Screening only. For subjects with RRMM see Section 8.1.2.1, R/R AML see Section 8.1.2.2, and R/R DLBCL see Section 8.1.2.3.
Molecular mutational status	At Screening only. For subjects with RRMM see Section 8.1.2.1, R/R AML see Section 8.1.2.2, and R/R DLBCL see Section 8.1.2.3.
All Subjects - Central Laboratories	
PK	
ADA	
Biomarkers	
MRD/ctDNA	- For subjects with RRMM, collect in Dose Escalation and Expansion. - For subjects with R/R AML or R/R DLBCL, only collect in Expansion.
Genomic DNA-seq control sample (saliva)	At Screening only. See Section 8.8.2.6.

(continued on next page)

Subjects with RRMM	
Local Laboratory	
Serum calcium corrected for albumin	From biochemistry panel. See Appendix 10.7 for formula to perform calculation.
Quantitative serum Ig panel (IgA, IgG, IgM, IgE, and IgD)	At Screening only.
Central Laboratories	
SPEP and UPEP (24-h urine sample) and interference assay sample	At Screening and time points listed on Table 1-1, Table 1-5, and Table 1-12.
Serum FLC and serum/urine IFE	
Bone marrow aspirate	To confirm CR/sCR, assess MRD, and for biomarker evaluations
Subjects with R/R AML	
Local Laboratory	
Peripheral blood assessment	AML blast cell count and CBC with differential including promyelocytes, myelocytes, and metamyelocytes.
Immunoglobulins (IgA, IgG, IgM)	At Screening only.
Bone marrow assessment	Bone marrow assessment for diagnosis and response.
Central Laboratories	
Bone marrow aspirate	
Subjects with R/R DLBCL	
Local Laboratory	
Immunoglobulins (IgA, IgG, IgM)	At Screening only.
Central Laboratories	
-	

ADA=anti-drug antibody; ALT=alanine aminotransferase; AML=acute myeloid leukemia; anti-HBc=antibodies to the hepatitis B core antigen; anti-HBs=antibodies to the hepatitis B surface antigen; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; CBC=complete blood count; CMV=cytomegalovirus; CR=complete remission; ctDNA=circulating tumor-derived deoxyribonucleic acid; DNA=deoxyribonucleic acid; FLC=free light chain; h=hour(s); HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IFE=immunofixation; Ig=immunoglobulin; INR=international normalized ratio; LDH=lactate dehydrogenase; MRD=minimal residual disease; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PT=prothrombin time; RNA=ribonucleic acid; R/R AML=relapsed or refractory acute myeloid leukemia; R/R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response; seq=sequencing; SPEP=serum protein electrophoresis; TLS=tumor lysis syndrome; UPEP=urine protein electrophoresis; WBC=white blood cell.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions

Definition of Adverse Events

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

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

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 one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

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

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

- Routine treatment or monitoring of the underlying disease
- Solely due to progression of the underlying 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 a SAE given above is not an SAE.

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. IRRs will be considered AESIs for GEN3014. Other AESIs are defined on the basis of an ongoing review of the safety data.

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 end of the GEN3014 infusion. For IRRs, the causality of the event should be judged as "related" by the investigator.

10.3.2 Reporting Period

This is trial specific and defined in Section 8.4.1 Adverse Event Reporting.

Events requiring immediate reporting are listed in Section 8.4.3.

10.3.3 Procedures for Recording and Reporting

All AEs, serious or non-serious, must be documented.

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

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

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

Disease-related events and outcomes not qualifying as AEs or SAEs are trial specific and provided in Section 8.4.5.

10.3.4 Evaluation of Adverse Events

Severity

The investigator will use the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), v5.0 (NCI-CTCAE, 2017) to describe the severity of AEs, except for TLS, which will be graded according to Cairo-Bishop et al (Coiffier et al., 2008).

Relationship to the Investigational Medicinal Product

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).

10.3.5 Follow up of Adverse Events and Serious Adverse Events

This is trial specific and defined in Section 8.4.6, Follow up of Adverse Events and Serious Adverse Events.

10.3.6 Tumor Lysis Syndrome

The 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 tumor lysis syndrome (LTLS) (Table 10-2) 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 10-3. Individual symptoms should be graded according to CTCAE.

In the event of Grade 1, Grade 2 or Grade 3 TLS (per Table 10-3), the dose modification guidelines (Section 6.6 and also listed below) will apply:

- During the trial, a planned dose of GEN3014 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, GEN3014 should be discontinued, unless approved by the Sponsor's medical monitor.

As noted in Section 6.6.1, during Dose Escalation, grade 4 TLS is considered a DLT.

Table 10-2 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 GEN3014. Based on (Coiffier et al., 2008).

Table 10-3 Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

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

ADL=activities of daily living; CHF=congestive heart failure; ULN=upper limit of normal.
* Not directly or probably attributable to GEN3014
† 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).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP): A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of trial intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal females who have undergone 1 of the following permanent sterilization methods listed below:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

    - A postmenopausal state is defined as no menses, in subjects >45 years of age, for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Contraception Guidance:

- 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 GEN3014, which may reduce the efficacy of the contraception method.
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 woman of child-bearing potential 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. Advisory non-binding guidance represented at the CTFG-meeting in Rome 2014 (CTFG, 2014).

10.5 Appendix 5: Estimation of Glomerular Filtration Rate Using Cockroft-Gault Formula

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

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

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

10.6 Appendix 6: New York Heart Association Criteria

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

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

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

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

10.7 Appendix 7: Corrected Serum Calcium

Serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium") using the following formula:

If calcium is expressed in mg/dL and albumin is expressed in g/dL:

Corrected calcium (mg/dL) =

serum calcium (mg/dL) + 0.8*(4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:

Corrected calcium (mmol/L) =

serum calcium (mmol/L) + 0.02*(40 - serum albumin [g/L])

Source: (Burtis and Ashwood, 1998)

10.8 Appendix 8: International Staging System (ISS) for Multiple Myeloma

Stage	International Staging System
I	Serum β2M <3.5 mg/L; serum albumin ≥3.5 g/dL
II	Not ISS stage I or III
III	β2M ≥5.5 mg/L

β2M=beta 2-microglobulin; ISS=International Staging System.
Source: (Palumbo et al., 2015)

10.9 Appendix 9: 2016 International Myeloma Working Group (IMWG) Uniform Response Criteria for Response and Minimal Residual Disease Assessment in Multiple Myeloma

IMWG criteria for response assessment including criteria for MRD[1]	
Response Subcategory	**Response Criteria**
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF, NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[2]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[3] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS or bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[4] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[5]
Standard IMWG response criteria[1,6]	
sCR	Complete response as defined below plus normal FLC ratio[7] and absence of clonal cells in bone marrow biopsy by IHC (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells[8,9]
CR	Negative IFE on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow aspirates
VGPR	Serum and urine M-protein detectable by IFE but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; - If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; - If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[10] of soft tissue plasmacytomas is also required.
MR	≥25% but ≤49% reduction of serum M-protein and reduction of 24-h urine by 50% to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[10] of soft tissue plasmacytomas is also required.
SD	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, MR, or PD

PD[11,12]	Any 1 or more of the following criteria: Increase of ≥25% from lowest confirmed response value in 1 or more of the following criteria: • Serum M-protein (absolute increase must be ≥0.5 g/dL); • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 hr). • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of the previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical Relapse	1 Clinical relapse requires 1 or more of the following: 2 Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or PFS but is listed here as something that can be reported optionally or for use in clinical practice; 3 Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); 4 Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[10] of the measurable lesion; 5 Hypercalcemia (>11 mg/dL) 6 Decrease in hemoglobin of ≥2 g/dL, not related to therapy or other non-myeloma related conditions; 7 Rise in serum creatinine by 2 mg/dL or more from the start of therapy and attributable to myeloma; 8 Hyperviscosity related to serum paraprotein
Relapse from CR (To be used only if the endpoint studied is disease-free survival)	Any 1 or more of the following: • Reappearance of serum or urine M-protein by IFE or electrophoresis; • Development of ≥5% plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)
Relapse from MRD negative (To be used only if the endpoint is disease-free survival)	Any 1 or more of the following: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma; • Reappearance of serum or urine M-protein by IFE or electrophoresis; • Development of ≥5% plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

CR=complete response; CRAB=calcium elevation, renal failure, anaemia, lytic bone lesions; DFS=disease-free survival; CT=computed tomography; FCM=flow cytometry; FDG=fluorodeoxyglucose; FLC=free light chain; h=hour(s); IFE=immunofixation; IHC=immunohistochemistry; mAb=monoclonal antibody; MM=multiple myeloma; MR=minimal response; MRD=minimal residual disease; NGF=next generation flow; NGS=next generation sequencing; MFC=multiparameter flow cytometry; PD=progressive disease; PET=positron emission tomography; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; SD=stable disease; SPD=sum of the product of the maximal perpendicular diameters of measured lesions; SUV=standardized uptake value; SUVmax=maximum standardized uptake value; VGPR=very good partial response.

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in 1 draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4 to 5 mL to avoid hemodilution.

1. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance); MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these requirements of FDG PET if imaging MRD-negative status is reported.

2. Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).
3. Bone marrow MFC should follow NGF guidelines. The reference NGF method is an 8-color 2 tube approach, which has been extensively validated. The 2-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The 8-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete 8-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.
4. DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).
5. Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma Criteria for PET use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least 2 consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.
6. Derived from international uniform response criteria. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ration 0·26 to 1·65 in additional to the CR criteria listed previously. VGPR in such patients requires ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for SD, will be considered unconfirmed until the confirmatory test is performed. The date of initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.
7. All recommendations regarding clinical uses relating to serum FLC levels and FLC ratio are based on results obtained with validated Freelight test (Binding Site, Birmingham, UK).
8. Presence/absence of clonal cells on IHC is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by IHC requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
9. Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional CR, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving mAbs should be differentiated from the therapeutic antibody.
10. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by SPD.
11. Positive IFE alone in a patient previously classified as achieving a CR will not be considered progression. For purposes of calculating time to progression and PFS, patients who have achieved a CR and are MRD-negative should be evaluated using criteria listed for PD. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.
12. In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Source: (Kumar et al., 2016)

10.10 Appendix 10: WHO Subtypes of AML

WHO Subtypes of AML
AML with recurrent genetic abnormalities
AML with myelodysplasia-related changes
Therapy related myeloid neoplasm
AML, not otherwise specified
Myeloid sarcoma
Myeloid proliferations related to Down syndrome

AML=acute myeloid leukemia; WHO=World Health Organization.
Source: (Arber et al., 2016).

10.11 Appendix 11: Response Criteria for AML

Complete Remission (CR):

Bone marrow aspirate and biopsy:
≤5% blasts
No Auer rods
No extramedullary leukemia

Peripheral blood counts:
No circulating blasts
Neutrophil count ≥1.0 $x10^9$/L
Platelet count ≥100 $x10^9$/L
Independent of red blood cell and platelet transfusion (defined as 1 week without red blood cell transfusion and 1 week without platelet transfusion).

Complete Remission with Incomplete Hematological Recovery (CRi):

Bone marrow aspirate and biopsy:
≤5% blasts
No Auer rods
No extramedullary leukemia

Peripheral blood counts:
No circulating blasts
Neutrophil count <1.0 $x10^9$/L, or platelet count <100 $x10^9$/L
Transfusion independence is not required.

Complete Remission with Incomplete Platelet Recovery (CRp)

Bone marrow aspirate and biopsy:
≤5% blasts
No Auer rods
No extramedullary leukemia

Peripheral blood counts:
No circulating blasts
Neutrophil count ≥1.0 $x10^9$/L, and
Platelet count <100 $x10^9$/L
Transfusion independence is not required.

Partial Remission (PR):

Bone marrow aspirate and biopsy:
≥50% reduction from baseline pretreatment with 5%-25% BM blasts
No Auer rods
No extramedullary leukemia
Or BM blasts <5% with persistent Auer rods

Peripheral blood counts:
No or a few circulating blasts
Neutrophil count ≥1.0 $x10^9$/L
Platelet count ≥100 $x10^9$/L

Morphologic Leukemia-Free State (MLFS):

Bone marrow aspirate and biopsy:
≤5% blasts
No Auer rods
No extramedullary leukemia

Treatment Failure: Failure to achieve at a least a PR

Relapse from CR, CRi, CRp or PR:

- Relapse after CR, CRi, or CRp is defined as the reappearance of leukemic blasts in the peripheral blood or ≥5% of blasts in the bone marrow aspirate not attributable to any other cause, or reappearance or new appearance of extramedullary leukemia.
- Relapse after PR is similarly defined with the reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to >25% not attributable to any other cause, or reappearance or new appearance of extramedullary leukemia.

Source: (Cheson et al., 2003)

10.12 Appendix 12: Standardized Reporting System for Genetic Abnormalities in Subjects with Acute Myeloid Leukemia

The panel below proposes a standardized reporting system for genetic abnormalities when presenting data correlating genetic findings with clinical outcome allowing for a better comparison of data among studies. This standardized report includes data from cytogenetic analysis and from mutation analyses of the *NPM1*, *CEBPA*, and *FLT3* genes.

Table 10-4 2017 ELN Risk Stratification by Genetics

Risk Category[1]	Genetic Abnormality
Favorable	• t (8;21) (q22; q22.1); *RUNX1-RUNX1T1* • inv (16) (p13.1q22) or t(16;16) (p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} [2] • Biallelic mutated *CEBPA*
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high} [2] • Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} [2] (without adverse-risk genetic lesions) • t (9;11)(p21.3; q23.3)[1]; *MLLT3-KMT2A*[1] • Cytogenetic abnormalities not classified as favorable or adverse[2]
Adverse	• t (6;9)(p23; q34.1); *DEK-NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1;q11.2); *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*−5 or del(5q); −7; −17/abnormal(17p) • Complex karyotype[2], monosomal karyotype[3] • Wild-type *NPM1* and *FLT3*-ITD^{high} [2] • Mutated *RUNX1*[4] • Mutated *ASXL1*[4] • Mutated *TP53*[5]

Note: Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific subsets indicated; excluding cases of acute promyelocytic leukemia.

1. The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations
2. Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.
3. Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
4. These markers should not be used as an adverse prognostic marker if they cooccur with favorable-risk AML subtypes
5. TP53 mutations are significantly associated with AML with complex and monosomal karyotype

Source: (Dohner et al., 2017)

10.13 Appendix 13: 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	

10.14 Appendix 14: Lugano Response Criteria

Table 10-5 Response Criteria – CT/MRI Scan

Response	Lymph Nodes	Non-measurable Lesion	Organ Enlargement	New Lesions	Bone Marrow
Complete Response (CR)	Target nodes/nodal masses regression ≤1.5 cm in longest diameter	Absent	Regress to normal	None	Normal by morphology
Partial Response (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 (13 cm)	None	Not applicable
No response or Stable Disease (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
Progressive disease (PD)	>1.5 cm and increase by ≥50% from nadir and increase from nadir 1. 0.5 cm for lesions ≤2 cm 2. 1.0 cm for lesions >2 cm	New or clear progression of pre-existing lesions	Spleen length increase of >50%	New nodes >1.5 cm New extranodal site >1.0 cm Assessable disease of any size attributable to lymphoma	New or recurrent involvement

Source: (Cheson et al., 2014).

Table 10-6 Response Criteria – PET/CT Scan

Response	Lymph Nodes	Non-measurable Lesion	Organ Enlargement	New Lesions	Bone Marrow
Complete Response (CR)	Score 1, 2 or 3 with or without a residual mass on 5PS[a]	Not applicable	Not applicable	None	No evidence of FDG-avid disease in marrow
Partial Response (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 Stable Disease (SD)	Score 4 or 5 with no significant change in FDG uptake	Not applicable	Not applicable	None	No change from baseline
Progressive disease (PD)	Score 4 or 5 with an increase in intensity of uptake	None		New FDG-avid foci consistent with lymphoma	New or recurrent FDG-avid foci

a. PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
Source: (Cheson et al., 2014).

10.15 Appendix 15: Country-Specific Requirements

10.15.1 Czech Republic

- At the Safety Follow-up visit, vital signs, hematology, biochemistry, and physical examination is required, as marked in Table 1-1, Table 1-2, Table 1-5, Table 1-6, Table 1-7, and Table 1-12.
- Section 5.2.1 Exclusion Criteria – Dose Escalation and Expansion Part A (GEN3014 Single Cohorts), Exclusion Criterion #2CZ: Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, or radiation therapy, within 2 weeks prior to the first dose of GEN3014, or major surgery within 4 weeks prior to the first dose of GEN3014.
- Section 5.2.2 Exclusion Criteria – Expansion Part B (Randomized H2H), Exclusion Criterion #2CZ: Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, or radiation therapy, within 2 weeks prior to the first dose of GEN3014, or major surgery within 4 weeks prior to the first dose of GEN3014.
- Section 6.7.3.3 Prohibited Concomitant Therapy: Live vaccines beginning 28 days prior to the first dose of GEN3014 and for 3 months following the last dose of GEN3014. Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.

10.16 Appendix 16: Abbreviations

Abbreviation	Definition
ABC	activated B-cell
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
anti-HBc	antibody to the hepatitis B core antigen
anti-HBs	antibody to the hepatitis B surface antigen
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
ART	active antiretroviral therapy
ASAP	as soon as possible
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}168h}$	area under the concentration-time curve from time zero to 168 h
$AUC_{0\text{-}last}$	area under the concentration-time curve from time zero to last quantifiable sample
BAS	biomarker analysis set
BCMA	B-cell maturation antigen
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BM	bone marrow
B-NHL	B-cell non-Hodgkin lymphoma
BOR	best overall response
CAR-T	chimeric antigen receptor T cell
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CI	confidence interval
Clcr	creatinine clearance
C_{max}	maximum (peak) concentration
CMV	cytomegalovirus
CR	complete remission

Abbreviation	Definition
CRF	case report form(s)
CRi	complete remission with incomplete hematologic recovery
CRO	contract research organization
CRp	complete remission with incomplete platelet recovery
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
Cx	Cycle (number)
ctDNA	circulating tumor-derived deoxyribonucleic acid
D/d	day
Dx	Day (number)
DDS	dose-determining set
DEC	Dose Escalation Committee
DL	dose level
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
FAS	full analysis set
Fc	fragment crystallizable
FDG	fluorodeoxyglucose
FEV1%PRED	percent predicted forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FLC	free light chain
FFPE	formalin-fixed, paraffin-embedded
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GDPR	General Data Protection Regulation
h	hour(s)

Abbreviation	Definition
H2H	head-to-head
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high-dose chemotherapy
HGBCL	high grade B-cell lymphoma
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IAS	immunogenicity analysis set
IAT	indirect antiglobulin test
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFE	immunofixation
IFNγ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous(ly)
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mBOIN	modified Bayesian Optimal Interval
min	minute(s)
MM	multiple myeloma
MOA	mechanism of action
MRD	minimal residual disease

Abbreviation	Definition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NGS	Next Generation Sequencing
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PAS	pharmacokinetic analysis set
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PMBCL	primary mediastinal large B-cell lymphoma
PT	prothrombin time
Q1W	every week
Q2W	every 2 weeks
Q3M	every 3 months
Q4W	every 4 weeks
$R_{A,AUC}$	accumulation ratio in AUC
$R_{A,Cmax}$	accumulation ratio in C_{max}
$R_{A,Ctrough}$	accumulation ratio in C_{trough}
RES	response evaluable set
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
R/R AML	relapsed or refractory acute myeloid leukemia
R/R DLBCL	relapsed or refractory diffuse large B-cell lymphoma
RRMM	relapsed or refractory multiple myeloma
sCR	stringent complete response
SAE	serious adverse event
sARRs	systemic administration-related reactions
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
seq	sequencing

Abbreviation	Definition
SPD	sum of the product of the diameters
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
$T_{1/2}$	elimination half-life
TCR	tissue cross-reactivity
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
t_{max}	time to maximum (peak) concentration
TNFα	tumor necrosis factor alpha
TTNT	time to next therapy
TTR	time-to-response
ULN	upper limit of normal
UNS	unscheduled
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
W	week
WOCBP	woman of childbearing potential

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INVESTIGATOR AGREEMENT

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

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

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

GCT3014-01 - Protocol Amendment - 31 Aug 2023
Signature Page for TMF-456592 v1.0

Reason for signing: Approved	Name: Jenny Chen Role: Approver Date of Signature: 31-Aug-2023 12:30:58 GMT+0000

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