Statistical Analysis Plan (SAP)

GCT3014-01

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

Primary Compound Number:	GEN3014 (HexaBody®-CD38)
Trial Phase (if applicable)	1/2
Date:	03 Nov 2022, Version 1.0 (original)

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Trial GCT3014-01 is based on the protocol dated 18 February 2022 (Global Amendment 3, version 5.0).

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

Abbreviations

AE	adverse event
AUC	area under the curve
AUC0-168h	area under the concentration-time curve from time zero to 168 hours
AUC0-last	area under the concentration-time curve from time zero to last quantifiable sample
BAS	biomarker analysis set
CBR	clinical benefit rate
CI	confidence interval
CD	cluster of differentiation
CRF	case report form(s) (paper or electronic as appropriate for this study)
Cmax	maximum concentration
Ctrough	lowest level before dosing
DBL	database lock
DCO	data cut-off
DDS	dose determining dataset
DLT	dose limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response
DPS	data presentation specification
ECG	electrocardiogram
FLC	free light chain
FPD	first subject dosed
FPI	first subject in
H2H	head-to-head
IAS	immunogenicity analysis set
IFE	immunofixation
Ig	immunoglobulin
IMWG	International Myeloma Working Group
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRD-	minimal residual disease negativity
MTD	maximum tolerated dose
NK	natural killer
ORR	objective response rate
OS	overall survival
PAS	pharmacokinetic analysis set
PFS	progression free survival
PK	pharmacokinetics
$R_{A,AUC}$	accumulation ratio in AUC
$R_{A,Cmax}$	accumulation ratio in Cmax
RES	response evaluable set
RNA	ribonucleic acid
R/R AML	relapsed or refractory acute myeloid leukemia
R/R DLBCL	relapsed or refractory diffuse large B-cell lymphoma
RP2D	recommended phase 2 dose
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
Std Dev	standard deviation
Tmax	time to maximum concentration

TLF	tables, listings, and figures
TTR	time to response

Response abbreviations

IMWG- RRMM

MRD-	MRD-negative
sCR	Stringent complete response (included in ORR)
CR	Complete response (included in ORR)
VGPR	Very good partial response (included in ORR)
PR	Partial response (included in ORR)
MR	Minimal response
SD	Stable disease
PD	Progressive disease

Lugano – R/R DLBCL

CR	Complete response (included in ORR)
PR	Partial response (included in ORR)
SD	Stable disease
PD	Progressive disease

IWG -R/R AML

CR	Complete remission (included in ORR)
CRi	Complete remission with incomplete hematological recovery (included in ORR)
CRp	Complete remission with incomplete platelet recovery (included in ORR)
PR	Partial remission (included in ORR)
MLFS	Morphologic leukemia-free state (included in ORR)
SD	Stable disease
DP	Disease progression
R	Relapse

1 INTRODUCTION

This statistical analysis plan describes in detail the analysis of the endpoints for trial GCT3014-01. GEN3014 (HexaBody®-CD38) is a fully human immunoglobulin (Ig)G1 monoclonal antibody (mAb) targeting the cluster of differentiation (CD)38 antigen. 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.

GCT3014-01 comprises the following parts (see Figure 1):

- Phase 1 Dose Escalation Part
  - Dose escalation in RRMM
  - Dose escalation in R/R AML

- Phase 2 Expansion Part A
  - Expansion arm in anti-CD38 mAb-naïve RRMM
  - Expansion arm in anti-CD38 mAb-refractory RRMM
  - Expansion arm in R/R DLBCL
  - Expansion arm in R/R AML

- Phase 2 Expansion Part B
  - A randomized H2H comparison of GEN3014 IV versus daratumumab SC in anti-CD38 mAb-naïve RRMM

The main analysis reporting difference between the parts is the ordering of objectives and the grouping of summary statistics. In the Dose Escalation, the primary objective is to determine the safety profile (summarized by DLTs, AEs and safety laboratory parameters), while in Phase 2 Expansion it is to further characterize the antitumor activity based on disease specific response evaluations:

- The International Myeloma Working Group consensus criteria (IWMG) 2016 for RRMM,
- The revised response criteria 2014 for Hodgkin and non-Hodgkin lymphoma (Lugano classification) for R/R DLBCL, and
- The International Working Group (IWG) 2003 response criteria for R/R AML.

The grouping factor in Dose Escalation is the dose level per disease type while in Phase 2 Expansion the results will be summarized by the (disease) cohort. Besides this and the different disease specific response criteria, the underlying details of the analyses and the statistical methodologies do not differ between escalation and expansion, or between diseases. This SAP is thus used for both parts, with above differences noted. To ease the presentation of the planned analysis, the word “cohort” will be used throughout, but this can also be thought of as the dose level in Dose Escalation. Layouts, programming notes and titles for the tables, listings and figures are further specified in the Data Presentation Specification (DPS).

1.1 Objectives and Endpoints

Table 1: Phase 1 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/antitumor activity) and PK/safety	• Dose concentration response (biomarkers and/or efficacy, safety) relationship

AE=adverse event; AUC0-last=area under the concentration-time curve from time zero to last quantifiable sample; AUC0-168h=area under the concentration-time curve from time zero to 168 hours; CBR=clinical benefit rate; CD=cluster of differentiation; Cmax=maximum concentration; Ctrough=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); RA,AUC=accumulation ratio in AUC: RA,Cmax=accumulation ratio in Cmax; RP2D=recommended phase 2 dose; RRMM=relapsed or refractory multiple myeloma; SAE=serious adverse event; tmax=time to maximum concentration; TTR=time-to-response.

Table 2: Phase 2 Expansion Part A

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	• CCI • 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: Phase 2 Expansion Part B

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	• CCI • 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.

1.2 Trial Design

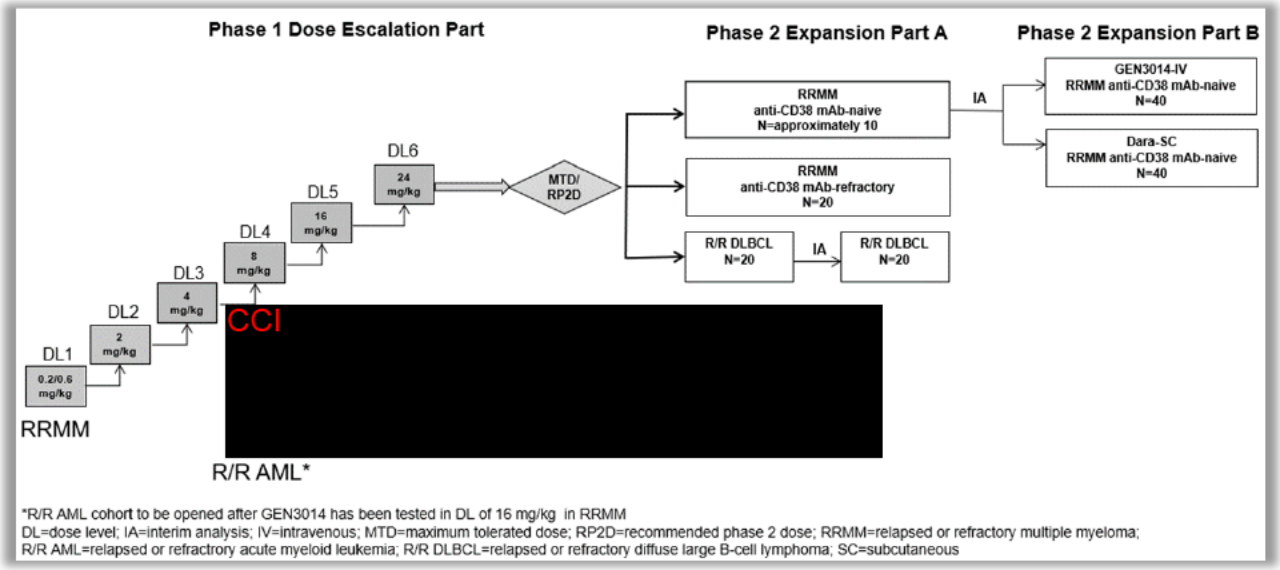

Figure 1: Trial Design

Key trial characteristics

- Dose Escalation is guided by modified BOIN rules
- Interim analyses are planned as follows in Expansion Part A:
  - Anti-CD38 mAb-naïve RRMM: When the initial 10 response evaluable subjects (including subjects who received GEN3014 at 16 mg/kg or 24 mg/kg from Dose Escalation Part A) have completed ≥2 cycles of GEN3014 treatment
  - R/R DLBCL: When the initial 20 response evaluable subjects have completed ≥2 cycles of GEN3014 treatment
- Data from the Dose Escalation and the Expansion cohorts may be analyzed separately.
- Primary safety and efficacy analyses based on the Dose Escalation data will be conducted on all subject data at the end of the Dose Escalation, in conjunction with declaring RP2D, at latest 6 months after last subject first dose. Separate deliveries may be planned for the RRMM and R/R AML disease cohorts as feasible.
    - Note: The delivery containing the primary safety and efficacy analysis in RRMM will be taken as the delivery supporting the clinical overview addendum that includes dose escalation data in RRMM.
- The primary analysis of each expansion cohort in Parts A and B will be conducted on all subject data, at latest 6 months after last subject first dose in respective expansion cohort.
- 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.

Further trial design details are provided in the protocol.

Subject-wise considerations

- First dose of GEN3014 is administered in split dose to mitigate risk of infusion related reactions.
- For each subject, the trial is partitioned into a screening phase, a treatment phase, a safety follow-up phase, and a survival follow-up phase. Not all phases need to be initiated.

1.3 Randomization and Blinding

The 1:1 randomization between GEN3014 and daratumumab SC in Expansion Part B will be stratified by body weight at baseline (≤70 kg vs >70 kg), CCI [redacted]. The randomization will be administered through a centralized IRT system which will dictate the treatment assignment and matching study drug kit for the subject. The randomization is not blinded.

2 STATISTICAL HYPOTHESES

There are no pre-defined hypotheses for GCT3014-01. The Dose Escalation part is designed to determine the RP2D and MTD (if reached), and the Expansion Part A explores 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 two anti-CD38 mAb molecules.

3 SAMPLE SIZE

Dose Escalation

- Up to 54 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

- 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 will include approximately 80 anti-CD38 mAb-naïve RRMM subjects randomized to GEN3014 or daratumumab SC in a 1:1 ratio (N=40 each cohort).

4 ANALYSIS SETS

4.1 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). The treatment effect will be assessed by the actual treatment given, i.e. subjects will be categorized by their actual treatment.

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

4.2 Response Evaluable Set (RES)

The RES comprises all subjects in the FAS that at the timing of data cutoff date (for any interim reporting of the ongoing data).

- Measurable disease (see below),
- 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)

Baseline measurable disease, based on laboratory data and/or scans, is defined as

RRMM

- 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

DLBCL

- 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

AML

- bone marrow aspirate and/or biopsy blasts ≥ 20% at screening
  or
- for subjects who's response to last prior therapy was complete remission:
  - bone marrow aspirate and/or biopsy blasts ≥ 5%, or
  - reappearance of blasts in the blood, or

- development of extramedullary AML.

4.3 Safety Set

See definition for FAS.

4.4 Per-Protocol Set

Not applicable

4.5 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.)

Per protocol: any DLTs observed in subjects in parallel cohorts will not directly contribute to the mBOIN design evaluation. Thus, to clarify, subjects in parallel cohorts are not included in the DDS.

4.6 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.

4.7 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.

4.8 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.

4.9 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.

5 STATISTICAL ANALYSES

5.1 General Considerations

Analyses will be carried out using SAS (Version 9.4 or higher), unless otherwise noted.

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (Std Dev), median, minimum, and maximum. Categorical variables will be summarized using absolute count and percentage (relative to analysis set).

Estimates of time to event variables will be provided based on Kaplan-Meier (KM) methods with the number and percentage of subjects with event or censoring reported. 95% CI of the KM estimate will be provided using the log-log transformation. Median times with 95% CI (based on the Brookmeyer and Crowley method) will be reported. Landmark event-free rates with 95% confidence intervals may also be presented.

5.1.1 Trial Days, Cycle Days and Treatment Periods

5.1.1.1 Trial Days

Trial Day 1 or Day 1 refers to the day of first drug administration. Trial day or relative day for a visit is defined as:

- Visit date - date of Day 1, if visit date < date of Day 1
- Visit date - (date of Day 1) +1, if visit date is ≥ date of Day 1

There is no 'Day 0'.

5.1.1.2 Treatment Periods

The treatment periods are three mutually exclusive segments:

- The pre-treatment period includes information collected from the date of informed consent until the day prior to the first dose of trial treatment (subjects not receiving trial medication will remain in the pre-treatment period for the reminder of their trial participation). Any information collected on the day of first dose where timepoint is also collected will be assigned to the pre-treatment period if occurring prior to time of first dose
- The on-treatment period begins on the date of the first dose of trial treatment (refer to bullet above for exception) and lasts up until date of safety-follow up visit, the date of start of subsequent anti-cancer therapy, date of trial discontinuation, date of loss to follow-up, date of administrative cut-off, or date of death, whichever occurs first

  - Note: Any information collected on the day of start of subsequent anti-cancer therapy, where timepoint is also collected, will be assigned to the post-treatment period if occurring after time of first dose of subsequent anti-cancer therapy

- The post-treatment period begins at end of the on-treatment period + 1 day

If incomplete data makes it impossible to definitively assign an observation to one of these periods, the data will be conservatively assigned to the on-treatment period.

5.1.2 Visit Windows

Any efficacy analysis that utilizes time to event approach will be based on an exact determination of time from C1D1 to the date of event/censoring.

Unless otherwise stated data will be presented as collected on the nominal visits, that is, if data are collected as part of CxDy visit in the CRF it will be presented as such in analyses irrespective of the subject's adherence to the protocol visit schedule and actual collection date. Unscheduled visits will not be displayed summaries but will be listed.

Disease assessments are not tied to nominal visits in eCRF but are scheduled to be performed on a regular basis per protocol. The analysis time window listed in Table 4 and Table 5 will be used to slot actual disease assessment date into planned disease assessment schedules for summary statistics for RRMM, AML and R/R DLBCL, respectively. The visit window is mainly for display disease assessment in a chronical order and will generally not be used in actual analysis.

Table 4: Analysis visit windows for efficacy summary listings in RRMM and AML

Analysis period	Target day (visit window per protocol)	Analysis visit window	Label on output
Baseline	1 (pre-dose C1D1)	Last data point prior to dosing	Baseline
Baseline for SPEP and UPEP (RRMM)	1 (-3 to 1)	Last data point prior to dosing	Baseline
Scheduled on-treatment disease assessments every 28 days	28 (± 3)	1 to 42	Week 4
	56 (± 3)	42 to 70	Week 8
	…	…	…
Unscheduled	-	-	Unscheduled <Day x>
End of treatment	-	-	End of treatment

Table 5: Analysis visit windows for efficacy summary listings in R/R DLBCL

Analysis period	Target day (visit window per protocol)	Analysis visit window	Label on output
Baseline	1 (pre-dose C1D1)	Last data point prior to dosing	Baseline
Scheduled on-treatment disease assessments Week 6,	42 (± 3)	1 to 63	Week 6
	84 (± 3)	64 to 105	Week 12

12, 18, and 24, then every 24 weeks thereafter	126 (± 3)	106 to 147	Week 18
	168 (± 3)	148 to 252	Week 24
	336 (± 3)	253 to 420	Week 48
	…	…	…
Unscheduled	-	-	Unscheduled <Day x>
End of treatment	-	-	End of treatment

Response assessments should be performed until confirmation of disease progression, start of new anti-cancer therapy, withdrawal of consent, or death, whichever comes first.

Details on how to slot subject data that systematically is performed off schedule is provided in the ADaM specification, but no data should be disregarded for efficacy evaluations due to this windowing.

5.1.3 Disease Specific Response Considerations

Each individual timepoint response per disease specific criteria is reported by investigator in eCRF. The best overall response (BOR) will be derived for the purpose of analyzing efficacy endpoints (ORR, DOR and CBR). Timepoint responses recorded after new anticancer therapy or progressive disease (PD), will be excluded from BOR derivation. Section 5.1.3.1 to 0 details disease specific derivations.

5.1.3.1 Considerations Related to IMWG 2016

Baseline measurable disease

Baseline measurable disease in RRMM subjects is defined as:

- 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.

RRMM subjects should also provide documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

Key response variables

Response to GEN3014 or daratumumab SC in RRMM subjects will be assessed in accordance with the IMWG Response Criteria (Kumar et al., 2016). Centrally analyzed samples will be used by the investigator to report the response in eCRF. The best overall response in RRMM subjects can be one of sCR, CR, VGPR, PR, MR, SD, PD or NE.

To support the responses based on the IMWG criteria, a detailed efficacy listing with below parameters is planned:

- SPEP as measured by the total amount of abnormal protein in the serum electrophoresis. (This may constitute one or more abnormal spikes in different protein bands.)
    - With IFE interpretation of the serum
- UPEP as measured by the total amount of abnormal protein in the urine electrophoresis
    - With IFE interpretation of the urine
- FLC with the kappa to lambda ratio, and the difference between the two chains
- The sum of the product of the perpendicular diameters (SPD) of the plasmacytomas (or longest diameter if only 1 is reported)
    - Radiated plasmacytomas are not evaluable for response, and can only be used to monitor progression
- Bone marrow plasma cells, as assessed by aspiration and/or biopsy.
    - If both aspiration and biopsy is obtained at same time point the highest value will be used
- Lytic bone lesions are used only to assess progression
    - In particular, the bone lesion eCRF assessment form will be used to assess progression with the two questions *Is there definite increase in the size of existing bone lesions since baseline?* and *Is there development of new bone lesions since baseline?*
    - For descriptive purposes only, the number of bone lesions will be reported as follows: The number of lytic lesions is assessed on the skeletal eCRF assessment form, and reported as 0, 1, 2, 3, >3, or "Unable to Determine" per anatomic location. The following rules are applied when deriving the total number of bone lesions:
        - If no anatomic location has ">3" or "Unable to Determine": sum the numerical values and sort into one of the following categories: "0", "1-3", or "4-10" or ">10"
        - If one or more anatomic location(s) has ">3" or "Unable to Determine": the total number of lytic bone lesions is set to "Unable to Determine"

5.1.3.2 Considerations Related to Lugano

The protocol categorizes lesions as measurable (nodes, or target), and non-measurable (or non-target) sites. For analysis purposes target and non-target lesions will be referred.

For subjects with FDG-avid tumors at Screening, all subsequent disease assessments will be performed with FDG-PET CT using the 5-point scale. 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 6.

Table 6: PET based response

Response	Target lesions (Nodes/measurable)	Non-target lesion (extranodal/non-measurable)	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

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 overall time point response based on the CT scans will be categorized per Table 7.

Table 7: 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

5.2 Subject Dispositions

Subject dispositions will be presented in flow diagrams in accordance with the current CONSORT statement.

The number of subjects in each analysis set will be tabulated as defined in Section 0 for all enrolled subjects. Frequencies and percentages of subjects who discontinued treatment or discontinued from trial, along with the primary reason for discontinuation will be provided for the FAS.

Time to treatment discontinuation in Expansion Parts A and B, will be presented graphically using a stacked cumulative incidence function accounting for competing risks (e.g., treatment discontinuation due to the reasons as collected in the eCRF). Time to treatment discontinuation and time to trial discontinuation will be estimated using Kaplan-Meier methods.

A by-subject listing will be generated to provide disposition status and early discontinuation reason.

5.3 Primary Endpoint(s) Analysis

Dose Escalation

The primary endpoints in the Dose Escalation phase are the DLTs (presented based on the DDS), general AEs and safety laboratory parameters (presented based on the FAS/SAF). Safety analyses are described in Section 5.5.

Expansion Parts A and B

The primary endpoint of the Phase 2 Expansion is the objective response rate (ORR) per disease specific criteria, as assessed by investigator. There is no pre-specified hypothesis that is to be tested.

5.3.1 Definition of Endpoint(s)

ORR is defined as the proportion of subjects in the analysis population (FAS is used for primary analysis) with a BOR of partial response (PR) or better according to the disease specific criteria. In detail, the disease-specific definitions of ORR are

- RRMM: a BOR of PR, VGPR, CR or sCR
- R/R DLBCL: a BOR of PR or CR
- R/R AML: a BOR of MLFS, PR, CRp, CRi, or CR.

5.3.2 Main Analytical Approach

The ORR and its 95% CI, calculated by the Clopper-Pearson (exact) method, will be presented by cohort. In conjunction with the ORR, the frequency and proportion in each response category will be reported.

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. Any stratified analysis will be done using the IRT stratification factor used for randomization.

The maximum percentage change from baseline (see further details in Section 5.1.3) at any time on trial, but before the first PD, will be presented using waterfall plots.

Individual subject data listings will be provided to support response derivation.

5.3.3 Sensitivity Analysis

No sensitivity analyses are planned.

5.3.4 Supplementary Analyses

To explore the treatment effect while trial is ongoing, the ORR may be presented also for the RES.

Due to the low sample size, no subgroup analyses are planned.

5.4 Secondary Endpoint(s) Analysis

5.4.1 CBR and VGPR in RRMM

The clinical benefit rate (CBR) will only be derived for the RRMM subjects, and is defined as a BOR of MR, PR, VGPR, CR or sCR.

Similarly, VGPR is defined for RRMM subjects with BOR of VGPR, CR or sCR.

CBR and VGPR will be reported with its exact 95% CI, calculated by the Clopper-Pearson method and will be presented together with the ORR.

5.4.2 CRR

The proportion of subjects in the analysis set with a complete response (CR) or better will be analyzed as the ORR, and may be presented together with the ORR.

5.4.3 DOR

Duration of response (DOR, months) is defined as time from date of first documented initial response (PR or better) to date of progression, or death, whatever comes first. As such, DOR is defined only for the subjects (in the analysis set) who achieve PR or better. DOR will be censored following the censoring scheme for time to event variables as presented in Table 8.

Table 8: Censoring scheme for time to event variables

Situation	Date of Progression or Censoring	Censoring Rule
Incomplete or no baseline assessments	C1D1, or date of randomization	Censored
No documented PD or death prior to analysis data cutoff, trial discontinuation, start of new anti-cancer treatment	Date of last valid tumor assessment with no documented PD before the situation*	Censored
Documented PD between adequate** assessment visits	First date of assessment demonstrating documented PD	Event
Death before first response assessment	Date of death	Event
Death between adequate** assessment visits	Date of death	Event
Death or documented PD after two or more consecutive missed visits***	Date of last valid tumor assessment prior to the missed visits*	Censored

*Excluding response assessments with NE as overall time point response. If no such assessment exists, the censoring date will be C1D1.
** No more than one missed visit, no anti-cancer therapy etc. before the death or documented progression.
*** Please refer to the DPS for the definition of two missed scans.

Clinical progression (as recorded in eCRF) does not constitute documented progression and will cause censoring (unless documented progression was recorded before clinical progression).

DOR will be estimated using the KM method and the result will be displayed graphically. The number and percentage of subjects with event or censoring will be reported. Median DOR (months) with associated 95% CI as well as first and third quartiles and range will be provided.

5.4.4 TTR

Time to response (TTR, months) is defined as time from C1D1, or randomization, to date of first documented response (PR or better). TTR will be presented descriptively (n, mean, standard deviation (Std Dev), median, minimum, and maximum) for the subjects achieving PR or better.

5.4.5 PFS

Progression-free survival (PFS, months) is defined as the time from C1D1, or randomization, to first documented PD or death due to any cause, whichever occurs earlier (see Table 8 for censoring rules). PFS will be derived for all subjects and analyzed using similar methods as DOR.

PFS event-free rate at a landmark time T is defined as the probability that a subject has not progressed and is alive at time T. (Subjects with an intermittent event prior to the landmark will not be a part of the analysis.) PFS event-free rates at 6, 9, and 12 months (or later times if available) will be presented along with 95% CI.

5.4.6 OS

Overall survival (OS, months) is defined as time from C1D1, or randomization, to death due to any cause, will be analyzed using the Kaplan-Meier method. The subjects who are alive or with no observed death will be censored at last contact date.

Median OS with associated 95% CI as well as first and third quartiles and range will be provided. Survival rates at 6, 9 and 12 months (or later times if available) will be presented along with 95% CI.

5.4.7 TTNT

Time to next therapy (TTNT, months) 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 derived for all subjects and analyzed using similar methods as DOR.

5.5 Safety Analyses

5.5.1 Extent of Exposure

GEN3014 will be administered as weight adjusted IV infusion (mg/kg) 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. Please note that the first dose will be equally split on C1D1 and C1D2. In Expansion Part B daratumumab SC will be administered as an SC flat dose (mg) injection at the same scheduled frequency.

Number of cycles initiated, duration of exposure, number of trial drug administrations (number of full dose infusions of GEN3014 and number of SC injections of daratumumab) and dose level (mg) per trial drug administration (on full dose infusions for GEN3014) will be summarized with descriptive statistics (n, mean, standard deviation (Std Dev), median, minimum, and maximum). The number and percentage of subjects with dose interruptions, delay, reasons for dose

interruptions (adverse event, drug administration issues, or other), and reasons for dose delay (adverse event, drug administration issues, or other) will be presented.

GEN3014 specific exposure statistics such as duration of full dose infusion (hours) and dose level per full dose infusion (mg/kg) will be provided. In these two statistics the split doses will not be included as they would bias the result.

5.5.1.1 Duration of Exposure

Duration of exposure in *months* is defined as

- (end of treatment date – date of first drug administration + 1)/ 30.4375

Duration of exposure in *cycles* is defined as

- (end of treatment date – date of first drug administration + 1)/ 28

where *end of treatment date* is defined as

- *min*(last date of trial drug administration + number of days up to next expected trial drug administration – 1; last contact date; date of administrative cut-off; date of death)

For cycle-specific statistics, date of first drug administration and date of last treatment administration will be derived for each period e.g. Cycle 1-2 (Q1W), Cycle 3-6 (Q2W) and Cycle 7+ (Q4W). Start date of each cycle specific-period is date of first trial drug administration in that period, and end date of each cycle-specific period will be *min*(date of starting next cycle-specific period (if any); end of treatment date).

5.5.1.2 Relative Dose Intensity

Dose intensity statistics will be summarized for the cycle-specific periods. Only subjects entering Cycle 3 per eCRF will be considered to contribute to Cycle 3-6 statistics below. Similar for Cycle 7+.

The planned dose intensity for Cycle 1-2 is dose level x 4 (mg/kg/cycle), for Cycle 3-6 it is dose level x 2 (mg/kg/cycle) and for Cycle 7+ it is dose level x 1 (mg/kg/cycle), where the subject's weight in kilogram (kg) should be the last obtained weight used for dose calibration at trial drug administration visit. Note that for the initial level 0.2/0.6 (mg/kg), the planned dose intensity for Cycle 1-2 is (0.2+0.6 x 3+0.6 x 4) / 2 (mg/kg/cycle).

Actual cumulative dose received (mg/kg), is calculated as the sum of all doses administered in the cycle-specific period, and will be summarized using descriptive statistics.

The relative dose intensity (%) is defined as

$$\frac{\text{Actual cycle-specific cumulative dose (mg/kg)}}{\text{Duration of cycle-specific exposure (cycles)}} \Big/ \text{Cycle-specific planned dose intensity}$$

5.5.1.3 Relative Dose Intensity Expansion Part B

For Expansion Part B the actual cumulative dose and relative dose intensity will be summarized similarly to as described in Section 5.5.1.2, with the exception that the unit of administered trial drug is mg (and not mg/kg).

The planned dose intensity (mg/cycle) for daratumumab SC is for Cycle 1-2 1800 x 4 mg/cycle, for Cycle 3-6 1800 x 2 mg/cycle and for Cycle 7+ 1800 mg/cycle.

The relative dose intensity for GEN3014 and daratumumab SC will be summarized as described in Section 5.5.1.2.

5.5.2 Adverse Events

5.5.2.1 Definition Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is defined as any AE with an onset date or worsening grade (relative to the last reported grade before the on-treatment period) within the on-treatment period, defined in Section 5.1.1.2.

A pre-treatment AE is defined as any non-treatment emergent AE with onset during the pre-treatment period, with no worsening during the on-treatment period.

Only SAEs judged by the investigator as related to GEN3014 should be reported during the post-treatment period.

5.5.2.2 Summaries of Treatment Emergent Adverse Events

Treatment emergent adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given SOC or PT, i.e., the most related occurrence, the event with the worst toxicity grade or the most severe occurrence. For derivation of the worst toxicity grade, all grade changes occurring at or after the time where the event becomes treatment emergent will be considered.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 25.0 or higher) and the severity of an AE, or the toxicity grade, will be based on NCI-CTCAE v5.0 (NCI-CTCAE, 2017), except for clinical TLS which is graded according to Cairo-Bishop et al (Coiffier let al, 2008); please note TLS will be included in all summaries below.

The following summaries of TEAEs will be provided:

- Overview of TEAEs

The following summaries will be tabulated by both SOC and PT, and/or by PT depending on relevance:

- TEAEs
- DLTs
- Most common (at least 10%) TEAEs
- Related TEAEs
- TEAEs by worst toxicity grade
- Grade 3 or higher TEAEs
- Most common (at least 5%) grade 3 or higher TEAEs
- Grade 3 or higher related TEAEs
- Fatal TEAEs (i.e., those TEAEs with Grade 5)
- Serious TEAEs
- Serious related TEAEs
- TEAEs leading to dose interruption
- TEAEs leading to dose delays
- TEAEs leading to withdrawal from trial treatment (i.e. drug withdrawn)

The following will also be tabulated

- TEAEs by SOC, PT and worst toxicity grade
- TEAEs by PT and worst toxicity grade
- Serious TEAEs by SOC, PT and worst toxicity grade
- Serious TEAEs by PT and worst toxicity grade

All adverse events will be listed by subject, with flags distinguishing pre-treatment, treatment emergent and post-treatment AEs.

Additional listings will be presented for all SAEs, all AEs leading to treatment discontinuation, and all AEs leading dose interruption or rate changes.

5.5.2.3 Adverse Events of Special Interest

IRRs will be considered as AESIs for GEN3014. The corresponding AESI for subcutaneous daratumumab SC are systemic administration-related reactions (sARR).

The number and percentage of subjects with treatment emergent adverse event of special interest will be presented by SOC, PT and worst toxicity grade. Additionally, the number and percentage of subjects with treatment emergent adverse event of special interest leading to treatment discontinuation and dose interruption will be summarized. Time to onset of first IRR, and time to resolution (for resolved cases) will be presented.

5.5.3 Treatment Emergent Fatal AEs and Deaths

The number and percentage of subjects who died due to related TEAE will be summarized by PT. All fatal adverse events will be presented in a separate listing, indicating relationship to treatment.

All deaths as reported on the eCRF death form will be summarized by primary cause of death. In addition, deaths occurring within 30 or 60 days of first GEN3014 dose, or within 30 or 60 days of last GEN3014 dose will be summarized by primary cause of death.

5.5.4 Additional Safety Assessments (if applicable)

5.5.4.1 Clinical Laboratory Data

Grading of laboratory values will be assigned programmatically as per CTCAE v5.0. The calculation of CTCAE grades will be based on the observed laboratory values only; clinical assessments will not be considered.

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 laboratory data with values flagged to show the corresponding CTCAE term and CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades that are defined with a CTCAE term:

- Worst post-baseline on-treatment CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Summary table of Grade 3 or higher CTCAE graded laboratory toxicities

For laboratory tests where grades are not defined by a CTCAE term:

- Shift tables using the "low/normal/high" classification to compare baseline to the worst on-treatment value

5.5.4.2 Vital Signs

The number and percentage of subjects meeting the below criteria at any post-baseline assessment will be summarized by cohort.

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- Weight: Increase of ≥ 10% from baseline

- Heart rate: ≥ 120 bpm with an increase of ≥ 15 bpm from baseline
- Temperature: > 38° C

Clinically notable below normal values

- Systolic BP: ≤90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Weight: decrease of ≥ 10% from baseline
- Heart rate: ≤ 50 bpm and a decrease ≥ 15 bpm from baseline
- Temperature: < 35° C

5.5.4.3 ECG

The ECGs will be recorded digitally at the sites by using the standard 12-leads. 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:

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

The number and percentage of subjects meeting the below criteria at any post-baseline assessment will be summarized by cohort

Highest post-baseline QTcF interval

- QTcF interval > 450 msec
- QTcF interval > 480 msec
- QTcF interval > 500 msec

Change from baseline in QTc interval

- QTcF interval increases from baseline > 30 msec
- QTcF interval increases from baseline > 60 msec

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.

The concentration of GEN3014, or daratumumab, in the serum samples will be determined by a validated, specific, and sensitive ligand binding assay, at the assay CRO. Based on the concentrations the sponsor will calculate the PK parameters (listed below) based on non-compartmental (NCA) methods.

The PK analysis and output to be generated are detailed in the next paragraphs. In short, GEN3014, or daratumumab, concentration data will be presented graphically and summarized by groups. Graphical exploration of dose-response will be presented.

5.6.1.1 Pharmacokinetic concentrations

Individual values will be listed chronologically for each serum concentration. Concentrations below the lower limit of quantification (LLOQ) will be treated as LLOQ/2 for summary statistics and graphs and reported as <LLOQ in data listings. Any missing concentration data will not be imputed.

Concentrations will be summarized by planned time point using both arithmetic and geometric means, standard deviations, coefficient of variations expressed as percentages (CV%), medians, minimums, and maximums.

GEN3014 concentration data will be presented graphically by actual time point, using individual curves of concentrations. All available data will be shown on these figures.

5.6.1.2 Pharmacokinetic parameters

Based on the availability of the data and quantifiable concentrations of GEN3014 (or daratumumab SC in Expansion Part B) available Table 9 lists the PK parameters to be derived for each subject. All pharmacokinetic parameters will be listed by subject and summarized by cycle and cohort.

Table 9: PK parameters

$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve, from time zero to the last quantifiable concentration (mass x time x volume^{-1})
AUC_{inf}	Area under the plasma concentration time curve from time zero to infinity (mass x time x volume^{-1})
C_{max}	Maximum observed drug concentration in plasma after each administration (mass x volume^{-1})
t_{max}	Time of maximum observed concentration (time)
$t_{1/2}$	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve (time)

CL	Apparent total plasma clearance (volume x time^{-1})
C_{trough}	Observed pre-dose drug concentration

Additional parameters such as dose normalized C_{max} and AUCs, apparent volume of distribution, accumulation ratios may be calculated to fully characterize the PK profiles of GEN3014.

All subjects in the PAS 1 for which PK parameters can be calculated will be included in the summaries. Descriptive statistics provided will include the number of subjects, arithmetic mean, standard deviation (SD), arithmetic coefficient of variation, reported as a percentage (CV%), median, minimum, and maximum. Geometric mean and geometric CV% will be calculated for continuous PK parameters. T_{max} will be presented as median, minimum, and maximum.

Dose-response between dose and PK parameters will be presented. Associations between PK parameters and covariates such as weight, age, as well as relationships between emerging observations of safety, efficacy or pharmacodynamic biomarkers and plasma exposure may be explored graphically by the sponsor, possibly outside the scope of this SAP depending on the findings.

If deemed applicable, compartmental modelling approaches may be performed by the sponsor outside of the scope of this SAP.

5.6.2 Pharmacodynamics

Pharmacodynamic summaries will be presented based on the BAS.

5.6.2.1 Cytokine, chemokine and immunophenotyping measures

Cytokine and immunophenotyping measures will be summarized in descriptive tables by time point, using mean, geometric mean, median, minimum, maximum, n, standard deviation, and geometric coefficient of variation (CV%).

Cytokine and immunophenotyping measures will also be graphed using median and standard error (SE) over time (by visit), where each line represents one cohort. Each cohort will be indicated with a different colour.

Cytokine and chemokines

The primary set of cytokines include IL-2, IL-6, IL-8, IL-10, IFNγ and TNFα. Cytokine data below LLOQ (if determined for the assay) will be handled as (LLOQ)/2 in summary statistics and reported as is in data listings.

A graphical overview of all cytokines in Cycle 1 data will be provided.

Immunophenotyping and complement analysis

The immunophenotyping parameters are

- T-cells: CD3+, CD3+CD4+, CD3+CD8+
- NK-cells: CD3-CD56+/CD16+,
- B-cells: CD3-CD19+,
- monocytes: CD14+,
- complement analysis parameters: C2 and CH50.

The baseline value of the parameter will be presented by cohort, as well as the maximum absolute change and maximum absolute percentage change. For T-cells the maximum increase/expansion (and maximum percentage increase/expansion) from baseline will be presented. For NK-cells, B-cells, monocytes and complement analysis parameters, the maximum decrease/depletion (and maximum percentage decrease/depletion) will be presented.

Absolute and percentage changes from baseline in Cycle 1 will be presented in figures.

5.6.2.2 CCI

CCI

5.6.3 Immunogenicity

At sample level, the presence or absence of any anti-drug antibodies to GEN3014 or rHuPH20 (for subjects treated with daratumumab SC in Expansion Part B), will be listed by subject and visit. Summarizes of positive anti-drug antibodies will be presented by visit. The number and percent of subjects with anti-drug antibodies will be summarized overall and by time point, using the Immunogenicity Analysis Set (IAS).

By using the *by subject and visit ADA status*, the *subject level ADA status* is defined as positive if

- Negative at baseline and at least one positive post-baseline result, or
- Positive at baseline and at least one positive post-baseline result with a titer at least 2-fold higher than baseline

subjects with no post-baseline ADA assessment will have a missing ADA status.

If assessed, neutralizing antibodies will be summarized (positive/negative).

Associations between ADA status (positive/negative, titer levels) and PK (AUC, C_{trough}), major safety signals and efficacy will be explored, if possible.

5.6.4 Rate of MRD Negativity and Duration of MRD Negativity

Minimal residual disease (MRD) negativity is defined as no malignant clone sequence being detected at a given threshold in PBMCs or ctDNA (e.g. for 10^{-5}, the clone sequence is not detected in the background of 100,000 nucleated cells). For evaluation of MRD negativity rate, subjects are considered MRD negative if there is at least one on-treatment MRD negative whole blood sample; all remaining subjects in the analysis set are considered MRD positive (e.g. those who only have MRD positive test results or those who have no MRD assessment data). Duration of MRD negativity is defined as the number of days from the first documentation of MRD- to the date of MRD status change (not MRD-). The primary MRD- threshold is selected as of 10^{-5}. Other thresholds, including 10^{-4} and 10^{-6}, may also be explored.

MRD- rate analyses will be performed in a similar manner as for ORR, and duration of MRD- analyses will be conducted in similar methods for DOR.

PFS and OS analysis by MRD negativity status may be performed to assess the relationship between MRD negativity status and PFS/OS as part of exploratory analyses.

5.6.5 Subgroup Analyses

Due to the heterogeneous population, and expected low sample size within each disease type, there are no subgroup analyses are planned for the escalation stage.

5.7 Interim Analyses

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

Data from the initial 10 anti-CD38 mAb-naive RRMM subjects belonging to the RES who received GEN3014 (at 16 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 in Expansion Part B 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%.

5.7.2 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 enrolment 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 subjects 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.

5.7.3 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 5-7 through Table 5-10 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 5-10 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 5-11 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 5-12 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 5-13 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.

5.7.4 Data Monitoring Committee or Other Review Board

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.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Changes to Protocol-planned Analyses

Not applicable.

6.2 Appendix 2: Definition of Baseline

For analysis purpose, baseline period will include the following evaluations or events:

- Evaluations or events occur before the date and time of the first dose of trial treatment
- Evaluations on the same date of the first dose of trial treatment but the time component (onset time of event or evaluation time and dosing time) is missing or not collected, then the following definitions will apply.
    - Laboratory tests, vital signs (including weight and height), PRO questionnaires, ECOG performance status, and constitutional symptoms on the same date of the first dose of trial treatment will be considered as baseline evaluations.
    - Adverse events onset on the same date of the first dose of trial treatment will not be considered as pre-treatment events.

If there are multiple valid assessments, the assessment that is closest to the day (and time if collected) of the first dose of trial treatment will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time if collected), the assessment with the latest visit will be considered as baseline, unless stated otherwise.

6.3 Appendix 3: Imputation Rules for Missing AE Date/Time of Onset/Resolution

Incomplete dates/and time of onset/resolution of AEs will be imputed to determine if the AE is to be classified as treatment emergent or not. The imputed dates and times will only be used for this purpose.

Imputation of date

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is **missing day only**, it will be set to:
    - First day (01) of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the trial medication start date
    - The day of trial medication start date, if the month/year of the onset of AE is the same as month/year of the trial medication start date, and month/year of the AE resolution date is different

  - The day of trial medication start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the trial medication start date and month/year of the AE resolution date are same

- If the onset date of an adverse event is **missing both day and month**, it will be set to the earliest of:
  - January 1 of the year of onset, if this date is on or after the trial medication start date
  - Month and day of the trial medication start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the trial medication start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is **missing day only**, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is **missing both day and month**, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

Imputation of hour and minute

If the hour and minute of the AE onset/resolution is missing they will be imputed as follows:

- A missing hour and minute of onset of an adverse event will be set to the earlier of:
  - 00:01 if the onset date is after the trial medication start date
  - The time of the trial medication start date if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

6.4 Appendix 5: Demographics and Baseline Characteristics

Descriptive statistics will be provided for the following demographic and baseline disease characteristics, further details, and possibly other variables, are provided in the DPS

- Age (<65 years, ≥65 years; summary statistics)
- Race (White, Black, or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Gender (Male, Female)

- Weight (summary statistics)
- Height (summary statistics)
- ECOG performance status (0, 1, 2)
- Time from initial diagnosis to first trial drug administration (summary statistics)
- Number of prior lines (summary statistics and by 1, 2, 3, 4, and >4 prior lines)
- Prior therapies (as listed in eCRF, e.g., prior anti-cancer therapy, hematopoietic stem cell transplant, radiotherapy, surgery, CAR-T)
- CD38 baseline expression levels (CD38-positive malignant cells, and CD-38 expression on malignant cells (MFI)
- β-2 microgloubin

6.4.1 RRMM disease specific characteristics

- Subtype of MM disease (IgA, IgD, IgG, IgM, Light Chain)
- Serum M-protein level (summary statistics)
- Urine M-protein level (summary statistics)
- Number of plasmacytomas (summarized by 0 or ≥1)
- Number of lytic lesions (None, 1-3, 4-10, > 10, Unable to Determine)
- Percentage bone marrow plasma cells (<5, ≥5 - <10, ≥10 - <30, ≥30 - <60, ≥60, Missing)
- ISS stage at screening (Stage I, Stage II, Stage III, Missing)
- Anti-CD38 mAb-naïve (yes or no)
- Time since last anti-CD38 treatment (summary statistics)

6.4.2 DLBCL disease specific characteristics

- DLBCL type (De novo, Transformed) for DLBCL subjects only
- Disease type prior to transformation (FL and histologic grade, MZL, Other) for DLBCL transformed subjects only
- Molecular classification (GCB, non-GCB, ABC) for DLBCL subjects only
- Disease burden (SPD ≥ 50 cm^2)
- Chromosomal alteration status (Double-hit, Triple-hit)
- Ann Arbor Staging
- IPI (0-2, ≥3)
- Presence of constitutional symptoms

6.4.3 AML disease specific characteristics

- %-bone marrow blasts (summary statistics)
- Peripheral blood smear (summary statistics)
- Absolute neutrophil count (summary statistics)
- Platelet count (summary statistics)
- Extramedullary disease (yes/no)

6.5 Appendix 6: Refractory and Relapsed Disease Status

The definition of refractory and relapsed are disease specific

Multiple myeloma (definitions follows Rajkumar et al 2011)

- Refractory myeloma can be defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy. There may be 2 categories of refractory myeloma: "*relapsed-and-refractory myeloma*" and "*primary refractory myeloma*":
    - *Relapsed and refractory myeloma* can be defined as disease that is nonresponsive while on prior (salvage) therapy, or progresses within 60 days of last therapy in subjects who have achieved minimal response (MR) or better at some point previously.
    - *Primary refractory myeloma* can be defined as disease that is nonresponsive in subjects who have never achieved a minimal response or better with any therapy.
- *Relapsed myeloma* can be defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories

DLBCL

- 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.
- Relapsed disease is defined as the reappearance or growth of lymphoma after at least 6 months duration of response (DOR).

AML

- Refractory is defined as not being able to achieve a CR after the initial therapy.

- Relapse is defined by BM blasts ≥5% in subjects who have been in complete remission (CR) previously, or reappearance of blasts in the blood, or development of extramedullary AML.

Note: For a subject without an evaluable or an unknown response to a prior line of treatment, the subject will be considered refractory to the prior treatment if disease progressed during treatment or within disease specific time after stopping treatment. Otherwise, the subject will be considered relapsed to the prior line of treatment.

6.6 Appendix 7: Prior and Concomitant Medications

The prior anti-cancer treatments that the subjects were refractory to, or relapsed from, will be summarized. Prior medications include non-trial medications that are taken prior to the first date of trial drug administration. Concomitant medications, defined as medications other than trial drug which are taken during on-treatment period. Prior and concomitant medications will be coded using the WHO Drug Dictionary.

Prior and concomitant medications will be tabulated by ATC code level 2 and generic term.

Prior therapy (which may differ dependent on disease type, RRMM, R/R DLBCL or R/R AML) will be listed and tabulated for type of therapy and relapse and refractory status. In addition, the number of lines of prior therapies and corticosteroid use will be summarized using descriptive statistics.

6.7 Appendix 8: Protocol Deviations

Protocol deviations will be identified, documented, reviewed, and assessed based on protocol deviation and non-compliance management plan. Important protocol deviations include those that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations will be listed and tabulated by type of deviation in the FAS.

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