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Protocol No: GCT3009-01

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

Statistical Analysis Plan

Interim and Final Analysis of Dose Escalation and Dose Expansion Parts

Version: v1.0

Date: 08Mar2020

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1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the interim and final statistical analyses of the Dose Escalation part and the Dose Expansion part of study GCT3009-01.

This statistical analysis plan (SAP) covers the analysis of both parts of the trial and is based on the following information and documents:

Trial Protocol	16 Dec 2019; v 4.0 (Amendment 2)
Unique Case Report Forms (CRFs)	19 Feb 2019; v1.0

1.2 Timing of statistical analyses

The following statistical analyses are planned for the **Dose Escalation part** of this trial:

- Dose escalation evaluations for each dose level: as needed.
- Primary safety and efficacy analyses will be conducted on all subject data at the end of the escalation.
- Follow-up analyses of safety and efficacy: as needed.
- Final safety and efficacy analyses will be conducted on all subject data at the same time as the final analyses for the Dose Expansion part.

The following statistical analyses are planned for the Dose Expansion part of this trial:

- Interim analysis, to evaluate safety data after 20 subjects (across the 3 diagnosis cohorts) have completed 2 cycles of treatment.
- Primary analysis, after the last subject enrolled in the Dose Expansion part has completed a sufficient amount of time on study.
- Follow-up analyses of safety and efficay: as needed.
- Final safety and efficacy analyses will be conducted on all subject data when the last subject (across Dose Escalation and Dose Expansion parts) has withdrawn from the trial.

2 Modification History

2.1 Changes to the trial protocol

The statistical analysis as specified in this SAP is consistent with the statistical analysis as specified in the trial protocol (version 4.0), with the following modifications.

- The definition of the Safety Analysis Set (SAF) in Section 4 does not require subjects to have "*at least one valid post-baseline assessment*."
- Section 11.4.1.1 of the protocol lists displays of safety information (summaries and listings of AEs and deaths) as primary endpoints for the Dose Escalation part. The primary endpoints are correctly listed in Section 3.

The Pharmacokinetic Analysis Set (PAS) was not included in the protocol, but is defined in Section 4 of the SAP.

2.2 Changes to previous SAP versions

This is the first version of the SAP for the Dose Escalation and Dose Expansion parts of this trial.

3 Trial Design

GCT3009-01 is a two-part trial, with a dose escalation portion and expansion portion. This analysis plan incorporates both parts of the trial.

3.1 Primary objectives

Dose Escalation

- Determine the MTD with and/or determine the Recommend Phase 2 Dose (RP2D) for GEN3009
- Establish the safety profile of GEN3009

Dose Expansion

- Evaluate (preliminary) anti-tumor efficacy

3.2 Secondary objectives

Dose Escalation

- Establish PK profile
- Evaluate immunogenicity
- Evaluate preliminary anti-tumor efficacy
- Evaluate preliminary clinical efficacy

Dose expansion

- Establish PK profile
- Evaluate safety and tolerability of GEN3009
- Evaluate clinical efficacy
- Evaluate immunogenicity

3.3 Exploratory objectives

Dose Escalation and dose expansion

- Assess potential biomarkers predictive of clinical response to GEN3009 and evaluate potential surrogacy with PFS and OS
- Assess pharmacodynamic markers related to mechanism of action

3.4 Treatment Design

This open-label, multicenter trial will be conducted in 2 parts. GEN3009 will be administered by intravenous (IV) infusions at 7 dose levels, ranging from [redacted] mg to CCI mg in 28-day cycles, in the

Dose Escalation part, where DLTs will be assessed and the MTD will be identified. Additional/intermediate dose levels may be explored based upon emerging data. Additional subjects will be treated at the RP2D in the Dose Expansion part. Figure 1 below shows further details.

Figure 1 GCT3009-01 Trial Design

The MTD and/or RP2D will be determined in the Dose Escalation part using a modified Bayesian Optimal Interval (mBOIN) design, which will enrol up to 60 subjects with R/R B-cell NHL including CLL/SLL. The Dose Expansion part will be conducted in 3 indications (DLBCL, FL, CLL/SLL), with a maximum sample size of 20 per indication.

No formal statistical hypothesis testing will be performed.

3.5 Treatment administration schedule

The Dose Escalation part of the trial will consist of approximately 7 dose level cohorts of subjects and additional intermediate dose levels may be explored based on emerging data, as described in protocol 4.1.1. The Dose Expansion part of the trial will include 3 diagnosis cohorts of subjects, with parallel enrolment, who will be treated with the RP2D as determined in the Dose Escalation part of the trial.

GEN3009 will be administered intravenously in 28 day cycles, as per Section 4.1 of the protocol:

- Cycles 1, 2, and 3: Administered on Days 1, 8, 15, and 22 (once weekly)
- Cycles 4, 5, 6, 7, 8, and 9: Administered on Days 1 and 15 (every 2 weeks)

- Cycles 10 and later: Administered on Day 1 (every 4 weeks)

3.6 *Sample size estimation*

As stated in Section 11.11 of the protocol:

> *Sample size for the Dose Escalation is expected to be up to 60 subjects based on simulations of the mBOIN design in order to provide adequate information for MTD estimation, the planning and design of future trials. The expected number of subjects depends on the true relationship between dose and DLT probability but is expected to lie between 20 to 30 subjects in realistic scenarios. Approximately 28 additional subjects may be recruited to dose levels below MTD where it is found relevant to further explore the PK, toxicity and efficacy.*

Table 16 of the protocol presents different scenarios based on the probability of a DLT occurring in the Dose Escalation part. The sample size of 60 subjects across 3 diagnosis cohorts in the Dose Expansion part was selected to provide additional safety and initial efficacy information, as well as more detailed data related to the mechanism of action..

3.7 *Cohort size during Dose Escalation part*

Accelerated Titration: The initial 3 dose level cohorts, constituting the accelerated titration part of the Dose Escalation part of the trial, will consist of a single subject. Single-subject cohorts may be expanded by 2 subjects at the same dose level, to obtain additional safety and PK/pharmacodynamics data. The cohort will also be expanded to a 3-subject cohort if the initial subject experiences a Grade ≥2 non-hematologic toxicity, or based on the decision of the sponsor's Safety Committee.

Standard Titration: The next 4 dose levels will consist of 3-subject cohorts. As per protocol 4.1.1.1, a dose level cohort may include only 2 subjects, provided neither experienced any Grade 2 or higher toxicity during the DLT observation period.

In the standard titration part, over-recruitment is allowed, so that each dose level cohort in the standard titration may consist of 2 to 4 subjects who are evaluable for DLT.

3.8 Randomization, blinding and unblinding procedures

Subjects are assigned to intravenous GEN3009 with defined doses (for the Dose Escalation part) or at the RP2D dose level (for the Dose Expansion part), as described in the protocol. No randomization is performed.

This is an open-label trial; therefore no blinding of treatment will be performed.

4 Analysis Sets

The assignment of subjects to the different analysis sets will be finalized prior to database snapshot (for the Dose Escalation part or Dose Expansion part as appropriate), based on a review of the data that is agnostic to dose level cohort, where applicable. This review is typically performed during a data review meeting but may also be performed via independent review of analysis set assignments by team members. Approval of final analysis set inclusion will be documented prior to the database snapshot. All subjects excluded from the different analysis sets will be listed, along with the reason for exclusion.

Screen Failures Analysis Set

The screening failure analysis set includes all subjects who were screened but not enrolled. Subjects who were rescreened and subsequently enrolled will be excluded from this analysis set.

Full Analysis Set (FAS)

The FAS comprises all subjects to whom trial drug has been assigned and who received at least 1 dose of GEN3009. Subjects will be analyzed according to their assigned treatment/dose (dose level and regimen planned).

Pharmacokinetic Analysis Set (PAS)

The PAS includes all subjects who have been exposed to GEN3009 and have had at least one pharmacokinetic sample collected that has provided a valid bioanalytical result. All subjects will be classified according to the dose level and treatment schedule which they received.

Safety Set (SAF)

The safety set consists of all subjects who receive at least 1 dose of GEN3009. Subjects will be classified according to actual treatment received.

Subjects who were treated with more than dose level and treatment schedule by mistake will be classified according to the dose level and treatment schedule they received the longest, or the highest dose level (in the case of equal durations). Subjects with a dose reduction due to adverse event will be classified according to the original dose level and treatment schedule.

Should the FAS and SAF conincide, the analyses that are planned to be presented for both will be based on the SAF only.

Dose-Determining Analysis Set (DDS)

The DDS consists of all subjects from the safety set who have either

- Received 80% - 125% of the planned dose
- Completed the DLT observation period
- Experienced a DLT during Cycle 1.

A treated patient who discontinues due to toxicity during the DLT observation period should be included in the DDS, regardless of the amount of dose received.

The DDS will be used for determination of the MTD, and will only be utilized during the Dose Escalation part. All subjects will be classified according to the dose level and treatment schedule (if applicable) which they received. Subjects who were treated with more than one dose level and treatment schedule by mistake will be classified according to the dose level and treatment schedule they received the longest, or the highest dose level (in the case of equal durations).

Response Evaluable Set (EFF)

The Response Evaluable set includes all subjects in FAS who have baseline evaluable disease and at least 1 post-baseline disease evaluation. Following the intent-to-treat principle, all subjects will be classified according to the dose level and treatment schedule to which they were assigned.

The Response Evaluable set will be used for sensitivity analyses during the primary and final analyses in the Dose Expansion part of the trial.

If not otherwise stated in the respective section, the statistical analyses will be performed for the following analysis sets:

Analyses	FAS	SAF	DDS	PAS	EFF
Demographics and baseline characteristics	✓	✓	✓		✓
Exposure and compliance	✓	✓	✓		
Previous and concomitant therapies	✓	✓			
Efficacy: Primary	✓				✓
Efficacy: Secondary	✓				✓
Safety		✓	✓		
Pharmacokinetics				✓	

Should the FAS and SAF coincide, the analysis will be based on the FAS only and noted in table footnote. A similar approach applies to the FAS and EFF.

The data recorded in the screening log will be listed for the Screen Failures Analysis Set, if applicable.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by dose level cohort or diagnosis cohort as applicable, for the different analysis sets as defined in Section 4. Results of the Dose Escalation part and the Dose Expansion part of the trial will be presented separately.

Summary table results for the Dose Escalation part will be presented by dose level cohort and overall as appropriate. Summary table results for the Dose Expansion part will be presented by diagnosis cohort (DLBCL, FL, and CLL/SLL), and overall as appropriate.

In general, continuous variables will be summarised using descriptive statistics, i.e. generally displaying number of subjects in the respective analysis population, number of subjects with data, number of subjects with missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum.

Categorical variables will be summarised by using frequency counts and percentages. In addition, the number of subjects with missing values will be displayed where appropriate. When the number of subjects with non-missing values is displayed by visit (i.e., the number of subjects with a certain assessment completed at a given visit), that number will be used to calculate the percentages for that visit. Otherwise, the number in the column header (e.g., the number in that cohort, etc.) will be used as the denominator unless otherwise specified.

Means, medians, and standard deviations will be presented by 1 additional decimal place more than the standard presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the subject data. Percentages will be presented to 1 decimal place if not otherwise stated.

If the number of subjects in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

Figures will be presented as necessary. Unless otherwise specified, by-visit figures will display information as presented in tables (e.g., based on analysis visit). Time-to-event figures and other figures not based on specific visits will include unscheduled visits.

Unless otherwise specified, all subject data collected as part of this trial (CRF data, laboratory results, etc.) will be presented in data listings. In general, data will be sorted by dose level cohort or diagnosis cohort (as appropriate), site, and subject, and when appropriate by visit or other identifiers for sequence or type of observation.

If not otherwise specified, all statistical tests and confidence intervals will be two-sided, based on $\alpha = 0.05$.

5.2 General definitions and calculations

5.2.1 Dictionaries

Medications and therapies will be coded using the World Health Organization drug dictionary (WHODRUG Global B3 Sep 2019 or later).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.1 or higher.

5.2.2 Baseline values

The **baseline value** is defined to be the last non-missing value which was assessed before the first dose of investigational treatment.

- If an assessment date, but not time, is collected, and the assessment date is the same as the date of first dose of investigational treatment, that assessment will be used to derive the baseline value (if it is non-missing).
- If the assessment time is collected, and the time of the first dose of investigational treatment is collected, and the assessment date is the same as the date of first dose of investigational treatment, that assessment may only be used to derive the baseline value if the assessment time is prior or equal to the start of administration of investigational treatment.
- If multiple assessments are collected on the same day, without recorded time of assessment, the algorithm in Section 5.8(d)(iii) will be followed.

Change from baseline is defined as the post-baseline value minus the baseline value, and will be missing if the baseline value is missing.

Percent change from baseline is defined as 100* (change from baseline)/baseline value. If the baseline value and post-baseline value are both 0, the percent change from baseline will be set to 0. If the baseline value is 0, or missing, and the post-baseline value is non-zero, the percent change from baseline will be set to missing.

5.2.3 Dosage calculations

Cumulative dose (mg) is calculated as the sum of all doses administered to a subject.

Actual dose intensity (mg/cycle) is calculated as cumulative dose / number of cycles initiated.

Cumulative planned dose (mg) is calculated as the sum of planned doses for each treatment administration visit in which respective dose is administered.

Planned dose intensity (mg/cycle) is cumulative planned dose / number of cycles initiated (as per Section 5.4).

Relative dose intensity is calculated as 100 * actual dose intensity / planned dose intensity.

5.2.4 Minimal residual disease (MRD) determination

The level of minimum residual disease (MRD) will be assessed based on results from B-cell receptor (BCR) sequencing at timing of the radiological assessments. The level of MRD may conceptually be classified as "negative" (if MRD level is below a cut-off) or "positive" (if MRD level is above a cut-off). Three cut-offs may be used to classify the level of MRD: 10^{-4}, 10^{-5}, and 10^{-6}, where 10^{-5} is considered as the primary cut-off, and the others may be used for sensitivity analysis.

Given a cut-off, the "overall MRD status" is defined as:

- "MRD negative (cut-off)" as having at least one MRD negative result while on treatment (may or may not have indeterminate result)
- "MRD positive (cut-off)" as lacking an MRD negative result while on treatment (subjects who are continuously MRD positive, MRD indeterminant, not tested, or missing MRD samples throughout trial)

5.2.5 Responses to Prior Anti-Lymphoma Therapy

Subjects are considered **refractory** to a prior therapy if they exhibited no response after at least 2 cycles of therapy, or reappearance or growth of lymphoma after a duration of response of < 6 months.

Subjects are considered **relapsed** if they responded, then exhibited the reappearance or growth of lymphoma after at least 6 months duration of response.

5.3 Categorization of responses

Responses, as assessed by the investigator and Independent Review Committeee (IRC; during the Dose Expansion part), will be categorized as follows, using the Lugano [2] or iwCLL [3] classification method. Further details are provided in Appendices 7, 8, 9 and 10 of the protocol (version 4.0).

The date of response (or progression) will be taken to be the initial date where the response (or progression) was identified. That date will be used for all calculations of duration of response, progression-free survival, etc.

In cases where the response is confirmed, the date of response (or progression) will be taken to be the initial date where the response (or progression) was identified. That date will be used for all calculations of duration of response, progression-free survival, etc.

Lugano or iwCLL Result	**Complete Response**	**Overall Response**	**Disease Control Status**
Complete Response or Complete Remission (CR)	Responder	Responder	In Disease Control
Partial Response or Partial Remission (PR), including nodular PR (nPR)	Non-Responder	Responder	In Disease Control
Stable Disease (SD) or No Response	Non-Responder	Non-Responder	In Disease Control
Progressive Disease (PD)	Non-Responder	Non-Responder	Not In Disease Control
Not Evaluable (NE)	Non-Responder	Non-Responder	Not In Disease Control
Missing response	Non-Responder	Non-Responder	Not In Disease Control

5.3.1 Complete Response or Remission

5.3.1.1 Complete Response per Lugano criteria, for B-cell NHL excluding CLL

Subjects meeting CR criteria based on FDG-PET CT (or CT/MRI and FDG-PET when PET CT not available) per the Lugano criteria will be recorded as CR on the CRF.

Those with documented bone marrow involvement at Screening will require a confirmatory bone marrow aspirate and/or biopsy within 30 days, as described in Table 9.1 of the protocol, within 30 days of the initial documentation of CR. If the bone marrow sample shows bone marrow involvement, the initial response of CR will be retroactively changed to PR.

Subjects without documented bone marrow involvement at Screening will not require further confirmation of their classification as complete responder.

5.3.1.2 Complete Remission per iwCLL criteria, for CLL

In order to meet CR criteria per the iwCLL, subjects must have a normocellular bone marrow sample, with no CLL cells or B-lymphoid nodules, as described in Appendix 8.

5.3.2 Partial Response

5.3.2.1 Partial Response per Lugano criteria, for B-cell NHL excluding CLL

Subjects achieving partial response per Lugano criteria, whether an initial assessment of PR or an unconfirmed CR which is later changed to PR on the basis of bone marrow involvement, do not require any further confirmation.

5.3.2.2 Partial Remission per iwCLL criteria, for CLL

Subjects achieving partial response per iwCLL criteria must meet improvement criteria as specified in Appendix 8 of the protocol. Nodal partial remission (nPR) is defined as subjects in remission with residual nodules or suspicious lymphocytic infiltrates in a bone marrow biopsy which often indicates a residual disease.

Subjects achieving a partial remission per iwCLL criteria may not require a bone marrow assessment if sufficient information on the hematopoietic system is available to determine partial remission.

5.3.3 Progressive Disease

Progressive disease must be confirmed by 2 consecutive scans, at least 4 weeks apart, as described in protocol 9.2.3.2.

5.4 Calculation of durations and times to events

Duration of an event occurring on or after first dose date, in days, is calculated as event end date – event start date + 1.

Durations in weeks will be calculated as durations in days divided by 7.

Durations in months will be calculated as durations in days divided by 30.4375.

Time from initial diagnosis will be calculated in months, from the initial diagnosis of the primary site to the first dose date: (first dose date – date of first diagnosis) /30.4375

Time from last anti-CD20 therapy to treatment with GEN3009 will be calculated in months, from the latest treatment end date of any agent administered as part of the last prior anti-lymphoma treatment that included an anti-CD20 compound to the first dose date: (first dose date – date of last anti-CD20 therapy +1) /30.4375

Total number of months on trial will be calculated as**: (**last contact date – first dose date + 1)/30.4375

Follow-up time will be calculated, in weeks, as: (date of last disease assessment by investigator – first dose date + 1) / 7.

Total treatment duration will be calculated in days as:

- If last cycle is Cycle 1, 2 or 3: last dose date – first dose date + 7
- If last cycle is Cycle 4 – 9: last dose date – first dose date + 14
- If last cycle is Cycle 10 or later: last dose date – first dose date + 28

Progression-free survival (PFS)

PFS is defined as the time in days from Day 1 of Cycle 1 to the day (+1) of first documented disease progression, or the day (+1) of death due to any cause, whichever comes first. Progression does not require confirmation (per Lugano criteria). PFS censoring will be based on 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 [4].

Duration of response (DOR) will be calculated in days as:
DOR = date of first documented progressive disease or death from any cause – date of first response + 1.

In the absence of progressive disease or death, responders will be censored per the FDA censoring rule utilized for PFS, as presented in Appendix I. First response is defined as first documented occurrence of CR or PR (including any complete responses pending confirmation). DOR will only be calculated for those subjects achieving CR or PR.

Overall survival (OS) will be calculated in days as:
OS = date of death from any cause – date of first dose of investigational treatment + 1

Subjects not known to have died will be censored at the last date known to be alive.

Time to next anti-lymphoma treatment (TTNT) will be calculated in days as:

TTNT = date of first recorded administration of subsequent anti-lymphoma therapy – date of first dose of investigational treatment + 1

In the absence of recorded subsequent anti-lymphoma therapy, subjects will be censored at the last non-missing disease assessment.

Time to response (TTR) will be calculated in days as:

TTR = date of first response – date of first dose of GEN3009 + 1

TTR will only be calculated for those subjects achieving CR or PR.

Sustained MRD negative response will be calculated as described in in Section 10.2.8.

5.5 Covariates and strata

Diagnosis cohort (DLBCL, FL, CLL/SLL) will be used as a covariate for analyses that are pooled across diagnosis cohorts in the Dose Expansion part, where appropriate.

The following covariates may be summarized and/or used in analyses as appropriate:

- Diagnosis cohort (DLBCL, HGBCL, PMBCL, FL, MCL, MZL, SLL, or CLL for Dose Escalation part; DLBCL, FL, or CLL for Dose Expansion part)
- Age (continuous or <65 vs. 65+ years)
- Race (categorized into no more than 4 groups, such as Caucasian, Asian, Black, or Other)
- Eastern Cooperative Oncology Group (ECOG) score at screening (actual score or 0-1 vs. 2-4)
- Presence of constitutional symptoms at Screening
- Body mass index (BMI) at screening (continuous or categorized as <18.5, 18.5-24.9, 25.0-29.9, and 30.0+)
- Number of prior anti-cancer therapies (categorized as 1, 2, 3, 4+, or grouped into smaller categories)
- Time from last anti-CD20 therapy till first dose of GEN3009, in days
- Geographic location, as summarized below
- Prior CAR-T exposure category (exposure vs. no exposure)
- Overall MRD negativity status, as described in Section 5.2.4.
- Overall presence or absence of anti-drug antibodies, as described in Section 11.8
- Presence or absence of anti-drug antibodies at Baseline
- Refractory or relapsed to the last line of prior anti-lymphoma therapy
- Refractory or relapsed to the most recent prior anti-CD20 therapy
- Refractory or relapsed to the most recent prior anti-CD20 therapy, when that is the most recent prior anti-lymphoma therapy

- Prior autologous stem cell transplant status

Missing values of covariates will not be imputed. Subjects will be excluded from subgroup analyses, etc. as appropriate.

Trial sites, countries and regions

Subjects will be recruited from across Europe and North America.

Trial sites or countries will be pooled to main regions and regions using the "Standard Country or Area Codes for Statistical Use provided by the Statistics Division of the United Nations Secretariat" [1] as per Appendix II.

In general, Main Region may be used as a covariate. Region may also be considered as a covariate. Regions with <5 subjects will be combined within Main Region, combining the smallest regions with others the same size, and the next larger size if necessary, until each region or pooled region has 5 or more subjects.

5.6 Subgroups

The covariates listed in Section 5.5 may be used in exploratory subgroup analyses during the Dose Expansion part, if sample size allows.

5.7 Missing data

In general, missing data will not be imputed and the data will be analysed as they are recorded.

No imputation of response will be performed.

Pharmacokinetic concentrations below the lower limit of quantification (LLOQ) will be imputed as LLOQ/2 for analyses, as described in Section 13.

Partial or missing dates and times

For incomplete start dates of a medication, event, or medical condition:

- A completely missing start date, coupled with an end date that may be after the first dose of trial medication, will be imputed as starting on the date of first dose of trial medication. (An *end date that may be after the first dose* is considered to be: a completely missing end date, an end date whose partial information permits it to be on or after the first dose, or a complete end date that is on or after the first dose).
- A partially missing start date, that may be on the date of first dose of trial medication (either the month and year are equal to the month and year of the first dose, with missing day, or the years are equal and the day and month is missing), that does not have a partial or complete end date indicating it end before the first dose, will also be imputed as starting on the date of the first date of trial medication.
- A completely missing start date, coupled with an end date that is before the first dose, will be set equal to the subject's birth date.
- A partially missing start date, either coupled with an end date that is before the first dose or whose partial information indicates that it is before the first dose, will be imputed as the earliest possible date (first day of the month, when month and year are present; January 1st, if only the year is present).

For incomplete start dates of a medication, event, or medical condition:

- Where possible, and the end date is completely missing, the event, medication, or condition will be assumed to be ongoing. (If necessary for computations of duration, the last known alive date may be used as an end date).
- For partially missing dates, the latest possible date will be used (the end of the month, when month and year are present; December 31st, if only the year is present).

Similarly, for incomplete start times:

- For events, medications, or conditions beginning on the date of first dose of trial medication, the start time will be imputed as the time of the start of the first dose of trial medication, unless partial information indicates otherwise, in which case it will be imputed as 00:00.
- All partial or missing start times on other days will be imputed as the earliest possible time.

Incomplete end times will be imputed as 23:59.

5.8 Observation and analysis times

Subject information may be presented by cycle day or study day, as appropriate.

Study days

Study day is defined as the number of days between the first dose of trial medication and a particular date, and is calculated as:

- Study day = Assessment date – Date of first dose of trial medication, where assessment date is before the date of first dose

- Study day = Assessment date – Date of first dose of trial medication + 1, where assessment date is on or after the date of first dose

Therefore, the date of the first dose of trial medication will be Day 1, and the day immediately prior will be Day -1.

Cycle days

Cycle day is presented by both cycle number and day number, where C2D1 represents Day 1 of Cycle 2. The first dose of trial medication for a given cycle is considered Day 1 of that cycle, and cycle day in general are calculated as for study day:

- Cycle day = Assessment date – Date of first dose of trial medication + 1, where assessment date is on or after the date of first dose

Cycle day is not defined for dates prior to the first dose of trial medication, or for dates greater than 28 days after the last dose of trial medication. In infrequent cases, a new cycle might be delayed; the days between the 28th day of the last cycle and the 1st day of the new cycle will be considered off-cycle days, and cycle day will not be defined. If a new cycle starts slightly earlier than the planned day for any reason, the first day of dosing in that cycle will be considered Cycle x Day 1, and the prior cycle will have <28 days.

Trial periods

For the Dose Escalation part only, the DLT assessment period (also referred to as the DLT observation period) is defined as 28 days from Cycle 1 Day 1, as per protocol 7.1. Therefore, this period will run from Cycle 1 Day 1 through Cycle 1 Day 28.

The trial participation period is divided into 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 medication. (Subjects not receiving trial medication will remain in the pre-treatment period for the duration of their participation.)
- The on-treatment period begins on the date of the first dose of trial medication, and stops 4 weeks (i.e. 28 days) after last dose of trial medication.
- The post-treatment period begins at end of 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.

Definition of analysis time points or time windows

Data reported on the CRF will be assigned to analysis visits as follows, where 'visit' refers to visit name or cycle day, as applicable. Data will be listed by nominal visit, as recorded on the CRF, and summarized in tables and figures using the analysis day:

a) Visits prior to the date of first dose of trial medication will be assigned to the Screening visit.

b) Scheduled post-baseline visits other than end of treatment or end of trial visits will be assigned to the nominal visit.

c) Regularly scheduled assessments occurring at an unscheduled visit, end of treatment visit, or end of trial visit will be assigned to the closest scheduled visit (or the later of the two visits, if equidistant between scheduled visits). For example, if a subject completes Cycle 3 Day 8 visit and returns 2 days later for an end of treatment visit, the assessments collected at that visit would be assigned to Cycle 3 Day 11.

d) If >1 assessment of a certain type is assigned to a given analysis visit:

   i. If only 1 assessment is non-missing, the non-missing results will be summarized.

   ii. If >1 assessment is non-missing, and only 1 assessment is within the visit window, the assessment within the visit window would be summarized.

   iii. If >1 non-missing assessments are within the visit window, and one was collected at the actual visit, that assessment will be used. Otherwise, the one that is closest to the planned time of the visit will be used.

5.9 Multiple Comparison/Multiplicity

No multiplicity adjustment is planned.

6 Subject Accounting and Disposition

6.1 Subject accounting

The number and percentages of subjects in each analysis set as defined in Section 4 will be presented by dose level cohort or diagnosis cohort (as appropriate), region, country and site.

6.2 Disposition and withdrawals

The number and percentage of subjects will be summarized by dose level cohort or diagnosis cohort (as appropriate), including:

- Subjects initiating Cycle 1, 2, 3 …
- Subject status by trial period: Not yet begun treatment, On treatment, Post-treatment but remaining on trial, and Withdrawn from Trial
- Death by trial period and cycle, if applicable
- Reasons for discontinuation, overall and by trial period

The time course of withdrawal from the trial will be presented by means of an incidence curve.

An overall listing of all subjects screened, including site, country, informed consent date and version, screening number, DNA informed consent flag, and analysis set flags will be provided. Additionally, a separate listing will be provided for subjects who were successfully screened but not treated, as well as a listing of screen failures. A listing of inclusion and exclusion criteria not met, for subjects in the FAS, will also be provided.

6.3 Protocol deviations

Important protocol deviations will be detailed in the Protocol Deviation Plan.

All violations of the inclusion criteria will be summarized by cohort and trial site for the FAS.

All subjects with protocol deviations as specified above will be listed.

7 Demographics and Background Characteristics

Demographic and baseline characteristics, as specified below, will be presented descriptively.

7.1 Demographics

The following demographic characteristics will be presented:

- Sex
- Age (years), as entered on the CRF, continuously and categorized as <65 and 65+ years
- Race and ethnic origins, as entered on the CRF
- Weight (kg) at baseline
- Height (cm) at baseline

7.2 Disease characteristics

The following baseline characteristics will be presented:

- Primary diagnosis (DLBCL, FL, CLL/SLL, etc.)
- Disease status at Screening
- ECOG performance status at screening
- Ann Arbor stage (for B-cell NHL) or Binet stage (for CLL/SLL) at initial diagnosis
- Time from initial diagnosis, in months (as per Section 5.4)
- Time from most recent recurrence/relapse or progression to first dose of GEN3009, in months (if applicable)

7.3 General medical history

The diseases are coded according to MedDRA, and will be classified as follows:

- Previous medical conditions, i.e. medical conditions that stopped prior to start of treatment
- Ongoing (concomitant) medical conditions, i.e. medical conditions still present after start of treatment

The frequency of diseases recorded from medical history will be presented after classification into previous and concomitant conditions by system organ class (SOCs) as well as the frequencies of preferred terms (PT) within each SOC.

Medical history will be summarized overall, and separately for previous medication conditions and ongoing medical conditions

7.4 Prior Anti-Cancer Therapy

Prior anti-lymphoma therapies are coded according to WHODRUG and stored with Anatomical Therapeutic Class (ATC) codes and generic names.
The number of prior anti-lymphoma therapies, the best response to the most recent regimen, the primary reason the most recent regimen was discontinued, and the number of cycles for the most recent regimen will be tabulated.

New anti-cancer therapies are addressed in Section 9.2.

7.5 Prior Radiotherapy

Prior radiotherapies are coded according to WHODRUG and stored with Anatomical Therapeutic Class (ATC) codes and generic names.

The presence or absence of prior radiotherapy, the site of radiotherapy, the type of radiotherapy, and best response to prior radiotherapy will be tabulated.

7.6 Prior Surgery

Prior surgeries will be coded according to MedDRA. All prior surgery will be listed by subject.

8 Exposure and Compliance

8.1 Dose Level Cohorts

All subjects receiving investigational treatment during this open-label trial will receive GEN3009. Subjects in the Dose Escalation part will receive dose levels as assigned; all subjects in the Dose Expansion part are expected to receive the RP2D.

8.2 Dosage and Treatment Duration

Descriptive statistics for the number of cycles initiated will be presented overall and by dose level cohort or diagnosis cohort (as appropriate).

The cumulative dose, actual dose intensity, cumulative planned dose, planned dose intensity, relative dose intensity, and treatment duration will be presented by cohort, separately for Cycles 1-3, 4-9, and 10+. The completion status and withdrawal reasons (withdrew due to AE, withdrew due to PD, or withdrew due to other reason), and subjects with dose adjustments (reductions,

interruptions, or permanent discontinuations) and reasons for adjustments, will be summarized by treatment cycle and cohort.

The total treatment duration and total number of days in trial will be summarized by cohort.

Follow-up time will be calculated, as the time from first dose of trial treatment until the last contact date of date of death, whichever comes last. Follow-up time will be summarized with univariate statistics, without adjusting for censoring, and presented using mean, median, SD, minimum and maximum.

Exposure information will be listed by subject.

8.3 Trial-Related Procedures, Brain Scans, and Lumbar Punctures

Trial-related procedures, brain scans, scans of other organs, and lumbar punctures will be listed chronologically by subject.

9 Medications and Therapies

9.1 Prior and Concomitant Medications

Medications are coded according to WHODRUG and stored with Anatomical Therapeutic Class (ATC) codes and generic names.

Medications will be classified as prior if the stop date and/or time was before the first dose of trial medication, and concomitant if begun after the first dose of trial medication or continuing to be used after the first dose of trial medication. Missing or partly missing stop dates will be imputed using the rules defined in Section 5.7, where applicable.

The number and frequency of concomitant medications will be summarized using therapeutic subgroup (ATC Level 2). If a subject has received more than 1 medication within an ATC level, he/she will be counted only once for that ATC level.

All prior and concomitant medications will be listed. Medications recorded as “pre-medications” on the CRFs will also be listed separately.

9.2 Subsequent Anti-Cancer Therapies

Subsequent anti-lymphoma therapies (initiated after first dose administration of GEN3009) will be categorized using WHODRUG, and summarized by ATC Level 2 and preferred term.

The time to next anti-lymphoma therapy will be summarized as per Section 10.2.5 Missing or partly missing stop dates will be imputed using the rules defined in Section 5.7, where applicable.

9.3 Diagnostic/Medical Treatment Procedures

Non-protocol specified procedures will be listed by subject.

9.4 New Tumor-Directed Surgery

All new tumor directed surgery related to the disease will be coded using MedDRA, and will be listed by subject.

10 Efficacy

The primary endpoint is the Overall Response Rate (ORR) using the Lugano criteria (for lymphoma) or iwCLL criteria (for CLL/SLL).

Response assessment will be conducted locally by investigators during the Dose Escalation part.

During the Dose Expansion part, assessments will be performed both by the investigators and IRC, where the primary endpoint will be based on investigator assessment.

The secondary efficacy endpoints include: Duration of Response (DOR), Complete Response Rate (CRR), Progression-free Survival (PFS), Overall Survival (OS), Time to Response (TTR), Time to Next anti-lymphoma Therapy (TTNT), and Minimal Residual Disease (MRD) rate.

Individual subject status over time will be presented via a swim lane plot. This figure may be split into separate plots based on cohort, stage, or subject characteristics as appropriate. Separate figures will be presented for assessments, by diagnosis cohort.

No statistical testing will be performed to evaluate the difference between diagnosis cohorts. Each cohort will be analysed independently of the other.

10.1 Primary efficacy analysis

The primary efficacy endpoint for the Dose Expansion part of this trial is the objective response rate (ORR), using the Lugano criteria for lymphoma and iwCLL for CLL. The ORR is considered a secondary efficacy endpoint for the Dose Escalation part. The main analysis of ORR will utilize the FAS.

10.1.1 Calculation of the Objective Response Rate

The ORR and its 95% confidence interval, based on Clopper-Pearson methodology, will be presented for each cohort.

The ORR and confidence interval will be calculated as per the following pseudocode:

```
PROC FREQ data=xxx;
     TABLE response / BINOMIAL (EXACT P=p0) ALPHA = 0.05 ;
     ODS output BINOMIALPROP=xxx
                BINOMIALCLS=xxx;
     run;
```

The interim analysis for the Dose Expansion part shall be conducted as described in Section 14, to evaluate safety data. No analysis of efficacy data is planned at that time. Therefore, no adjustment to alpha spending for the final analysis will be performed.

Handling of missing data

No imputation of overall response will be performed. subject

Sensitivity and Robustness Analyses

In order to assess the treatment effect using different assumptions from those in the FAS analysis, the following analyses may also be performed at the final analysis for the Dose Expansion part:

- Evaluation of ORR as assessed by IRC
- Evaluation of ORR as assessed by the Investigator, using EFF set
- Evaluation of ORR as assessed by the IRC, using EFF set

10.2 Secondary efficacy analyses

The secondary analyses, including analysis of DOR, CR, PFS and TTR, are described below. As with the primary endpoint, response assessments are conducted by investirgators in the Dose Escalation and Dose Expansion parts, and may also be conducted by the IRC in the Dose Expansion part. Endpoints based on response per IRC may be used for sensitivity analyses.

10.2.1 Duration of response

DOR will be derived for all subjects achieving treatment response. The number of subjects achieving treatment response, as well as the numbers subsequently achieving progressive disease or death, and the number censored, will be presented by cohort. Subjects without a documented progression or death will be censored following the rule laid out in Section 5.3.1.

The median DOR and its 95% confidence interval based on Kaplan-Meier estimates will be presented, as well as the first and third quartiles and their confidence intervals. DOR will also be presented graphically, using Kaplan-Meier curves.

The proportion of subjects with ongoing response, together with their 95% confidence intervals, will be calculated at monthly intervals starting at 1 month, based on Kaplan-Meier methodology.

The following pseudocode will be used to analyze duration of response and other similar times to event:

```
PROC LIFETEST data=xxx OUTSURV=s1 TIMELIST=xx CONFTYPE=loglog;
     WHERE COHORT=xxx;
     TIME survtime*censor(xxx);
     ODS OUTPUT QUARTILES=q1;
     run;
```

10.2.2 Complete response/complete remission rate

CR rate is defined as the proportion of subjects with CR as best overall response. The CR will be reported jointly with the ORR, and using the same methodology as for the ORR.

10.2.3 Progression-free survival

PFS will be summarized, analysed, and presented graphically as described for DOR. Subjects without a documented progression or death will be censored following the rule laid out in Section 5.3.1.

If feasible, PFS analysis may be also stratified by overall MRD status (negative or positive as per definition in Section 10.2.7)

10.2.4 Time to response

TTR will be derived for all subjects achieving PR or CR. TTR will be summarized using descriptive statistics.

10.2.5 Overall survival

OS will be summarized, analysed, and presented graphically as described for DOR. If a subject is not known to have died, then OS will be censored, and the censoring date will be the latest date the subject was known to be alive (on or before the cut-off date).

OS, using the FAS, will also be summarized and graphed separately for overall MRD negativity status as described in Section 5.2.4.

Survival status, as assessed at regularly scheduled intervals after the completion of treatment, will be listed chronologically by subject.

10.2.6 Time to next anti-lymphoma therapy

TTNT will be derived for all subjects receiving trial treatment. The number of subjects treated, as well as the numbers subsequently undergoing a non-trial anti-lymphoma therapy and those censored without undergoing another anti-lymphoma therapy, will be presented by cohort.

TTNT will be summarized, analysed, and presented graphically as described for DOR.

10.2.7 Proportion of MRD negative subjects

The proportion of MRD negative subjects, as defined in Section 5.2.4, will be summarized by cycle (with the proportion being dependent on number of subjects starting each cycle) and across trial duration, for each cohort. Summarizes will be presented as described for the primary efficacy endpoint, using the FAS.

Similar summaries will be presented for the subgroup of complete responders.

10.2.8 Sustained MRD negative response

Once CR is reached, the MRD level will be assessed on a 6-monthly interval. The proportion of subjects (out of the number subjects included in FAS) with sustained MRD negativity (at cut-offs as described in Section 10.2.7) for ≥ 6 months, and ≥ 12 months, will be summarized and presented as for the primary efficacy endpoint.

As well as summarizing this statistic for the FAS, it will also be summarized similarly for those subjects reaching CR at any time point during treatment.

10.3 Other efficacy analyses

Additional efficacy analyses will include the following. They will be evaluated descriptively and exploratively:

10.3.1 Disease control rate

The disease control rate, defined as the proportion of subjects with a best overall response as CR, PR or SD. The disease control rate will be reported jointly, and using the same methodology, as for the ORR, using both the Lugano and iwCLL criteria.

10.3.2 Measurable and Non-Measurable Lesions

All measurable and non-measurable lesion results will be listed.

The sum of the products of the perpendicular diameters (SPD) for measurable lesions will be included in listings, as well as summarized by visit and best (greatest) reduction per subject. SPD will also be summarized by ADA subgroup, as described in Section 11.8.

Changes in SPD for measurable lesions will also be presented graphically as follows:

- Mean + SE plots over time for actual values
- Mean + SE plots over time for percent change from baseline
- Waterfall plot of best (greatest) reduction per subject
- Individual profile plots of the cross-products of the measurements of each lesion, over time

11 Safety

The primary endpoints for the Dose Escalation part include the number of DLTs during the DLT observation period, the frequency and severity of AEs and SAEs, changes from baseline in laboratory results, and changes from baseline in vital signs. The frequency and severity of AEs and SAEs and the changes from baseline in laboratory results and vital signs are secondary endpoints for the Dose Expansion part.

11.1 Adverse events

Adverse events (AE) will be coded using MedDRA, and the National Cancer Institute Common Terminology Criteria for AEs (CTCAE criteria v5.0 or higher). They will be presented by primary System Organ Class (SOC) and Preferred Term (PT), or by PT only (in descending order) by dose cohort and overall. Subjects will be summarized at most one time per SOC and at most one time per PT, unless otherwise specified.

Adverse events are collected from the first GEN3009 dose until 30 days after the last GEN3009 dose. Treatment-emergent adverse events (TEAEs) are defined as AEs which begin, or worsen, during the on-treatment period ending 4 weeks after the last dose of trial medication as defined in Section 5.4. Adverse events collected during the post-treatment period will be flagged in data listings, and excluded from summaries, and will not be categorized as TEAEs.

The following summaries of TEAEs will be presented:

- All TEAEs, by SOC and PT
- All TEAEs, by PT, in order of descending frequency
- Serious TEAEs adverse events (SAEs), by SOC and PT
- Non-serious TEAEs, by SOC and PT
- TEAEs of CTCAE grade 3 or higher, by SOC and PT
- Non-serious TEAEs of CTCAE grade 3 or higher, by SOC and PT
- Related non-serious TEAEs of CTCAE grade 3 or higher, by SOC and PT
- TEAEs leading to dose reduction or dose interruption, by SOC and PT
- TEAEs leading to permanent discontinuation of trial treatment, by SOC and PT
- TEAEs by SOC, PT, and severity, where subjects are presented at the highest recorded severity level within SOC and PT
- Related TEAEs, by SOC and PT
- Related serious TEAEs, by SOC and PT
- TEAEs by SOC, PT, and relationship, where subjects are presented at the highest recorded relationship within SOC and PT

- Fatal TEAEs

The following tables will also be presented by overall ADA status, as per Section 11.8.

- Non-serious TEAEs of CTCAE grade 3 or higher, by SOC and PT

- Fatal TEAEs

All adverse events will be listed by subject, with those beginning during the post-treatment period flagged. Additional listings will be presented for all SAEs, all AEs leading to withdrawal of treatment, non-serious AEs of grade 3 or higher, and fatal AEs.

In addition, adverse events will be presented graphically by the incidence of AEs over infusion number, and using a swim lane plot to monitor the severity of AEs over time.

11.1.1 Dose-Limiting Toxicities (DLTs)

Adverse events that are assessed by the investigator to be related to GEN3009, which occur during the DLT observation period of the Escalation Period as described in Section 5.8, and meet the specific criteria listed in protocol 7.1, are classified as DLTs. These criteria include: all Grade 5 toxicities; hematologic events including thrombocytopenia, neutropenia and anemia of Grades 3 or 4 and meeting certain additional criteria; and non-hematologic AEs of Grade 3 or higher excluding certain fevers, hypotension, laboratory values, nausea, vomiting, diarrhea, fatigue/asthenia, or alopecia, which meet certain additional criteria.

All DLTs will be listed, and summarized by SOC and PT.

11.1.2 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) may be identified throughout the course of the trial, and will include infusion-related reactions (IRRs).

TEAEs that are symptoms of AESIs may be summarized separately, with toxicity grades corresponding to the AESI category.

11.1.2.1 Infusion-Related Reactions (IRRs)

IRRs are defined as per protocol 10.1.4 as any AEs occurring during infusion or where the onset of the event occurs within 24 hours after the end of the infusion. Some events occurring within that window may be judged to not be infusion-related by the investigator.

All IRR signs and symptoms will be listed chronologically by subject. IRRs may be summarized by cycle and infusion number.

11.1.3 Deaths and Fatal AEs

Fatal adverse events will be summarized by dose level cohort or diagnosis cohort (as appropriate), SOC, and PT. All fatal adverse events will be presented in a separate listing, with post-treatment AEs flagged.

All deaths will be summarized by cohort, period (on-treatment or post-treatment), and primary cause of death. Death information will be listed by subject as well.

11.2 Vital signs and pulse oximetry

Actual values and change from baseline in vital signs will be summarized by cohort, period, visit and time point (where applicable). Oxygen saturation will be presented similarly.

The following clinically notable values will be flagged in listings. A separate table will present the number and percent of subjects meeting these criteria, by visit.

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

11.3 Clinical laboratory results

11.3.1 Haematology, chemistry, and urinalysis

Haematology, chemistry and urinalysis laboratory results will be graded programmatically as per CTCAE, where all results not meeting CTCAE grading criteria (for tests which are evaluated using CTCAE) will be assigned grade 0. The worst (highest) post-baseline CTCAE grade will be determined for each subject and laboratory test. Post-baseline labs will be defined by those recorded during the on-treatment period, as defined in Section 5.8.

For these laboratory tests where grades are not assigned via CTCAE, results will be categorized as low, normal, or high based on laboratory-provided normal ranges. If the laboratory provides categorizations in addition to normal ranges, laboratory-provided normality results will be used in lieu of programmatic categorization. The worst post-baseline normality classification will be determined for each subject and laboratory test, and will be considered the one furthest from the normal range boundary.

All recorded haematology, chemistry, and urinalysis results will be listed, with CTCAE grades or normality classifications indicated as applicable. Additional listings will present CTCAE grade 3 and 4 laboratory results.

Actual results and changes from baseline will be summarized by dose level cohort or diagnosis cohort (as appropriate), period, cycle, and study day.

For laboratory tests graded by CTCAE, shift tables will compare the baseline CTCAE grade to the worst post-baseline (e.g., worst on-treatment) CTCAE grade. Laboratory tests not graded by CTCAE will be presented using shift tables to evaluate the normality classification (low, normal, or high) at baseline as compared to the worst post-baseline (e.g., worst on-treatment) value.

A plot of the mean and standard error of each laboratory result will be displayed graphically over time.

11.3.2 Pregnancy test results

All laboratory results for pregnancy tests will be listed.

11.3.3 Serology

All laboratory results for HIV antibody, hepatitis B, hepatitis C, and cytomegalovirus (CMV) will be listed.

11.3.4 Tumor Lysis Syndrome Surveillance

All tumor lysis syndrome surveillance information will be listed by subject.

11.3.5 Tumor and bone marrow biopsy and aspirate results

All biopsy results will be listed chronologically by subject. Tumor biopsy and bone marrow biopsy and aspirate results will be listed separately.

11.3.6 Archived Tumor Tissue

All archival tumor tissue information will be listed by subject.

11.4 ECG

Electrocardiography results will be collected, and analysed by a central vendor.

QTcF will be categorized as defined in International Conference on Harmonization (ICH) E14: <=450 ms, >450-480 ms, >480-500 ms, and >= 500ms. Changes from baseline in QTcF will also be flagged if the changes are >30-60 ms or >60 ms.

Actual values and changes from baseline will be summarized by cohort, period and time point. In addition, the number and percent of subjects falling in each QTcF category, both for actual values and changes from baseline, will be presented. All electrocardiography results will also be listed chronologically.

11.5 Physical Examination

All available data will be listed, including performance of overall physical examination and date, and assessments of lymph nodes.

All abnormal findings will be recorded in medical history or adverse events, as appropriate. As such, summaries of abnormal findings will be included in medical history summaries (as per Section 7.3) or adverse event summaries (as per Section 11.1). No stand-alone summaries of physical examination results will be performed.

11.6 ECOG

All ECOG performance status results will be listed, and summarized by dose level cohort or diagnosis cohort (as appropriate), period and time point.

11.7 Constitutional Symptoms

All constitutional symptoms will be listed, and summarized by dose level cohort or diagnosis cohort (as appropriate), period and time point.

11.8 Anti-Drug Antibodies

The presence or absence of any anti-drug antibodies will be listed by subject and time point. The number and percent of subjects with anti-drug antibodies will be summarized overall and by time point.

Overall ADA status will be derived as follows:

- At least one positive result = "*positive for ADA*"
- No positive result, and at least one negative result and (may or may not have one or more indeterminate results) = "*negative for ADA*"
- Only indeterminate results, or no results = "*indeterminate"*

11.9 Hospitalization

All information regarding hospitalizations will be listed by subject.

11.10 Transfusions

All transfusion information will be listed by subject.

11.11 Chromosomal Alteration Status

All chromosomal alteration information will be listed by subject.

11.12 Radiographic Assessments

All FDG PET-CT scan (or CT/MRI and FDG PET when PET-CT scan not available) results will be listed.

11.13 Supplemental Safety Forms

Results of supplemental safety forms will be listed.

12 Biomarker Investigation

All biomarker results will be presented using the Safety Set, unless otherwise specified.

Results from circulating tumor DNA (ctDNA), DNA, RNA, and B-cell Receptor (BCR) clonality will not be listed or summarized herein, but will be presented in a separate biomarker technical report where appropriate.

12.1 Peripheral cytokine, complement and immunophenotyping measures

CCI

12.2 Protein Expression

CCI [redacted]

13 Pharmacokinetic (PK) Analyses

Venous blood samples are collected prior to GEN3009 dosing, and specified time points after dosing, as described in Table 1-3 (Dose Escalation), Table 1-6 (Dose Expansion) and Section 9.5 of the protocol, for the measurement of plasma concentrations of GEN3009. Samples will also be collected at the End of Treatment visit.

The concentration of GEN3009 in plasma samples will be determined by a validated, specific, and sensitive ligand binding assay, at the assay CRO.

13.1 The PK analysis and output to be generated are detailed in the next paragraphs. In short, GEN3009 concentration data will be presented graphically and summarized by dose group and ADA status. The sponsor will calculate PK parameters based on non-compartmental methods and will provide the results to be included in the Tables, Listings and Figures as part of this SAP. Graphical exploration of the relationships between exposure and covariates, observations of safety, efficacy or pharmacodynamic biomarkers will be performed by the sponsor outside of the scope of this SAP. GEN3009 Concentration data

Individual observations of plasma concentration will be listed chronologically for each subject. Concentrations below the lower limit of quantification (LLOQ) will be reported as <LLOQ in data listings and omitted from summary statistics and graphs.

GEN3009 concentration data will be presented graphically, using individual curves of concentrations. All available data will be shown in these figures. Separate figures will be presented showing the plasma concentration-time profiles after the first dose of Cycle 1 and Cycle 2.

Concentrations will be summarized using both arithmetic and geometric means, standard deviations, coefficient of variations expressed as percentages (CV%), medians, minimums and maximums. Summaries will be presented overall and by ADA status, as described in Section 11.8.

13.2 Pharmacokinetic parameter calculations

Pharmacokinetic parameters will be calculated by the sponsor based on non-compartmental methods using Phoenix 64 (version 8.1 or later). The following parameters will be derived for each subject for the Cycle 1 and Cycle 2 profiles:

$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve, from time zero to the last quantifiable concentration (mass x time x volume^{-1})
$AUC_{0\text{-7days}}$	Area under the plasma concentration time curve, from time

	zero to seven days (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 (λz) of a semi logarithmic concentration-time curve (time)
CL	Apparent total plasma clearance (volume x time^{-1})

Elimination half-life $t_{1/2}$ and associated parameters (AUC_{inf} and CL) will be reported only for cases where a sufficient number of observations above the lower limit of quantification (LLOQ) are available in the linear elimination phase. The $AUC_{0\text{-}7days}$ will be calculated only if the plasma concentration after 7 days (the Day 8 predose sample) has a quantifiable result or if $t_{1/2}$ can be calculated. Additional parameters – such as dose normalized C_{max} and AUCs, apparent volume of distribution, accumulation ratios between the Cycle 2 and Cycle 1 exposures – may be calculated to fully characterize the PK profiles of GEN3009.

All pharmacokinetic parameters for each profile (Cycle 1 and Cycle 2) will be listed by subject and summarized by dose level and by ADA status. All subjects in the PK dataset for which PK parameters could be calculated will be included in the descriptive statistics for those parameters. 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.

If deemed applicable, compartmental modelling approaches may also be applied.

13.3 Relationships between parameters and covariates

Relationships between PK parameters and covariates such as dose level, weight, age, indication, as well as relationships between emerging observations of safety (e.g. IRR, cytokines, QTcF), efficacy or pharmacodynamic biomarkers (e.g. peripheral blood B-cells and CH50) and plasma exposure will be explored graphically by the sponsor. If deemed relevant, these relationships may be further investigated by population modelling approaches.

14 Interim Analyses

DLTs will be evaluated after the completion of DLT observation periods for each dose level cohort, using the mBOIN approach, during the Dose Escalation part.

A single interim analysis will be performed during the Dose Expansion part, to analyse the safety data after 20 subjects have completed 2 cycles.

No other formal interim analyses are planned for this trial.

14.1 DLT Evaluation during Dose Escalation part

After all subjects within a dose cohort have completed the DLT observation period as described in Section 5.8, the Dose Escalation Committee (DEC) will review the data and propose initiation of the

next dose cohort (as appropriate). The sponsor's Safety Committee must endorse the proposal before the next dose cohort can begin enrolling.

Dose escalation will be conducted following an mBOIN design, as described in protocol 4.1.1.1 and Yuan et al 2016 [5]. After the DLT observation period has been completed for a given cohort, the frequency of DLTs in that dose level will be evaluated to determine if the next cohort should stay on the same dose, escalate to the next higher dose level, or de-escalate to the next lower dose level.

Based on a target toxicity level of 25%, the mBOIN design results in an escalation border of λ_1 = 0.197 and λ_2 = 0.298, as stated in the protocol. To summarize, if the DLT frequency is ≤0.197, escalation would be recommended; 0.198 – 0.297 would indicate staying at the same dose level; and DLT frequency ≥ 0.298 would suggest a de-escalation.

Further, a certain dose level can no longer be investigated if an additional DLT-free cohort on the same level would lead to de-escalation. This is summarized in Table 10 of the protocol. For example, a cohort of 3 people experiencing 3 DLTs might be de-escalated, and the next lower cohort meet criteria for escalation; if 3 more people were added to the higher cohort, the 3 DLTs among now 6 subjects would automatically meet de-escalation criteria. Therefore, once 3 DLTs are experienced in a cohort of 3, that dose level is terminated.

Following the completion of the DLT observation period, the Dose Escalation Committee will recommend the dose level for the next cohort of subjects, based on the mBOIN algorithm recommendation and a review of the safety data. The DEC's recommendation will need to be endorsed by the Safety Committee before enrolling the next cohort.

The Dose-Determining Set is used for all analyses to support dose escalation decisions.

The following statistical summaries and listings may be presented. Dose escalation decisions may also be made based on raw data listings from the clinical database.

- Summary of subject demographics
- Summary of TEAEs during the DLT observation period
- Listing of adverse events, by dose level cohort and subject

14.2 Interim Analysis during Dose Expansion part

The objective of the interim analysis during the Dose Expansion part is to evaluate safety data.

This analysis will be performed after 20 subjects (across the 3 diagnosis cohorts) have been exposed and followed for 2 cycles. Subjects who have been treated, but withdrawn from the study prior to the end of the second cycle, will be included.

The cut-off date for the interim analysis will be based on the 20th subject in the Dose Expansion part completing the second cycle (i.e., 8 weeks after the first dose), with additional time allowed for data entry and cleaning as necessary.

This interim analysis is performed to review safety data. No pre-specified stopping criteria will be utilized.

The interim analysis results will be presented using the FAS or Safety Set, unless otherwise specified. The following statistical summaries and listings will be presented:

- Summary of subject accounting and disposition, using the FAS, as described in Section 6
- Summary of subject demographics, using the FAS, as described in Section 7

- Summary of TEAEs by SOC and PT, using the Safety Analysis set, as described in Section 11.1
- Listing of adverse events, by subject and time point

15 Statistical Analyses for Safety Monitoring

The statistical analysis for safety monitoring is specified in a separate DMC charter.

16 Data Exchange Procedures

All analyses will be communicated to the sponsor and DMC through the use of Clinipace's Secure File Exchange (SFE) site.

17 Software

The data will be analysed using SAS version 9.3 or higher.

18 Abbreviations

AE	Adverse Event
ADA	Anti-Drug Antibodies
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Class
$AUC_{0\text{-}7\ days}$	Area under the plasma concentration time curve, from 0 to 7 days (Cycle 1 Day 1 only)
$AUC_{0\text{-}\infty}$ (AUC_{inf})	Area under the plasma concentration time curve, from time 0 extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the plasma concentration time curve, from time 0 to the last measurable non-zero concentration
CI	Confidence Interval
C_{max}	Maximum observed concentration of GEN3009
CMV	Cytomegalovirus
CR	Complete Response or Complete Remission
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose-Determining Analysis Set
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFF	Response-Evaluable set
FAS	Full analysis set
FDA	US Food & Drug Administration
FL	Follicular Lymphoma

HGBCL	High Grade B-cell Lymphoma
ICH	International Conference on Harmonization
IRC	Independent Review Committee
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MZL	Marginal Zone Lymphoma
nPR	nodal Partial Remission
NE	Not Estimable
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PK	Pharmacokinetics
PMBCL	Primary mediastinal B-cell Lymphoma
PR	Partial Response or Partial Remission
PT	Preferred Term
QTcF	Fridericia's correction to the QT interval
R/R	Relapsed or Refractory
RP2D	Recommend Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable Disease
SFE	Secure File Exchange
SLL	Small Lymphocytic Lymphoma
SOC	System Organ Class
$t_{1/2}$	Terminal phase half-life
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
T_{max}	Time of maximum observed concentration
TTNT	Time to Next Anti-Lymphoma Therapy
TTR	Time To Response
WHODRUG	World Health Organization Drug Dictionary

19 References

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20 Appendices

Appendix I: Progression and Censoring Criteria for Analyses of Progression-Free Survival and Duration of Response

These censoring rules will be applied to PFS and DoR, as per Section 5.4.

Situation	Date of Progression or Censoring	Censoring Rule
Incomplete or no baseline tumor assessments	Cycle 1 Day 1 (in lieu of randomization)	Censored
Progression documented between scheduled visits	Earliest of: - Date progression assessment showing new lesion (if progression is based on new lesion) - Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment dis-continuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression assessment with no documented progression	Censored
Next anti-lymphoma treatment started	Date of last progression assessment with documented non-progression before start of new treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented non-progression	Censored

Appendix II: Categorization of Countries

Main Region	Region	Country
Northern America	Northern America	United States
Europe	Northern Europe	Denmark
	Southern Europe	Spain
	Western Europe	Netherlands

The following appendices will be produced following the finalization of the SAP.

Appendix III: Proposed List of Tables

Appendix IV: Proposed List of Listings

Appendix V: Proposed List of Figures