Statistical Analysis Plan

NCT Number: NCT04074330

Title: Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma

Study Number: TAK-981-1501

Document Version and Date: Version 2.0, 03 March 2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-981-1501

Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma

PHASE 1/2

Version: **FINAL 2.0**

Date: 03 March 2023

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1.1 Approval Signatures

Study Title: Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma

Approvals:

[redacted] PhD
[redacted] Oncology Statistics

Date

Amendment History:

Date	Version Number	Amendment Type
03 Mar 2023	Final Version 2.0	Substantial
18 June 2020	Initial SAP 1.0	Not applicable

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	absolute neutrophil count
AE	adverse event
$AUC_{0-\infty}$	area under the plasma/blood/serum concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration versus time curve from time 0 to time t
BLRM	Bayesian Logistic Regression Modeling
CL	total clearance after intravenous administration
C_{max}	maximum observed concentration
CR	complete response
CRS	cytokine release syndrome
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FL	follicular lymphoma
GGT	gamma glutamyl transferase
IFN	interferon
IRR	infusion-related reaction
IV	intravenous
LDH	lactate dehydrogenase
MAD	maximally administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PAD	pharmacologically active dose
PD	progressive disease (disease progression)

Abbreviation	Term
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QTc	corrected QT interval
RBC	red blood cell
R-CHOP	rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin) and prednisone
RP2D	recommended phase 2 dose
SMC	Safety Monitoring Committee
SUMO	small ubiquitin-like modifier
SUMO1	small ubiquitin-like modifier 1
SUMO2	small ubiquitin-like modifier 2
SUMO3	small ubiquitin-like modifier 3
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	first time to reach maximum (peak) plasma concentration
TEAE	treatment-emergent adverse events
TLS	tumor lysis syndrome
TTP	time to progression
WHO	World Health Organization
Vss	volume of distribution at steady state after intravenous administration

4.0 OBJECTIVES

The study will be conducted in 2 parts:

- Phase 1 dose escalation guided by Bayesian Logistic Regression Modeling (BLRM), and a Japan-Specific Lead-in in patients with both indolent and aggressive CD20+ r/r Non-Hodgkin Lymphoma (NHL).
- Phase 2 study with 3 treatment arms with select r/r Follicular Lymphoma (FL) and r/r Diffuse large B-cell lymphoma (DLBCL) indications, conducted according an adaptive 2 stage design for a single proportion.

The study objectives will be separated based on the phase of the study.

4.1 Primary Objectives

Phase 1 Dose Escalation:

- To determine the safety and tolerability of TAK-981 in combination with rituximab in patients with r/r NHL.
- To establish the recommended Phase 2 dose (RP2D) of TAK-981 in combination with rituximab.

Phase 1 Japan-Specific Lead-in Expansion:

- To evaluate the safety and tolerability of TAK-981 in Japanese patients with r/r CD20+ NHL.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL.

4.2 Secondary Objectives

- To characterize the PK profile of TAK-981 in combination with rituximab, for both Phase 1 and 2.

Phase 1:

- To determine the maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of TAK-981 when administered in combination with rituximab.
- To assess the preliminary antitumor activity of TAK-981-rituximab combination.
- To assess target engagement of TAK-981 (SUMO-TAK-981 adduct formation) and SUMOylation pathway inhibition in blood and skin.

Phase 1 Japan-Specific Lead-in Expansion:

- To characterize the PK profile of TAK-981 in Japanese patients.

- To assess the preliminary antitumor activity of TAK-981 as single agent and in combination with rituximab in Japanese patients.
- To assess target engagement of TAK-981 (SUMO-TAK-981 adduct formation) and SUMOylation pathway inhibition in blood and skin in Japanese patients.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL as measured by disease control rate (DCR), duration of response (DOR), time to progression (TTP), and progression-free survival (PFS).
- To evaluate the safety and tolerability of TAK-981 in combination with rituximab.

4.3 Exploratory Objectives

4.3.1 Exploratory Objectives (Global Study; Not Applicable to Patients Enrolled in China)

[redacted]

4.3.2 Exploratory Objectives (China-Specific)

[redacted]

[redacted]

4.4 Study Design

This study is an open-label, multicenter, Phase 1/2 study investigating the combination of TAK-981 and rituximab in adult patients with r/r CD20+ NHL. The study consists of 2 phases, phase 1 (Dose Escalation and Japan-specific Lead-in), and phase 2 (Expansion in select r/r FL and r/r DLBCL indications).

The study will consist of a screening period (Day –28 to −1), a treatment period, an end-of-treatment (EOT) visit 30 (+10) days after the last dose occurring when treatment is discontinued for any reason, and a progression-free survival (PFS) follow-up period lasting for a maximum of 12 months for each patient after their last dose of study drug to monitor survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives TAK-981. One cycle of treatment will be defined as 21 days. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will receive treatment with TAK-981 and rituximab for up to 12 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the study or study drugs occurs.

Patients in the Japan-specific Lead-in will be treated with TAK-981 single agent on Days 1, 4, 8 and 11 in treatment cycles of 21 days. Once the starting dose of TAK-981 has been deemed safe, patients in the combination cohorts will be treated with increasing doses of TAK-981 up to the upper dose level found safe for the Phase 2 expansion as determined in the global Dose Escalation.

Treatment may be continued beyond disease progression, with sponsor approval, if, in the opinion of the investigator, the patient continues to experience clinical benefit.

Phase 1: Dose Escalation

The phase 1 portion of the study is a dose escalation of TAK-981 in combination with rituximab at a fixed dose in patients with indolent or aggressive relapsed or refractory (r/r) CD20+ non-Hodgkin Lymphoma (NHL), to identify the maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) and schedule of the combination. PAD can be defined retrospectively once MTD is reached and it can be below MTD or coincide with it.

The selected starting dose of TAK-981 in this study will be 10 mg. (Note, as of Protocol Amendment 6, patients are enrolling into the ≥90 mg twice weekly cohort). TAK 981 will be administered as a 1-hour intravenous (IV) infusion on Days 1 and 8 or Days 1, 4, 8, and 11 in cycles of 21 days. Alternative dosing schedules may be investigated.

Rituximab and TAK-981 will be administered intravenously until disease progression or unacceptable toxicity.

Dose escalation of TAK-981 will be guided by a Bayesian Logistic Regression Modeling (BLRM) design with overdose control. Approximately 35 patients will be enrolled until either MTD or a PAD is identified. A minimum of 3 patients will be enrolled in the dose level 1 cohort. The recommended phase 2 dose (RP2D) will be determined from the collective experience in the clinic considering the safety data, preliminary pharmacokinetic (PK) data, preliminary pharmacodynamic data, and any early antitumor activity observed along with the statistical inference from the BLRM.

A Safety Monitoring Committee (SMC) composed of the principal investigators, and sponsor clinician will regularly review safety data to ensure patients' safety throughout the phase 1 portion of the study and make decisions on dose escalation. Dose escalation decisions will be made based on the DLTs meeting the criteria above that occur during the first 3 weeks of treatment for each patient.

For the first infusion Cycle 1, Day 1 (C1D1) of TAK-981 in combination with rituximab during dose escalation every patient must be hospitalized for drug administration and observation (for a minimum of 18 hours after the end of TAK-981 infusion). Hospitalization is not required after the first 3 patients at a dose level (DL) or expansion of previously cleared DL, and only if the risk of infusion reactions is considered low based on previous experience. If Grade 3 or greater IRR or cytokine release syndrome (CRS) are not observed at PAD or MTD, or if the safety data from the ongoing first-in-human TAK-981-1002 study support the removal of the requirement of hospitalization for the first dose of TAK-981, the decision will be made by the SMC.

Patient enrollment will be staggered between the first and second patients by 72h during dose escalation at all DLs. At each DL, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through the Day 4 (72h) without clinically significant acute toxicities. If more than 3 patients are to be enrolled in a DL or if de-escalation is indicated, staggering will not be required unless indicated by safety findings.

Phase 1: Japan-Specific Lead-in Expansion Study Design

The Japan-Specific Safety Lead-in is an open-label study to evaluate the tolerability of Phase 2 dose levels and schedule of TAK-981 in combination with rituximab determined during Dose Escalation in the TAK-981-1501 study.

The Japan-Specific Lead-in will consist of 2 cohorts:

- TAK-981 single agent cohort: Patients will be treated with TAK-981 at 60 mg administered as a 1-hour IV infusion on Days 1, 4, 8 and 11 in cycles of 21 days. TAK-981 will be administered until disease progression or unacceptable toxicity. Following a rule-based 3 + 3 + 3 design for the single agent cohort, a lower dose level of 40 mg will be considered if 60 mg is not tolerated. The Japan Safety Monitoring Committee (JSMC) consisting of sponsor clinician and Japanese investigators, will determine whether the TAK-981 starting dose is tolerable in Japanese patients, and will determine the initiation of the combination cohorts in Japan-Specific Lead-in. Additional dose levels are not planned to be evaluated in the single agent cohorts.

- Patients in the combination cohorts will be treated with escalating doses of TAK-981 with fixed dose of rituximab up to the upper dose level of the Phase 2 doses determined in the global Dose Escalation. TAK-981 dose escalation will follow a rule-based 3 + 3 + 3 design, starting from the dose level considered safe in the single agent cohort in Japan-Specific Lead-in with a fixed dose of rituximab of 375 mg/m2 administered IV on Days 1, 8, and 15 during Cycle 1 and on Day 1 from Cycle 2 Day 1 onwards. TAK-981 will be administered as a 1-hour IV infusion, and the dosing schedule will be considered upon discussion and agreement between Japanese investigators and sponsor referring to the Phase 2 dose schedule selected in global Dose Escalation. The Phase 2 dose levels in Japanese subjects will be determined from the collective experience in the clinic considering the safety data, preliminary PK data, preliminary pharmacodynamic data, and any early antitumor activity. Rituximab and TAK-981 will be administered intravenously as per dosing schedule until disease progression or unacceptable toxicity.

In combination with rituximab, TAK-981 dose escalation and cohort expansion decisions are reviewed and approved by the JSMC. The combination cohorts will be initiated after the JSMC review and approval of the safety data, considering no significant toxicity observed for TAK-981 in combination with rituximab based on the latest safety data from dose escalation part and single agent cohort of Japan-Specific Lead-in. The JSMC may require the enrollment of additional patients to any of the single agent or combination cohorts to develop PK and/or pharmacodynamic data in Japanese patients. The JSMC may decide to further expand dose levels to support the potential development of other regimens and/or NHL indications.

Japan-Specific Lead-in will enroll patients with indolent or aggressive CD20+ r/r NHL. Patients who participated in Japan-Specific Lead-in will receive TAK-981 under inpatient hospitalization during Cycle 1. During Cycle 1, patients will be hospitalized for 21 days (Cycle 1). Patient enrollment will be staggered between the first and second patients by 72 hours at all dose levels. At each dose level, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through Day 4 (72 hours) without clinically significant acute toxicities. If more than 3 patients are to be enrolled in a dose level or if de-escalation is indicated, staggering will not be required unless indicated by safety findings.

Intrapatient dose escalation will be permitted only when patients in the next dose level cohort have completed assessment for Cycle 1 and a decision has been made that this dose level does not exceed the MTD. Patients in the single-agent cohort will be permitted to be treated with the combination when patients in the subsequent combination cohort have completed assessment for Cycle 1 and JSMC has decided that the dose of TAK-981 combination with rituximab is tolerable in Japanese patients.

Phase 2: Expansion in Select Indications

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with rituximab in patients with select r/r NHL types and indications. The following cohorts will be enrolled:

- Cohort A: r/r diffuse large B-cell lymphoma (DLBCL) progressed or relapsed after chimeric antigen receptor (CAR) T-cell therapy (CAR-T).
- Cohort B: r/r DLBCL progressed or relapsed after 2-3 prior lines of systemic therapy and no prior therapy with CAR T-cells.
- Cohort C: r/r follicular lymphoma (FL) progressed or relapsed after 2-3 prior lines of systemic therapies.

Each cohort will be assessed separately using an adaptive 2-stage design for a single proportion. For Stage 1, each cohort will be analyzed when a prespecified number of patients have been enrolled and had the potential to have at least 1 post-treatment radiologic evaluation of the disease. If the prespecified minimal response rate is not achieved in the first stage for a given cohort, that cohort will be closed to enrollment. However, if a clear clinical benefit has been observed for patients in the cohort (eg, a majority of patients have recorded stable disease at Week 8 and no complete response [CR] or partial response [PR] is recorded) then enrollment into Stage 2 may be allowed for this cohort. If the required response rate during Stage 1 or a good clinical benefit is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients for that cohort has been reached. The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have completed the 6-month disease assessment/survival follow-up.

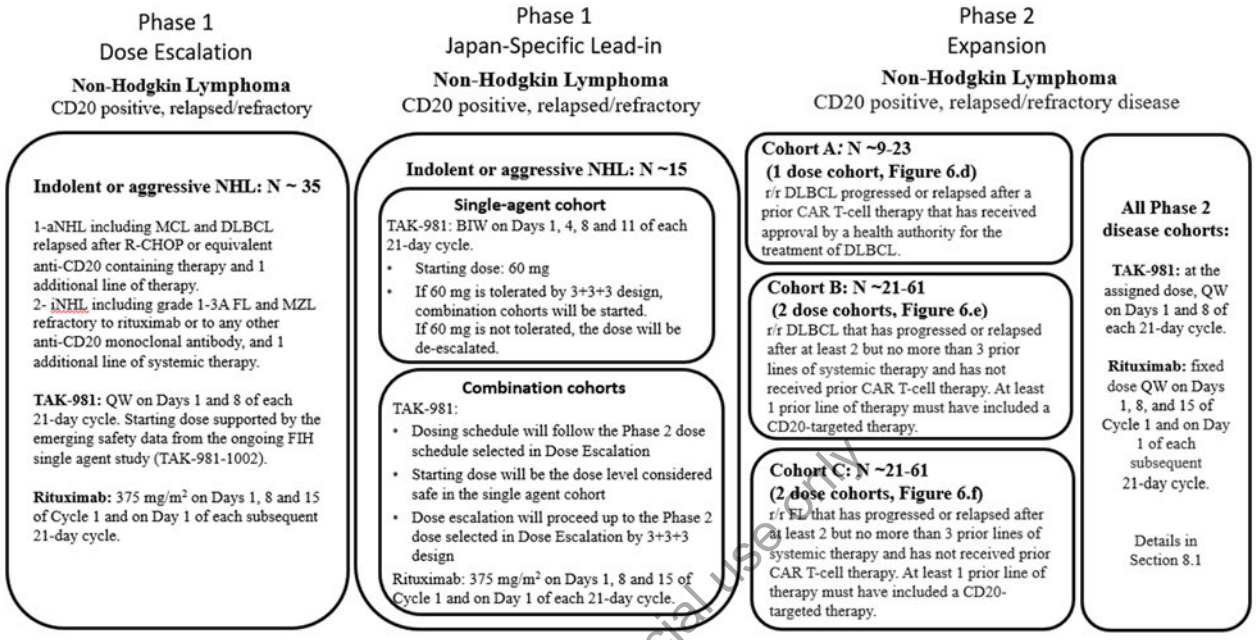
TAK-981 will be evaluated at a dose of 120 mg once weekly (QW) (the upper dose tested in Phase 1) as well as at the dose of 60 mg QW (a lower yet biologically active dose) in a 21-day cycle, both in combination with a fixed dose of rituximab, in the Phase 2 expansion. The dose cohorts will be: Cohorts B 120 mg/C 120 mg and Cohorts B 60 mg/C 60 mg. This data will be used to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

During Phase 2, an Independent Data Monitoring Committee will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

Patients enrolled in sites in China will participate in Phase 2 of the study.

The overall study schematic is displayed in Figure 4.a.

Figure 4.a TAK-981-1501: TAK-981 Study Schematic



aNHL: aggressive Non-Hodgkin Lymphoma; BIW: twice weekly; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; FIH: first-in-human; FL: follicular lymphoma; iNHL: indolent Non-Hodgkin Lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; QW: once weekly; R-CHOP: rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin®) and prednisone; r/r: relapsed or refractory.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- Phase 1:
  - Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0; except CRS which will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS.
  - Occurrence of DLTs within the first 21 days of treatment in Cycle 1.
- Phase 2:
  - ORR (CR + PR) as defined by the investigator according to Lugano Classification for lymphomas.

5.2 Secondary Endpoints

- PK parameters after the first dose of TAK-981 on C1D1 and Cycle 1, Day 8 (C1D8) (data permitting).:
  - C_{max}.
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the plasma concentration versus time curve from time 0 to time t (AUC_{0-t}).
  - Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Total clearance after IV administration (CL).
  - V_{ss}.

  Phase 1:

  - ORR, DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.
  - TAK-981-SUMO adduct formation and SUMO pathway inhibition in skin/blood.

  Phase 2:

  - Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0; except CRS, which will be graded according to ASTCT Consensus Grading for CRS.
  - DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.

5.3 Exploratory Endpoints

5.3.1 Exploratory Endpoints (Global Study; Not Applicable to Patients Enrolled in China)

[redacted]

[redacted]

Collection of samples for exploratory endpoints are dependent upon local guidelines and regulations (including feasibility of sample export), as well as institutional review board (IRB)/independent ethics committee (IEC) approval.

5.3.2 Exploratory Endpoints (China-Specific)

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that up to approximately 195 patients will be enrolled in this study, including the dose-escalation phase (approximately up to 35 patients), the Japan-specific Lead-in (approximately up to 15 patients), and the 5 expansion cohorts (A 120 mg, B 120 mg, B 60 mg, C 120 mg, and C 60 mg) for phase 2 (up to approximately 145 response-evaluable patients) to evaluate efficacy in patients with select lymphoma.

Dose escalation phase (phase 1):

It is estimated that up to approximately 35 DLT-evaluable patients will be enrolled in this study for the dose-escalation phase.

An adaptive BLRM that implements escalation with overdose control will be used to for purposes of dose escalation recommendations and estimation of the MTD and/or PAD. We assume a group of approximately 3 patients will be enrolled in a combination dose cohort based on an adaptive design using BLRM with safety data evaluation and PK guidance. The actual cohort size during the study is flexible and may be different from 3 patients. The total number of patients in the dose escalation is dependent on the observed safety profile and PK/PD guidance, which will determine the number of patients per combination dose cohort, as well as the number of dose escalations required to achieve MTD and/or PAD. The selection of the next recommended dose will be determined from BLRM along with consideration of other safety, clinical, PK, and pharmacodynamic data, including data from the FIH study (TAK-981-1002).

The description, prior calibration, and operating characteristics of the BLRM are included in the Appendix H in the Protocol.

Japan-specific Lead-in (Phase 1):

It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled in Japan-specific Lead-in Expansion, which will allow us to adequately characterize minimum of 3 dose levels. A ruled-based 3 + 3+ 3 design will be used for dose escalation.

Efficacy evaluation phase (phase 2):

After MTD/PAD is defined, up to approximately 145 response-evaluate patients with 2 specified types of lymphomas will be enrolled in parallel in a phase 2 study to evaluate the efficacy of TAK-981.

The primary endpoint for the phase 2 portion is overall response rate (ORR) (CR + PR) as assessed by the investigator according to Lugano criteria for patients with lymphoma. The sample size consideration for disease-specific patient populations is adaptive design based on Simon's two-stage design for a single proportion (Lin and Shih 2004) with the following hypotheses of ORR.

[redacted]

Table 6.a [redacted]

[redacted]

Table 6.b [redacted]

[redacted]

Table 6.c [redacted]

Patients enrolled at the Phase 2 dose levels in the Phase 1 portion of this study may be pooled with patients in the Phase 2 portion of this study for safety evaluations. However, only patients enrolled in a Phase 2 cohort will be considered for statistical efficacy analyses of Phase 2 responses.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will display the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data.

All available efficacy and safety data will be included in data listings and tabulations as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Baseline values are defined as the last observed value before the first dose of study medication.

Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

The summary tables will be presented separately for escalation phase (include escalation cohort, overall for dose escalation phase), expansion phase (by expansion cohort and overall for expansion phase and overall for expansion phase). Summary tables with subjects with the same dose/regimen pooled across escalation and expansion phase may also be provided. In addition, selected summary tables for Japan-specific lead-in phase may be provided separately.

Screen failure subjects will be grouped and listed.

At the time of the SAP amendment, the expansion phase portion is being terminated with limited number of patients and an abbreviated CSR will be written for this study, therefore certain analyses described in this SAP may not be conducted. Details will be documented in the CSR.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it was collected unless otherwise specified. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.

- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.3 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then impute to first dose date
  - If month and year are different than month and year of first dose date, then impute to first date of the month
- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be used instead
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then it is imputed with 1st dose date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the stop dates to ensure the stop date does not occur before start date

Adverse events with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However, if it is to be done, the rules are outlined above. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

7.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
  - If year is known, but day and month are missing, then 1st of January of the year will be imputed
- If all is missing, then impute date to Date of Birth (DOB)
  - If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB)

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, then impute date to 31st of December in the year of last dose

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

7.1.5 Conventions for Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.

- When only a year is present,
  - If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.
- If no components of the onset date are present the date of last dose + 1 will be imputed.

7.2 Analysis Sets

The Analysis Sets (Analysis Populations) will include the following:

Safety analysis set: Patients who have received at least 1 dose, even if incomplete, of study drug will be used for all safety analyses and for some efficacy analyses.

PK analysis set: Patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients enrolled in the Phase 1 portion of the study who experienced a DLT at any time after initiation of the first infusion of TAK-981 or who completed all planned infusions of TAK-981 as per schedule plus 3 infusions of rituximab without experiencing a DLT. The DLT-evaluable population will be used to determine the RP2D/MTD.

Response-evaluable analysis set: Patients who have received at least 1 dose of study drug, have sites of measurable disease at Baseline, and 1 postbaseline disease assessment, or were discontinued due to symptomatic deterioration or death before a postbaseline evaluation happens, will be used for analyses of response.

Pharmacodynamic analysis set: Pharmacodynamic analysis sets to assess target engagement of TAK-981 and SUMOylation pathway inhibition:

- Patients who have provided evaluable skin biopsies (screening sample and postdose sample) will be included in the *skin pharmacodynamic analysis dataset*.
- Patients who have provided evaluable blood samples (C1D1 predose sample and at least 1 postdose sample) will be included in the *blood pharmacodynamic analysis dataset*.

[redacted]

Japanese PK analysis set: Patients in Japan-Specific Lead-in with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be included in Japanese PK analyses.

Japanese DLT-evaluable analysis set: The Japanese DLT-evaluable analysis set will include patients enrolled in the Japan-Specific Lead-in who experienced a DLT at any time after initiation of the first infusion of TAK-981 or who completed all Cycle 1 doses of TAK-981 without experiencing a DLT in the single-agent cohort of the Japan-Specific Lead-in, and all planned infusions of TAK-981 as per schedule plus 3 infusions of rituximab in patients treated with the combination. The Japanese DLT-evaluable population will be used to evaluate the tolerability of Japanese patients.

7.3 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each population, and will be presented by escalation cohort and overall for escalation phase (phase 1), and by each expansion cohort and overall for expansion phase (phase 2). The primary reason for study termination will also be summarized similarly in this table.

All percentages will be based on the number of patients in the safety population.

A listing will present data concerning patient disposition.

Disposition summary in Japan-specific lead-in phase will be provided separately by dose cohort and overall.

7.4 Demographic and Other Baseline Characteristics

Demographics will be summarized for escalation cohort and overall for phase 1, and by each expansion cohort and overall for phase 2. Demographic data will also be presented in a by-patient listing. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate. Age will be calculated from date of birth to date of informed consent.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Baseline characteristics including disease initial diagnosis, time since initial diagnosis, current diagnosis, [redacted]

Eastern Cooperative Oncology Group (ECOG) performance status, FDG-PET scan result, ECHO and MUGA status will be summarized. Tumor Evaluation Lymphoma including tumor identification, anatomical location, laterality will also be summarized.

Summary for demographic and baseline characteristics in Japan-specific lead-in phase will be provided separately by dose cohort and overall.

7.5 Medical History and Concurrent Medical Conditions

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (whether it is resolved or ongoing).

7.6 Medication History and Concomitant Medications

A separate table will summarize the numbers and percentages of patients who received prior therapy, including prior anticancer, prior radiation, prior surgery or procedure, and best response to the last prior anticancer therapy.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by ATC Pharmacological Subgroup and WHO drug generic term for the safety population, the signing of ICF through 30 days after the last dose of study treatment, or to the start of subsequent systemic anticancer therapy, whichever occurs first.

Concomitant medications will also be presented in a by-patient listing.

Concomitant procedures will not be coded but will be presented in a by-patient listing.

7.7 Study Drug Exposure and Compliance

Extent of Exposure:

The exposure to study drugs (TAK-981 and rituximab) will be characterized by total amount of dose taken in mg, total number of doses taken, relative dose intensity (%), number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, ≥6, ≥9, ≥12 and ≥15 treated cycles for patients in the safety population. A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Duration of treatment (days), and number and percentages of patients who had >=3, >=6, … weeks of treatment will be summarized for patients in the safety population.

Relative dose intensity (RDI) (%) for will be presented overall and by cycle for each IP (TAK-981 and rituximab).

Overall RDI (%) is defined as 100 x (Total amount of dose taken) / (Total prescribed dose of all treated cycles), where a treated cycle is defined as a cycle in which the patient received any amount of any study drug.

For RDI by cycle the similar formula is used as overall relative dose intensity and will be calculated for treated cycles.

Cycle RDI (%) is defined as 100 x (Total amount of dose in cycle) / (Total prescribed dose of in cycle)

Prescribed dose is determined by the dose level to which a patient is scheduled to receive and will take into consideration of planned dose reduction or escalation during the study.

Relative dose intensity will also be displayed as <50%, 50% - <= 80%, 80% - < 100%, = 100%, and > 100%.

The extent of exposure will be summarized by escalation cohort, overall for dose escalation phase, by safety expansion cohort, and overall in safety expansion phase.

Dosing data will also be presented in a by-patient listing.

Action on Study Drug:

Action on study drug will be summarized by Cycles 1- 6, Cycle 7- 12, Cycles 13-18, Cycle ≥19 and total, for each dose escalation cohort, overall for dose escalation phase, for each safety expansion cohort, and overall in safety expansion phase.

Summary for extent exposure and action on study drug in Japan-specific lead-in phase will be provided separately by dose cohort and overall.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

Phase 1:

Efficacy is not the primary objective for this study in the phase 1 portion. The efficacy analysis will mainly focus on the phase 2 portion of this study.

In the phase 1 portion of this study, efficacy parameters such as ORR, DOR and PFS will also be summarized as appropriate. Disease response will be categorized and presented in listings.

Phase 2:

The primary endpoint for phase 2 portion is ORR (CR + PR) as defined by the investigator according to Lugano criteria for lymphoma response, from Cheson 2014 [3].

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study.

The primary efficacy analysis will be based on the response-evaluable population.

Estimates of the ORR (CR + PR) will be presented with 2-sided 95% exact binomial confidence intervals.

7.8.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include ORR, DCR, DOR, TTP and PFS. No formal statistical tests will be performed for these secondary endpoints.

DCR is defined as the proportion of patients who achieve stable disease (SD) or better (CR+PR+SD determined by the investigator) during the study in response-evaluable population.

DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders (PR or better). Responders without documentation of PD will be censored at the date of last response assessment that is SD or better.

PFS is defined as the time from the date of the first dose administration to the date of first documentation of PD or death due to any cause, whichever occurs first. PD will be determined by Response Evaluation Criteria in Lymphoma for patients with lymphoma. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better.

Patients who received any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to or on the date of initiation of the subsequent anticancer therapy.

TTP is defined as the time from the date of the first dose administration to the date of first documented progress disease (PD). Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment that is SD or better. Patients who die during treatment without PD will also be censored at the date of last response assessment that is SD or better. Patients who received any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment that is SD or better prior to or on the date of initiation of the subsequent anticancer therapy.

ORR will be summarized using descriptive statistics with 95% confidence interval for response-evaluable analysis set.

DCR will be summarized is a similar way as ORR.

PFS will be analyzed descriptively using Kaplan-Meier (K-M) method for safety analysis set. The K-M survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% confidence intervals will be provided.

DOR and TTP will also be analyzed using K-M method for response-evaluable analysis set.

Waterfall plot of best %change of target lesion size from baseline and swimmer plot of response with duration will be provided.

Efficacy endpoints will be presented in individual subject listings for Japan-specific lead-in phase.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic (PK) Analysis

The PK of TAK-981 will be characterized in this study (ie, rituximab PK will not be characterized).

PK parameters will be estimated using noncompartmental methods with Phoenix WinNonlin. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be determined, as permitted by data:

- C_{max}.
- t_{max}.
- $AUC_{0-\infty}$.
- AUC_{0-t}.
- $T_{1/2z}$.
- CL.
- V_{ss}.

PK parameters will be summarized using descriptive statistics. Individual TAK-981 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort. The above parameters will not be estimated for the sparse PK samples collected during the phase 2 portion of study.

The PK data collected in this study are intended to contribute to future population PK analyses of TAK-981. These population PK analyses may include data collected in other TAK-981 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

7.9.2 Pharmacodynamic (PD) Analysis

The analysis of blood and skin biomarker profiles for each dose and timepoint tested will be tabulated. When possible, the dynamic range for each biomarker and fold change will be determined to better understand TAK-981 biological activity range and duration of pharmacodynamic effect, and help to determine the PAD/RP2D for the TAK-981/rituximab combination. [redacted]

7.10 Other Outcomes

7.10.1 PK/PD Analysis

Data permitting, the PK and pharmacodynamic data collected in this study will be analyzed to understand the exposure-response relationship for TAK-981 in combination with rituximab. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 in combination with rituximab and for determination of PAD.

To determine the appropriateness of the PAD/MTD and schedule, a totality of evidence approach will be used that will integrate all available data from the dose escalation and the phase 2 portions of the study including:

1. Multicycle safety/tolerability of TAK-981 in combination with rituximab.
2. Single and multiple dose PK of TAK-981.
3. Single and multiple dose pharmacodynamic biomarkers of TAK-981 (in circulation, skin, and tumor) including target engagement (adduct formation) and SUMO2/3 inhibition [redacted]
4. Antitumor response with TAK-981 in combination with rituximab administration.
5. Relative dose intensity.

Dose-exposure-response relationships will be explored to describe the PK-safety, PK-pharmacodynamics, and PK-antitumor response relationships of TAK-981, and the results of such quantitative pharmacology analyses will be used to inform selection of the RP2D/schedule of TAK-981 in combination with rituximab.

In addition, the PK-pharmacodynamic data collected in the study during dose escalation may be used to inform the quantitative systems pharmacology model that may be used to further refine the dose/schedule for TAK-981. Furthermore, the PK-pharmacodynamic data collected in this study may be pooled with similar data from other clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and quantitative systems pharmacology modeling may not be presented in the clinical study report for this study but will be presented in a separate report.

7.10.2 [redacted]

[redacted]

A single 12-lead standard safety ECG will be performed to assess eligibility at Predose Screening and Cycle 1, Day 8, and post- end of infusion (+1 h window) on Cycle 1, Day 8.

[redacted]

Patients are required to be in supine position for 15 minutes, which is the ECG collection window (ie, at least 5 minutes before and up to 10 minutes during the 3 ECGs collected for each planned time point). [redacted]

7.11 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

7.11.1 Dose Limiting Toxicities (DLTs)

The incidence of DLTs within the first 21 days of treatment in Cycle 1 in phase 1 will be tabulated for each dose group using DLT-evaluable analysis set. In addition, to assess the relationship between toxicities and TAK-981 doses, the preferred term of individual toxicities will be summarized by frequency and intensity for each dose group.

A by-subject listing of DLTs which occur during the treatment will be presented by schedule and dose level for DLT-evaluable analysis set. Subjects will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

Summary of incidence of DLTs and by-subject listing of DLTs will also be presented for Japanese DLT-evaluable analysis set.

7.11.2 Adverse Events

7.11.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Severity (toxicity grade) for each AE will be determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0; except cytokine release syndrome (CRS) which will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS.

All AEs will be presented in a by-patient listing. Treatment-emergent AEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

Summary of AEs will be summarized by escalation cohort and overall for escalation phase (phase 1), and by each expansion cohort and overall for expansion phase (phase 2). Adverse

events will be tabulated according to MedDRA by system organ class, high level term, and preferred term and will include the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients).
- SAEs (related and regardless of relationship).
- Treatment-emergent AEs leading to study drug modification and discontinuation.

Patients with the same AE more than once will have that event counted only once within each body system, once within each high-level term, and once within each preferred term.

Treatment-emergent AEs will also be summarized by CTCAE grade (or ASTCT grade for CRS). Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high-level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by preferred term. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in dose modification of study drug, treatment-emergent AE resulting in discontinuation of study drug, and on-study deaths.

In addition, Summary of AEs in Japan-specific lead-in phase will be provided separately by dose cohort and overall.

By-patient listing of grade 3 or higher treatment-emergent AE will also be provided, where the cycle day information for the AE onset and end dates will be included in the listing.

7.11.2.2 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

7.11.2.3 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

7.11.2.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

7.11.3 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratories will be used only when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The actual values of laboratory test results and percent change from baseline will be summarized according to the scheduled sample collection time point. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE v5.0 for toxicity from baseline to post baseline worst on study CTCAE grade, if available. Parameters to be tabulated are included in Table 7.a.

Table 7.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit Hemoglobin Leukocytes with differential ANC CD4/CD8 count and ratio Platelet count	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin (total) (Blood) Urea nitrogen (BUN) Calcium Bicarbonate ($HCO3^-$) or Carbon dioxide (CO_2) Creatinine (Standard) C Reactive protein Chloride Glucose Lactate dehydrogenase (LDH) Magnesium Phosphate Potassium Sodium Protein (total) Urate	Activated partial thromboplastin time (aPTT) Prothrombin time (PT) Fibrinogen

ANC: absolute neutrophil count.

The chemistry laboratory parameters for TLS monitoring will include the following: creatinine, uric acid, potassium, phosphorus, calcium, albumin, and corrected calcium, if available.

By-patient listings to be presented include hematology, clinical chemistry, clinically significant laboratory values, etc.

Mean laboratory values over time will be plotted for key lab parameters, including hemoglobin, leukocytes with differential, neutrophils, platelet count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and standard C-reactive protein. The analysis for other lab parameters may be performed as needed.

The number and percentage of patients with clinically significant laboratory values will also be tabulated as appropriate.

7.11.4 Vital Signs

The actual values of vital sign parameters (blood pressure, heart rate, oxygen saturation [Japanese specific lead-in only] and temperature) and weight will be summarized over time.

Change of vital signs from baseline values will also be summarized over time. Vital sign values will also be presented in a by-patient listing.

The number and percentage of patients with clinically significant vital sign measurements will be tabulated as appropriate.

7.11.5 12-Lead ECGs

Descriptive statistics for the actual values and changes from values at baseline in Electrocardiograms (ECGs) will be listed by time point.

QTc interval will be calculated using Bazett's correction and Fridericia's correction, if necessary. The formulas are:

$$QTc\ (Bazett) = QT / (RR^{0.5})$$

$$QTc\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTc intervals will be performed for each time point. The number and percentage of patients in each QTc interval (< 450 msec, 450-480 msec, > 480-<500 msec, and ≥ 500msec) will be summarized at baseline and each of the subsequent time points. Categories of changes from baseline (≥ 30msec and ≥ 60 msec) will be summarized as well. Maximum QTc intervals and maximum changes from baseline will also be summarized similarly in a separate display.

ECGs abnormalities will be presented in a data listing.

7.11.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Group Performance Status and shifts from baseline to post baseline assessment over time, and ECOG score frequency table over time will be summarized. Shifts from baseline to the worst post baseline score will be tabulated.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

To be updated as needed.

8.0 REFERENCES

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4. Cheson BD, Ansell S, Schwartz L, Gordon LI, Advani R, Jacene HA, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 2016;128(21):2489-96.
5. Lin Y, Shih WJ. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. Biometrics 2004;60(2):482-90.

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