Statistical Analysis Plan

NCT Number : NCT04776018

Title: A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK-981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Study Number: TAK-981-1503

Document Version and Date: Version 2.0, 17 April 2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-981-1503

A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK 981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

PHASE 1b/2

Version: **2.0**

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Principal Statistician, Oncology Stats

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17 April 2023	Version 2.0	Substantial
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1.1 Approval Signatures

Study Title: A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK 981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Approvals:

[redacted] PhD
[redacted] Oncology Statistics

Date

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{∞}	area under the plasma/blood/serum concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration versus time curve from time 0 to time t
BIW	twice weekly
BMA	bone marrow aspirate
CBR	clinical benefit rate
CL	total clearance after intravenous administration
C_{max}	maximum observed concentration
CR	complete response
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end-of-treatment
[redacted]	[redacted]
GGT	gamma glutamyl transferase
iBOIN	Bayesian Optimal Interval Design with Informative Prior
iCR	immunophenotypic complete response
IFN	interferon
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LYRIC	lymphoma response to immunomodulatory therapy criteria
MAD	maximally administered dose
mCR	molecular complete response
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MM	multiple myeloma
mITT	modified intent-to-treat

Abbreviation	Term
MR	minimal response
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QTc	corrected QT interval
QW	weekly
RBC	red blood cell
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
sCR	stringent complete response
SD	stable disease
STD	standard deviation
SMC	Safety Monitoring Committee
SUMO	small ubiquitin-like modifier
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	first time to reach maximum (peak) plasma concentration
TEAE	treatment-emergent adverse events
TLS	tumor lysis syndrome
TTNT	time to next treatment
TTP	time to progression
WHO	World Health Organization
VGPR	very good partial response
Vss	volume of distribution at steady state after intravenous administration

4.0 OBJECTIVES

The study will be conducted in 2 phases:

- Phase 1b dose escalation of TAK-981 guided by Bayesian Optimal Interval Design with Informative Prior (iBOIN) in combination with fixed doses of mezagitamab or daratumumab and hyaluronidase-fihj, respectively in patients with relapsed and/or refractory multiple myeloma (RRMM).
- Phase 2 study of TAK-981-based monoclonal antibody combinations with multiple treatment arms in patients with RRMM.

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

4.1 Primary Objectives

The primary objectives are:

Phase 1b:

- To determine the safety and tolerability of TAK-981 in combination with mAbs in patients with RRMM.
- To determine the recommended Phase 2 dose (RP2D).

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with monoclonal antibodies in patients with RRMM.

4.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK profile of TAK-981 in combination with anti-CD38 mAb.
- To assess immunogenicity of anti-CD38 monoclonal antibodies (mezagitamab and daratumumab) to help interpreting PK profile, efficacy and safety of TAK-981 in combination with monoclonal antibodies.

Phase 1b:

- To evaluate preliminary efficacy of the TAK-981-monoclonal antibody combination according to standard International Myeloma Working Group (IMWG) criteria.
- To assess target engagement of TAK-981 (TAK-981- small ubiquitin-like modifier [SUMO] adduct formation) and SUMOylation pathway inhibition in blood.

Phase 2:

- To further characterize efficacy of TAK-981 in combination with anti-CD38 mAb in RRMM
- To evaluate the safety and tolerability of TAK-981 in combination with anti-CD38 mAb.

4.3 Exploratory Objectives

[redacted]

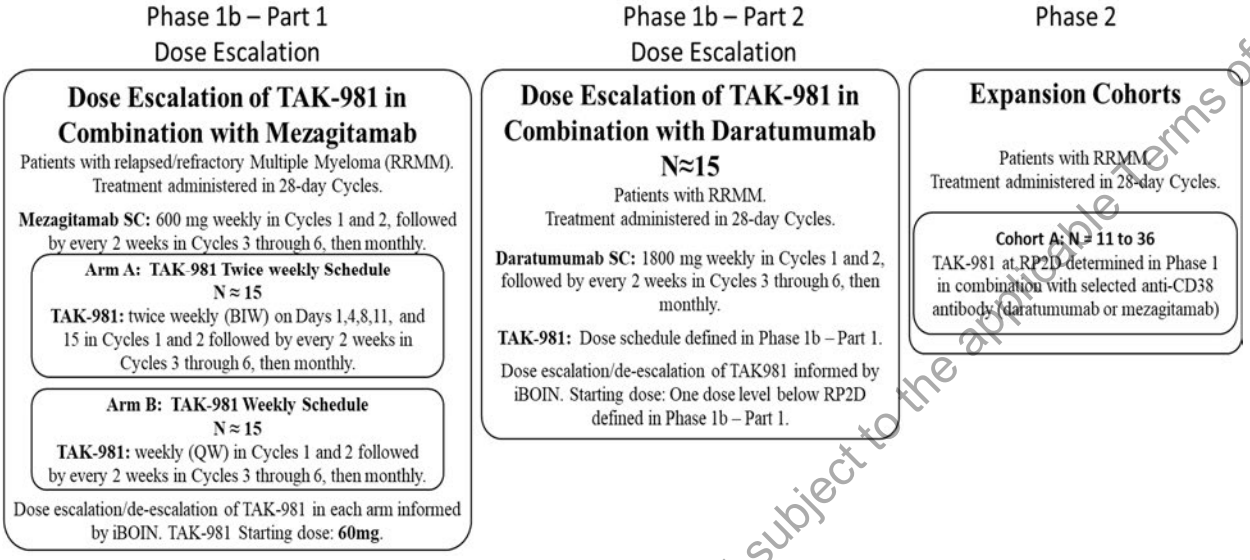
4.4 Study Design

This study is an open-label, multicenter, Phase 1b/2 study investigating the combination of TAK-981 and mAbs in adult patients with RRMM. The study will be conducted in 2 phases (Figure 4.a):

1. Phase 1b dose escalation of TAK-981 guided by Bayesian Optimal Interval Design with Informative Prior (iBOIN) in combination with fixed doses of mezagitamab or daratumumab and hyaluronidase-fihj, respectively in patients with RRMM.
2. Phase 2 study of TAK-981-based mAb combination in patients with RRMM.

Treatment cycle duration is 28 days. TAK-981 in combination with the mAbs will be administered for up to 24 cycles or until disease progression or unacceptable toxicity, whichever comes first. Patients with demonstrated clinical benefit may continue treatment beyond 24 cycles with the agreement of the sponsor/ designee.

Figure 4.a Study Schema



Patient participation will include a screening phase, a treatment phase, and a follow-up phase (see Section 9.0 of the protocol). The screening phase will be up to approximately 28 days before Cycle 1, Day 1 (C1D1). The treatment phase will extend from C1D1 until patients experience disease progression or unacceptable toxicity, or until any other discontinuation criterion is met (Refer Section 9.7 of the protocol). The follow-up phase of the study begins once a patient discontinues study treatment and completes the end-of-treatment (EOT) visit; study follow-up continues until the study ends or the patient completes OS follow-up (Refer Section 9.10 of the protocol).

4.4.1 Phase 1b Study Design

The Phase 1b part of the study will enroll patients with RRMM with the purpose of defining the RP2D and schedule of TAK-981 in combination with mezagitamab or daratumumab and hyaluronidase-fihj, respectively. The first part of the Phase 1b will determine the dose and schedule of TAK-981 in combination with a fixed dose and schedule of mezagitamab. The second part of the Phase 1b will determine the dose of TAK-981 for the combination with daratumumab and hyaluronidase-fihj. The RP2D and recommended schedule with be used in the Phase 2 expansion.

4.4.1.1 Phase 1b Part 1

Dose escalation of TAK-981 will be guided by iBOIN (see Section 8.5 and Appendix H of the protocol for details). Up to approximately 15 patients will be enrolled to each of the TAK-981 schedules until either maximum tolerated dose (MTD) or a pharmacologically active dose (PAD) is identified:

- Arm A: TAK-981 given IV twice weekly (BIW) on Days 1, 4, 8, 11, and 15 in Cycles 1 and 2 followed by every 2 weeks in Cycles 3 through 6, then monthly. TAK-981 will be given in combination with mezagitamab.
- Arm B: TAK-981 given IV weekly (QW) on Days 1, 8, 15, and 22 in Cycles 1 and 2 followed by every 2 weeks in Cycles 3 through 6, then monthly. TAK-981 will be given in combination with mezagitamab.

The starting dose for TAK-981 will be 60 mg; the rationale for the initial TAK-981 dose is provided in Section 4.4 of the protocol. The dose of mezagitamab is the established RP2D at 600 mg.

Once enrolled into the study, patients will be assigned to a treatment arm in a nonrandomized, sequential manner based upon the recruitment status of the TAK-981 arm schedule, as communicated by the sponsor/ designee. A minimum of 3 patients will be enrolled in the first dose cohort. In the first dose cohort, patient enrollment will be staggered between the first and second patients by 7 days. The second and third patients can be dosed concurrently if the first patient in the cohort has gone through the Day 8 visit without clinically significant acute toxicities. Subsequent dose cohorts will not require staggering between patients.

Dose escalation will begin with the BIW schedule and will be followed by the QW schedule at the same starting dose level. TAK-981 dose escalation will be evaluated separately for each of the TAK-981 schedules.

Dose escalation decisions will be made by a Safety Monitoring Committee (SMC), composed of the principal investigators and sponsor. The SMC will regularly review safety data to ensure patients' safety throughout the Phase 1b portion of the study. Dose escalation will follow an iBOIN design. Dose escalation decisions will take into consideration primarily the DLTs observed in Cycle 1 in the patients enrolled in each dose level/schedule according to the rules in Section 8.5 of the protocol (DLT rules). Available safety information beyond Cycle 1, PK and pharmacodynamic information from previously dose patients will also be considered.

Evaluation of intermediate doses or doses up to that evaluated and found safe in the TAK-981 monotherapy study TAK-981-1002, alternative dosing schedules (dosing interval), and expansion of an existing dose level are all permissible following agreement by the SMC, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, efficacy, exposure, or pharmacodynamics of TAK-981. The dose escalation/de-escalation rules based on iBOIN design will be considered as a guidance for the next dose level, however, the final decision on the dose will be made by the SMC.

4.4.1.1.1 Selection of RP2D for TAK-981 in Combination With Mezagitamab

The selection of an RP2D which includes the dose level and schedule of TAK-981 in combination with mezagitamab will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 1 portion of the trial which will include, but is not limited to safety data, preliminary PK data, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity. The RP2D may not be higher than either the MTD as determined by iBOIN. Upon review of available phase 1 data and agreement on the RP2D by the SMC, the Phase 1b Part 2 portion of the study of the combination of TAK-981 with daratumumab and hyaluronidase-fihj may begin.

4.4.1.2 Phase 1b Part 2

In the second part of Phase 1b, the RP2D of TAK-981 in combination with daratumumab and hyaluronidase-fihj will be determined.

Dose escalation of TAK-981 will be guided by iBOIN as described in Section 8.5 of the protocol. The starting dose for TAK-981 will be one dose-level below the RP2D defined for the combination with mezagitamab in Phase 1b Part 1 (RP2D-1). The dose of daratumumab is the approved dose of 1800 mg. A minimum of 3 patients will be enrolled in the first cohort of this combination, and up to approximately 15 patients will be enrolled for the dose escalation. The SMC will regularly review safety data and make decisions for dose escalation.

4.4.1.2.1 Selection of RP2D for TAK-981 in Combination With Daratumumab and Hyaluronidase-fihj

The selection of an RP2D of TAK-981 in combination with daratumumab and hyaluronidase-fihj will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 2 portion of the trial which will include, but is not limited to safety data, preliminary PK data, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity. The RP2D may not be higher than the MTD as determined by iBOIN.

4.4.1.3 Selection of CD38 Antibody for Phase 2

The selection of the anti-CD38 antibody (mezagitamab or daratumumab and hyaluronidase-fihj) for combination with TAK-981 in Phase 2 will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 1 and 2 portions of the trial which will include, but is not limited to safety data, selected RP2D, frequency of dose reduction/discontinuation observed for anti-CD38 antibody, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity.

4.4.2 Phase 2 Study Design

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with an anti-CD38 antibody (mezagitamab or daratumumab and hyaluronidase-fihj) in patients with RRMM. Patients will be treated with the RP2D and recommended schedule of TAK-981

with fixed doses of the anti-CD-38 mAb, mezagitamab or daratumumab and hyaluronidase-fihj. (TAK-981, mezagitamab, and daratumumab and hyaluronidase-fihj administration details are in Section 8 of the protocol).

An adaptive 2-stage design for a single proportion will be used in Phase 2. For Stage I, each cohort will be analyzed when a prespecified number of patients (as defined in Section 6.0) have been enrolled and had the opportunity to complete 4 cycles of treatment. Enrollment may be paused until the Stage I analysis is completed. If the prespecified minimal response rate is not achieved in the first stage, enrollment will be closed. If the required response rate during Stage I or a good CBR is observed as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients has been reached (as defined in Section 6.0). The final analysis of the primary endpoints will take place when all ongoing patients have had the opportunity complete the 12-month disease assessment.

4.4.2.1 Early Stopping Rules

In the Phase 2 portion of the study, Grade 4 or higher drug-related AEs will be monitored starting from the first 11 response-evaluable patients and then every 4 response-evaluable patients up to the approximate maximum number of patients 36.

Accrual to the study will be suspended if:

- Grade 4 drug-related AEs meet the stopping bounds of the number of ≥4/11, ≥4/15, ≥5/19, ≥6/23, ≥7/27, ≥7/31, ≥8/35, ≥8/36; or
- At any time if 1 or more patients present with fatal drug-related AEs.

After review and consideration by the SMC, a decision will be made as to whether accrual can be resumed.

The stopping bounds for Grade 4 drug-related AEs are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rule is met, there is 80% probability that the true toxicity rate is greater than 16% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are:

- Phase 1b:
  - Frequency and severity of TEAEs for all dose groups.
  - Occurrence of DLT in Cycle 1.

- Phase 2:
  - ORR (response of at least partial response [PR]) based on investigator's assessment according to standard International Myeloma Working Group (IMWG) disease response criteria.

5.2 Secondary Endpoints

The secondary endpoints are:

- TAK-981 concentration-time data.
- Anti-mezagitamab or anti-daratumumab antibody (ADA): negative, transient or persistent positive, high or low ADA titer.
- Sparse PK evaluations of mezagitamab or daratumumab

Phase 1b:

- ORR, clinical benefit rate (CBR), DOR, time to progression (TTP), time to next treatment (TTNT), PFS based on IMWG criteria and overall survival (OS).
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood.

Phase 2:

- Frequency and severity of TEAEs.
- CBR, DOR, TTP, TTNT and PFS based on IMWG criteria and OS.
- Percentage of Participants with MRD negative status as determined by next-generation sequencing (NGS).
- MRD negative rate at 1 year, defined as percentage of participants who have achieved MRD negative status at 1 year.
- Durable MRD negative rate, defined as the number of participants who have achieved MRD negative status (at 10^-5) at 2 BMAs examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

5.3 Exploratory Endpoints

[redacted]

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Overall this study will enroll up to approximately 81 patients in North America and/or globally. Approximately 15 patients will be enrolled in each dosing schedule in Phase 1b Part 1 and in Phase 1b Part 2. Up to approximately 36 patients will be enrolled in Phase 2.

The iBOIN design will be implemented for the dose escalation phase. It is estimated that up to approximately 30 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981 combining with mezagitamab, with up to approximately 15 patients for each dosing schedule.

After RP2D is defined, dose escalation of TAK-981 in the combinations of daratumumab and hyaluronidase-fihj will be evaluated using the similar iBOIN design. It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate dose escalation doses for this combinations.

Efficacy Evaluation (Phase 2):

[redacted]

[redacted]

Table 6.a [redacted]

[redacted]

Patients enrolled at the Phase 2 dose levels in the Phase 1 portion of this study will be included in the Phase 2 analysis of this study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will display the number of observations, mean, standard deviation (STD), 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 STDs will be presented to 2 more decimal places than the recorded data. 95% Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

In general, the summary tables for efficacy endpoints will be provided by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2; the summary tables for non-efficacy endpoints (disposition, baseline and demographics, medical history, medication history, exposure, patient reported outcomes, safety analysis) will be provided by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined unless specified otherwise.

Screen failure subjects will be grouped and listed at the end.

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 indicate 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 start 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 Prior Medications/Therapy and 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 (DOB = screening date – age[years]*365.25)

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 who receive at least 75% of planned TAK-981 doses, all mAb doses, and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the Phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Response-evaluable analysis set:. The response-evaluable analysis set is a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 posttreatment evaluation. The response-evaluable population will be used for the analyses of response rates, TTR, DOR, and PFS for patients in Phase 1b and Phase 2.

Modified intent-to-treat (mITT) analysis set: The mITT population is defined as all patients who receive at least 1 dose of any study drug in the Phase 2 part of the study, or who receive at least 1 dose of any study drug and are treated at the Phase 2 dose level in the Phase 1 part of the study. The mITT population may be used for the sensitivity analyses of efficacy endpoints. Summary of demographics, baseline characteristics and exposure may also be considered as appropriate.

Pharmacodynamic analysis sets:

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

- 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]

[redacted]

7.3 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each analysis population as defined in Section 7.2, and will be presented by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for 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.

Demographic and Other Baseline Characteristics WHO drug generic term for the safety population, from date of first dose of study treatment through 30 days after the last dose of study treatment.

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.

7.4 Study Drug Exposure and Compliance

Extent of Exposure:

The exposure to study drugs (TAK-981, mezagitamab, daratumumab) 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, ≥3, ≥4, ≥5,…., ≥14, ≥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) will be calculated as (date of last study drug dose – date of first study dose + 1) for each study drug and will be summarized with descriptive statistics.

Relative dose intensity (RDI) (%) will be presented overall and by cycle.

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 dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined.

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

Action on Study Drug:

Action on study drug could include dose increased (TAK-981 only), dose reduced, dose delayed, drug infusion interrupted (TAK-981 only), drug withdrawn, dose interrupted.

Action on study drug will be summarized by Cycles 1- 6, Cycle 7- 12, Cycles 13-18, Cycle ⩾19 and total, for each dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, for expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined.

7.5 Efficacy Analysis

7.5.1 Primary Efficacy Endpoint(s)

Phase 1b:

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

In the Phase 1b portion of this study, efficacy parameters such as ORR and CBR will be summarized as appropriate. Disease response will be categorized and presented in listings.

Phase 2:

The primary endpoint for Phase 2 portion is ORR for each regimen based on investigator's assessment based on IMWG response criteria.

Overall Response Rate (ORR)

The ORR is defined as the proportion of patients who achieved a confirmed PR or better during the study per investigator assessment as defined by IMWG Response Criteria. Response evaluations after the start of alternative anti-multiple-myeloma therapy will not be taken into account in the calculation of ORR.

The primary efficacy analysis will be provided based on the response-evaluable analysis set by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2.

The ORR will be summarized by frequencies and percentages and estimates of the ORR will be presented with 2-sided 95% exact binomial confidence intervals.

The primary efficacy analysis of ORR will also be provided for mITT population and modified response-evaluable population.

7.5.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include are described below for Phase 1b and Phase 2.

Response evaluations after the start of alternative anti-multiple-myeloma therapy will not be taken into account in the calculation of efficacy endpoints.

No formal statistical tests will be performed for these secondary endpoints.

Phase 1b:

Secondary efficacy endpoints in Phase 1b portion include ORR, CBR, DOR, TTP, TTNT, PFS based on based on IMWG criteria and OS.

Phase 2:

Secondary efficacy endpoints in Phase 2 portion include CBR, DOR, time to response, TTP, TTNT, PFS, and OS.

Overall Response Rate (ORR)

Similar to analysis of ORR for phase 2 in Section 7.5.1, analysis of ORR will be provided based on the response-evaluable analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b--Part 2.

Clinical Benefit Rate (CBR)

The CBR includes patients with a response of at least stable disease for at least 3 months or better (strigent complete response [sCR], immunophenotypic complete response [iCR], molecular complete response [mCR], complete response [CR], very good partial response [VGPR], partial response [PR], minimal response [MR] or stable disease [SD]) during the study per investigator assessment as defined by IMWG Uniform Response Criteria. The CBR will be summarized by frequencies and percentages based on response-evaluable analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. Estimates of the CBR will be presented with 2-sided 95% exact binomial confidence intervals.

The CBR will also be summarized for mITT population and modified response-evaluable population.

Duration of Response (DOR)

The DOR will be calculated for those patients with a confirmed PR or better in the response-evaluable analysis set. The DOR is defined as the number of days from the first documentation of a confirmed response until progressive disease or until the last adequate response assessment if there is no progressive disease (censored). If the patient dies from causes other than progression, the patient will be censored.

DOR (months) = (date of progression or censor – date of confirmed response + 1)/30.4375.

The analysis of DOR will be provided by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2 based on those patients with a confirmed PR or better in the response-evaluable analysis set. The Kaplan-Meier method will be used to estimate the distribution of DOR. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

The DOR analysis will be repeated for patients with a confirmed PR or better in the mITT population and modified response-evaluable population.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose to the date of PD per IMWG criteria, or the date of death due to any cause, whichever occurs first.

Patients without documentation of PD will be censored at the date of the last response assessment. 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. Patients with no post baseline response assessment will be censored on day 1 unless they have a death event.

PFS (months) = (earliest date of progression or death or censor – date of first dose + 1)/30.4375.

The analysis of PFS will be based on safety analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. The Kaplan-Meier method will be used to estimate the distribution of PFS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier PFS probability estimates with 95% CIs at 3, 6 and 12 months (or later time points if data permits) will be presented. The number of patients with events along with the type of events (death or progressive disease) and the number of patients censored will be summarized.

The analysis of PFS will be repeated for the mITT population and modified response-evaluable population.

Time to Response (TTR)

Time to response is defined as the time in weeks from first dose to the date of first documentation of confirmed objective response (PR or better). Patients with no confirmed PR or better will be censored on the last date of adequate response assessment. Patients with no post baseline response assessment will be censored on day 1.

TTR (months)= (date of confirmed response or censor – date of first dose + 1)/30.4375).

The analysis of TTR will be based on response-evaluable analysis set. The Kaplan-Meier method will be used to estimate the distribution of TTR by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. Kaplan-Meier curves, the 25th, 50th (median), and 75th percentiles, along with

associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley, and Kaplan-Meier estimates with 95% CIs at 3 and 6 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.

The analysis of TTR will be repeated for the mITT population and modified response-evaluable population.

Time to Next Treatment (TTNT)

TTNT is defined as the time from the date of first dose to the date of the first dose initiation of the next line of antineoplastic therapy, for any reason. Patients who have not started the second-line therapy will be censored at date of last known to be alive subsequent anti-cancer therapy.

The analysis of TTNT will be based on safety analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. The Kaplan-Meier method will be used to estimate the distribution of TTNT. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

The analysis of TTNT will be repeated for the mITT population and modified response-evaluable population.

Time to Progression (TTP)

TTP is defined as the time from the date of the first dose to the date of the first documentation of PD as defined by standard disease criteria. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment. Patients who die during treatment without PD will also be censored at the date of last response assessment. 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.

The analysis of TTP will be based on the safety analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. The Kaplan-Meier method will be used to estimate the distribution of TTP. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

The analysis of TTP will be repeated for the mITT population and modified response-evaluable population.

Overall Survival (OS)

OS is defined as the time from the date of the first dose to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

The analysis of OS will be based on safety analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2. The Kaplan-Meier method will be used to estimate the distribution of OS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier PFS probability estimates with 95% CIs at 3 and 6 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.

The analysis of OS will be repeated for the mITT population.

7.5.3 Additional Efficacy Endpoint(s)

Best Overall Response

Best overall response is defined as the best response recorded after the first dose of study drug until subsequent anti-multiple-myeloma therapy.

Best Overall Response (unconfirmed): This will be the best response reported by the investigator; ordered from best to worst: sCR, iCR, mCR, CR, VGPR, PR, MR, SD, PD. The best response can also be Not Evaluable (NE) or No assessment performed if this is the only investigator assessment of response available for the patient.

Best Overall Response (confirmed): This will be the best response reported by the investigator; ordered from best to worst: sCR, Complete Response, VGPR, Partial Response, Minimal Response, Stable Disease, Progressive Disease, NE.

Confirmed Response: All response categories (sCR, iCR, mCR, CR, VGPR, PR, MR, SD, PD) require 2 consecutive assessments made at any time before the initiation of alternative anti-multiple-myeloma therapy. There is no requirement on the time between the two visits. Consecutive visits are needed for response confirmation, except if there is one or two NE/ND assessments in between.

For categories other than PD, the consecutive assessment usually means next cycle (a few days apart might not be appropriate). Either one or two consecutive occurrences of “ND” or “NE” between responses can be skipped when confirming a response such as:

PR -> NE -> PR: PR is considered to be confirmed in this case.
CR -> ND -> CR: CR is considered to be confirmed in this case.
VGPR => NE -> PR: PR is considered confirmed in this case

If the subject only has one assessment, the confirmed response should be “NE”.

Confirmation of SD:

Like all other response categories (CR, sCR, iCR, mCR, VGPR, PR, and PD), SD needs two consecutive assessments (with no evidence of PD) to confirm. For the following case, the best confirmed response is PD if there is an alternative therapy after PD. SD is not confirmed as only one SD is recorded.

BL(baseline) → SD → PD

Alternatively, for example, SD-> PR (or SD -> NE -> PR) would be considered as confirmed SD.

Confirmation of PD:

In practice, sometimes it is difficult to have two consecutive PDs entered in clinical database to confirm PD.

1. If only one PD is recorded as the last available assessment on study or the last available assessment on study prior to the alternative therapy, it can be counted as a confirmed PD. It will be considered as an event for DOR, TTP, PFS analyses.

BL → SD → PD → Alternative therapy/End – It is a confirmed PD

2. If only one PD value is recorded in the middle as below, it will not be counted as a confirmed PD. It will not be considered as an event for DOR, TTP, PFS analyses.

BL → SD → PD → SD → SD → Alternative therapy/End – It is a confirmed SD, not confirmed PD.

Best overall response will be summarized by frequencies and percentages based on response-evaluable analysis set by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2.

The summary will also be repeated for mITT population and modified response-evaluable population.

Best M-Protein Response

The best m-protein response is defined as the percent change from baseline to the best (lowest) value post-baseline. For subjects with measurable serum m-protein at baseline, the best m-protein response is based on serum m-protein. For subjects with non-measurable serum m-protein at baseline, but measurable urine m-protein at baseline, the best m-protein response is based on the urine m-protein. A waterfall plot of the best m-protein response will be generated. The plot will have the following information:

1. Response.
2. Dose cohort.
3. Urine M-protein/Serum M-protein.

7.6 Pharmacokinetic/Pharmacodynamic Analysis

7.6.1 Pharmacokinetic (PK) Analysis

The PK of TAK-981 will be characterized in this study. For mezagitamab and daratumumab, onlyPK concentration from sparse sampling will be summarized.

PK parameters for TAK-981 will be estimated using noncompartmental methods with Phoenix WinNonlin software for patients in the dose escalation phase. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be estimated, as permitted by data, for samples collected during C1D1 and C1D15:

- C_{max} (maximum observed plasma concentration).
- t_{max} (time of first occurrence of maximum observed concentration).
- AUC_{∞} (area under the plasma concentration-time curve from time 0 to infinity).
- AUC_t (area under the plasma/blood/serum concentration-time curve from time 0 to time t).
- $t_{1/2z}$ (terminal disposition phase half-life).
- Total clearance (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 mezagitamab and daratumumab concentration-time data will be presented in listings and tabulated using summary statistics by dose cohort as well. 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 serial and sparse 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.

7.6.2 Pharmacodynamic Analysis

The analysis of blood and bone marrow 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 to help determine the PAD/RP2D for the TAK-981 in each antibody combination. In addition, candidate response biomarkers will be evaluated.

7.7 Other Analysis

7.7.1 PK/ Pharmacodynamic 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 anti-CD38 mAbs. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 in combination with mezagitamab or daratumumab and hyaluronidase-fihj 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 mAbs.
2. Single and multiple dose PK of TAK-981.
3. Single and multiple dose pharmacodynamic biomarkers of TAK-981 and mezagitamab or daratumumab and hyaluronidase-fihj (in circulation, and BMA) including target engagement (adduct formation) and SUMO2/3 inhibition in blood, [redacted]
4. Antitumor response with TAK-981 in combination with mAbs 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 mAbs.

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 CSR for this study but will be presented in a separate report.

7.7.2 MRD Analysis

MRD negativity is defined as the absence of MRD and MRD positivity is defined as the presence of MRD. MRD assessment will be conducted on BMA collected at screening and at time of suspected CR and VGPR. The BMA collected at screening will be used to identify the patient's MM clones at baseline. The presence and abundance of these specific tumor clone(s) will be evaluated in the BMA sample collected in patients who achieve a VGPR or CR to determine the presence or absence of residual disease.

MRD negative rate at 1 year is defined as percentage of participants who have achieved MRD negative status at 1 year.

Durable MRD negative rate is defined as the number of participants who have achieved MRD negative status (at 10^-5) at 2 BMAs examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

The number and percentage of patients with MRD negative status as determined by NGS will be summarized by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, and by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2.

MRD negative rate at 1 year and durable MRD negative rate will be also summarized similarly.

7.7.3 [redacted]

[redacted]

7.8 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 population.

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

7.8.1 Dose Limiting Toxicities (DLTs)

The incidence of DLTs will be tabulated for each dose group. 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 by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2.

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

The DLT-evaluable analysis set will be used for the analysis of DLT.

7.8.2 Adverse Events

7.8.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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.

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).
- Serious AEs (SAEs) (related and regardless of relationship).
- Treatment-emergent AEs leading to study drug modification (includes reduction, delay, interruptions).
- Treatment-emergent AEs leading to study drug 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 the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. 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 any treatment arm) 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 discontinuation of study drug, and on-study deaths.

In general, TEAEs will be summarized by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined.

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.

7.8.2.2 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent SAEs 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).

7.8.2.3 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.

7.8.2.4 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).

7.8.3 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 (eg, 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 local laboratories will be used as there are no central laboratory test results available for this study.

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 dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined. 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 toxicity from baseline to post baseline worst on study CTCAE grade based on NCI CTCAE v5.0, if available. Grading may also be based on NCI CTCAE v4.03 if grading based on NCI CTCAE v5.0 cannot be programmatically derived. Parameters to be tabulated for shift tables are included in Table 7.a. In addition, shift table will also be constructed for immunosafety markers to tabulate changes in baseline categories (below normal range, within normal range, above normal range)

to post baseline worst on study categories (below normal range, within normal range, above normal range).

Table 7.a Clinical Chemistry and Hematology Tests to be summarized

Hematology	Serum Chemistry		Coagulation
Hematocrit Hemoglobin Leukocytes Lymphocytes Neutrophils (ANC) Platelet (count) CD4/CD8 count and ratio	Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin (total) Calcium Creatinine	Glucose Lactate dehydrogenase (LDH) Potassium Sodium Standard C-reactive protein	None

ANC: absolute neutrophil count; EDC: electronic data capture.
[a] neutrophils captured as ANC in EDC.

By-patient listings to be presented include all parameters for hematology, clinical chemistry, coagulation (Protocol Table 9.a), urinalysis(Protocol Table 9.b), immunosafety markers (Protocol Table 9.c).

Mean laboratory values over time will be plotted for key lab parameters, including hemoglobin, leukocytes, lymphocytes, 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.

7.8.4 Vital Signs

The actual values of vital sign parameters (blood pressure and heart rate) and weight will be summarized over time by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined. 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.

7.8.5 12-Lead ECGs

Descriptive statistics for the actual values and changes from values at baseline in Electrocardiograms (ECGs) will be provided 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 (≥30 msec 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.

Summaries of ECG as described above will be provided by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined.

ECGs abnormalities will be presented in a data listing.

7.8.6 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 by dose cohort, overall for Phase 1b-Part 1 and Phase 1b-Part 2, by expansion cohort (and overall if more than 1 expansion cohort) for Phase 2, and overall for both phases combined.

7.9 [redacted]

[redacted]

7.9.1 [redacted]

[redacted]

Table 7.b [redacted]

[redacted]

7.9.2 [redacted]

[redacted]

[redacted]

Table 7.c [redacted]

7.9.3 [redacted]

[redacted]

7.10 Interim Analysis

Although no formal interim analysis is planned, investigators and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort in the dose escalation phase (see Section 8.5 of the protocol) and during Phase 2, as described in Section 4.4.2.1.

During the Phase 2 part of the study, if any arm shows an ORR below the futility boundary in the first stage, then the enrollment in that specific arm will be stopped (see Section 6.0).

7.11 Changes in the Statistical Analysis Plan from the Protocol

Not Applicable.

8.0 REFERENCES

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[redacted]

ELECTRONIC SIGNATURES

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