Statistical Analysis Plan

NCT Number: NCT03648372

Title: An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies

Study Number: TAK-981-1002

Document Version and Date: Version 2.0, 14 April 2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-981-1002

An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy, and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies

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PHASE 1/2

Version: Final 2.0

Date: 14 April 2023

Prepared by:

[redacted], PhD
[redacted], Oncology Stats
[redacted], MS
[redacted], Oncology Stats

Based on:

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Amendment History:

Date	Version Number	Amendment Type
14 April 2023	Version 2.0	Substantial
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1.1 Approval Signatures

Study Title: An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy, and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies

Approvals:

[redacted], PhD
[redacted], Oncology Statistics

Date

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ΔAUC	change in area under the concentration-time curve
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_τ	area under the concentration-time curve during a dosing interval
AUC_τ/Dose	steady-state, dose-normalized area under the concentration-time curve during a dosing interval
BED	biologically effective dose
BUN	blood urea nitrogen
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide
CPK	creatine phosphokinase
CR	complete response
C_{trough}	observed concentration at the end of a dosing interval
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DOSD	duration of stable disease
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FL	follicular lymphoma
GGT	gamma glutamyl transferase
IDMC	independent data monitoring committee
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MAD	maximally administered dose

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Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression free survival
PK	pharmacokinetic(s)
PR	partial response
PTR	peak-trough ratio during a dosing interval, at steady state
QD	once daily
Rac	accumulation ratio
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
$t_{1/2}$	terminal disposition half-life
t_{max}	first time to reach maximum (peak) plasma concentration
TTP	time to progression
TTR	time to response
WHO	World Health Organization

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4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

Phase 1:

- To determine the safety and tolerability of TAK-981 as a single agent in patients with advanced or metastatic solid tumors and lymphomas.
- To establish the recommended Phase 2 dose (RP2D) of TAK-981.

Phase 2:

- To evaluate preliminary efficacy (as measured by overall response rate [ORR]) of TAK-981 in patients with select solid tumors or relapsed/refractory CD20+ non-Hodgkin lymphoma (NHL) indications.

4.2 Secondary Objectives

The secondary objectives are:

Phase 1:

- To assess the preliminary antitumor activity of TAK-981.
- To assess target engagement of TAK-981 (small ubiquitin-like modifier [SUMO]-TAK-981 adduct formation) and SUMOylation pathway inhibition in skin and peripheral blood cells.
- To characterize the pharmacokinetics (PK) profile of TAK-981.

Phase 2:

- To evaluate the efficacy of TAK-981 in select solid tumor and CD20+ NHL indications as measured by overall response rate (ORR), time to response (TTR), duration of the response (DOR), disease control rate (DCR), time to progression (TTP), and progression-free survival (PFS).
- To evaluate overall survival (OS).
- To evaluate the safety and tolerability of TAK-981.
- To collect plasma concentration-time data for TAK-981.

4.3 Exploratory Objectives

[redacted]

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[redacted]

4.4 Study Design

This is a phase 1/2, open-label, dose-escalation and dose expansion study designed to evaluate safety, tolerability, preliminary efficacy, and PK of single agent TAK-981 in adult patients with locally advanced or metastatic solid tumors or lymphomas (Figure 4.a).

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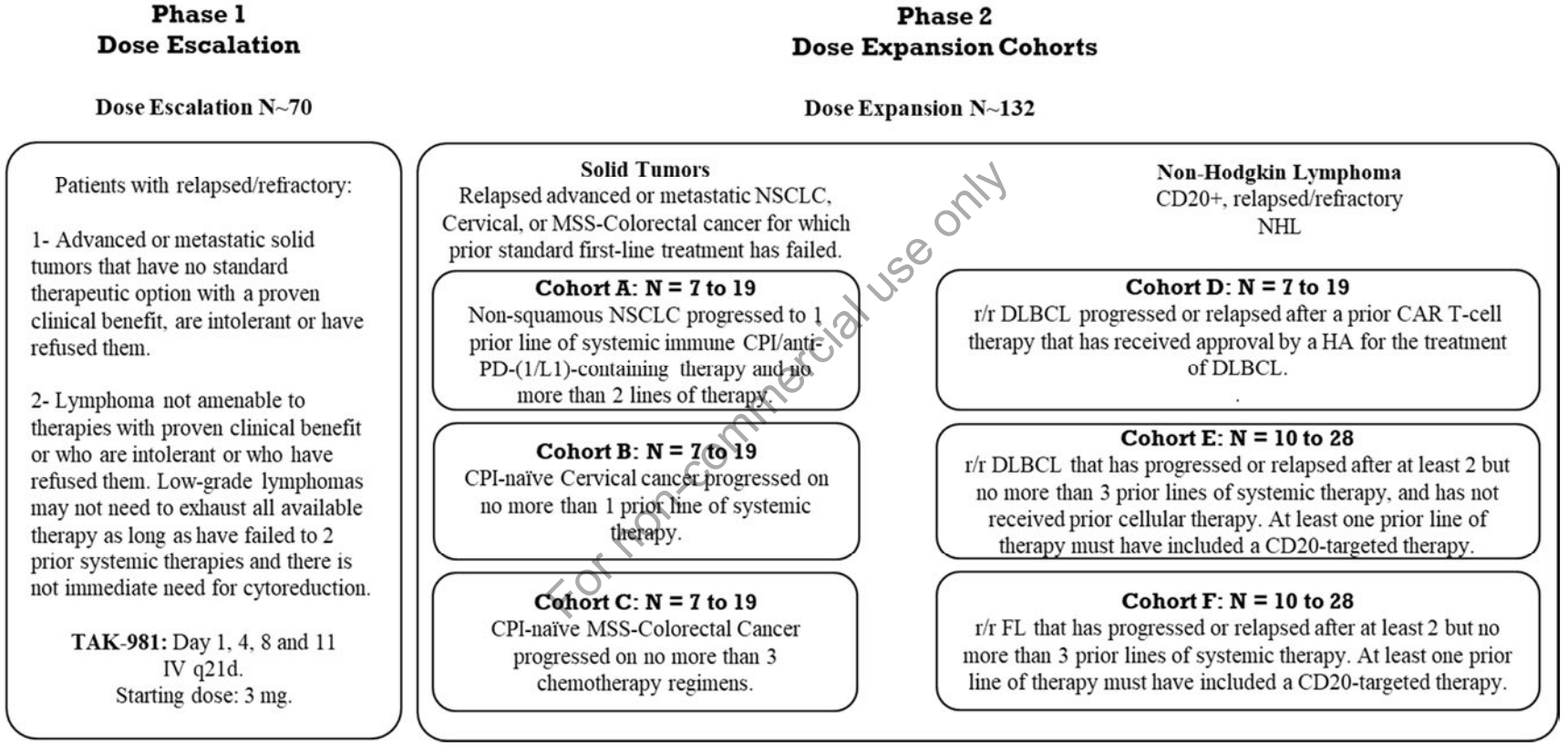
Figure 4.a TAK-981-1002 Study Design



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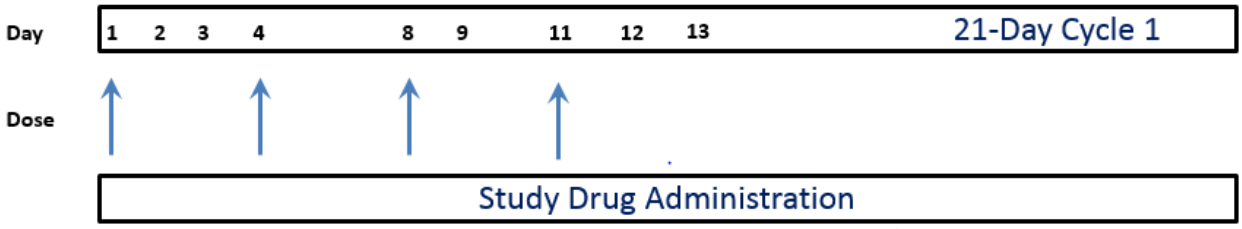
Abbreviations: CAR, chimeric antigen receptor; CPI, checkpoint inhibitor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HA, health authority; IV, intravenous; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; r/r, relapsed/refractory; q21d, every 21 days; SOC, standard of care.

4.4.1 Phase 1 Dose Escalation

Patients will be treated in cohorts with increasing doses of TAK-981, administered as a 1-hour IV infusion on Days 1, 4, 8, and 11 of a 21-day cycle until a discontinuation criterion is met. The overall dosing regimen is displayed in Figure 4.b.

Figure 4.b TAK-981 Dosing Regimen



The study will begin with a dose escalation. Dose escalation intervals progress from 3 mg to 160 mg (with a provision of 1 mg at dose level 1). The upper dose level corresponds approximately to the human equivalent dose of the maximum tolerated dose (MTD) in dogs. Patient enrollment will be staggered between the first and second patients during dose escalation 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 the Day 4 visit 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 may not be required if there are no clinically significant safety findings suggestive of infusion reaction or CRS.

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Dose escalation of TAK-981 will be cohort-based with an adaptive design using Bayesian logistic regression modeling (BLRM) (see Appendix G for details). Approximately 70 patients will be enrolled until the RP2D of TAK-981 is identified. Single agent RP2D could be based either on the MTD based on the observation of DLTs (Section 8.2.1 in the protocol) or a biologically effective dose (BED) that is ≤MTD.

A minimum of 3 patients will be enrolled in the starting dose cohort. Dose escalation and cohort expansion decisions are reviewed and approved by the Safety Monitoring Committee (SMC), composed of the sponsor clinician and the investigators, which may decide that a fourth patient can be recruited to the same cohort before the first 3 patients complete the DLT assessment period. While the first 3 evaluable patients will be used to determine dose expansion, if the fourth patient experiences a DLT, their respective AE(s) will be taken into consideration regarding cohort determination, during the end of cohort meeting. The rationale for such an addition is to have an extra patient in the cohort should 1 of the 3 earlier patients be unevaluable, or if a patient within the cohort experiences a DLT, which would require cohort expansion to 6 patients. From dose level 2 onwards, an adaptive BLRM guided by the Escalation with Overdose Control principle will be used in successive escalation cohorts (Section 8.2.2 in the protocol).

Single agent RP2D will be based either on the MTD determined by the BLRM (Section 8.2.1 in the protocol) or a BED that is ≤ MTD. The BED of TAK-981 is defined as the dose at which there is evidence of pharmacodynamic effects including the presence of SUMO-TAK-981 adducts and inhibition of SUMO2/3 conjugates, [redacted]

[redacted]

If clinical safety, PK, and pharmacodynamics are supportive, the protocol schedule can be modified to evaluate a less intensive administration of TAK-981 (eg, Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 in 21-day cycles). Once RP2D is defined, patients on schedules other than RP2D may be transitioned to the RP2D schedule upon discussion and agreement between the investigator and sponsor.

Circumstances that may warrant enrollment hold include the determination of an overall excess of toxicity:

1. The study will be stopped if the cumulative frequency of DLTs or DLT-like AEs (those AEs meeting the criteria of DLT outside of the DLT-evaluation period) is greater than 40% at any point during the trial.
2. For the 70 patients expected to be treated during the dose-escalation, the study will be stopped if 3 fatal AEs related to TAK-981 occur, at least 2 of them within the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (excluding deaths that happen during the exploration of a dose level that is above the MTD). Additionally, if 2 fatal AEs related to TAK-981 within the same System Organ Class occur during the treatment of the first 12 patients, enrollment will be also halted.

The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients, depending on the nature and severity of the safety risk. A final decision to terminate the study or a protocol amendment will be made only after a full review of the safety data by the SMC and safety management team.

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4.4.2 Phase 2 Expansion in Select Cancer Indications

Once the RP2D is defined, the study will explore the efficacy and safety of TAK-981 in patients with select cancers. The following cohorts will be enrolled (Figure 4.a):

- Cohort A: Nonsquamous NSCLC.
- Cohort B: Cervical cancer.
- Cohort C: MSS-CRC.
- Cohort D: Relapsed/refractory DLBCL progressed or relapsed after CAR T cell therapy.
- Cohort E: Relapsed/refractory DLBCL that have not received prior cellular therapy.
- Cohort F: Relapsed/refractory FL.

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 (as defined in Section 13.3 in the protocol) have been enrolled and had the potential to have at least 1 posttreatment scan (ie, after the first disease assessment, 2 months from C1D1). 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 clinical benefit has been observed for patients in the cohort (eg, the majority of patients have recorded stable disease (SD) at Week 8 and per investigator assessment are benefiting from treatment), then enrollment into stage 2 may be allowed for this cohort with agreement from participating investigators. 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 (as defined in Section 13.3 of the protocol). The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have had the opportunity complete the 6 months disease assessment.

During Phase 2, an independent data monitoring committee (IDMC) will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints:

The primary endpoints are:

Phase 1:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the National Cancer Institute Common Terminology Criteria for Adverse Events (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.
- DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- Overall response rate (ORR) (Complete Response[CR] + Partial Response [PR]) as defined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria for solid tumors or Lugano classification for lymphomas.

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5.2 Secondary Endpoints:

The secondary endpoints are:

- PK parameters after the first dose of TAK-981 on Cycle 1 Day 1 (C1D1) and Cycle 1, Day 8 (data permitting):
  - maximum observed plasma concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC_{last}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Terminal disposition phase half-life ($t_{1/2z}$).

– Total clearance (CL) after intravenous administration.

– volume of distribution at steady state (V_{ss}) after intravenous administration.

Phase 1:

- ORR, DCR, DOR, TTP, TTR and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS
- 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,TTR and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS

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5.3 Exploratory Endpoints:

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that up to approximately 70 patients will be enrolled in Phase 1 (dose escalation) and up to approximately 132 patients will be enrolled in Phase 2 cancer treatment expansion cohorts.

Dose Escalation Phase (Phase 1)

It is estimated that up to approximately 70 DLT-evaluable patients will be enrolled in this study for the dosing escalation of TAK-981 in Phase 1. A minimum of 3 patients per cohort will be enrolled in the starting dose cohort. In case of no DLT, an adaptive BLRM guided by the Escalation With Overdose Control principle will be used in successive escalation cohorts for purposes of dose escalation recommendations and estimation of the MTD. The logistic regression model will be adapted and

updated after each group of patients enrolled in the current dose level cohort. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.16): under-dosing.
- [0.16, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The selection of the next recommended dose will be determined from BLRM along consideration of other safety, clinical, PK, and pharmacodynamic data.

The details of the BLRM are included in Appendix G of the protocol. The details of dose-escalation are specified in Section 8.2.2.

Efficacy Evaluation Phase (Phase 2)

Once the MTD/BED is defined, up to approximately 132 response-evaluable patients with 6 specified types of solid tumors and 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 ORR (CR + PR) as assessed by the investigator according to RECIST v1.1 for patients with solid tumors and Lugano criteria for patients with lymphoma. The sample size consideration for disease-specific patient populations is adaptive design based on Simon's 2-stage design for a single proportion with the following hypotheses of ORR.

For solid tumor cohorts A, B, and C and lymphoma cohort D (Figure 4.a):

The hypotheses for stage 1 are the following:

H_0: ORR $< p_0$ where $p_0 = 15\%$

H_1: ORR $\geq p_0$ where $p_0 = 15\%$

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted) at stage 1, additional patients will be enrolled based on the number of responders in stage 1 and their data will be collected in the second stage.

The hypotheses at the end of stage 2 for a low desirable ORR, p1, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_1$ where $p_1 = 35\%$

H_1: ORR $> p_1$ where $p_1 = 35\%$

The hypotheses at the end of stage 2 for a high desirable response, p2, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_2$ where $p_2 = 45\%$

H_1: ORR $> p_2$ where $p_2 = 45\%$

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Because it is desirable to have higher power for detecting more improvement of the new therapy (p_2 versus p_0), for solid tumor cohorts A, B, and C and lymphoma cohort D (Figure 4.a), assuming a power of 80% for high desirable response and 70% for low desirable response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 6.a).

Table 6.a Sample Size for Each Cohort and Each Stage (Solid Tumor Cohorts A, B, and C and Lymphoma Cohort D)

	Stage		Total Number of Patients in Each Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of stage 1				
Number of patients	7	19	19	0.1/70%
Number of responses [a]	≥2 and ≤4	≥5		
High response at the end of stage 1				
Number of patients	7	13	13	0.1/80%
Number of responses	≥5	≥6		

[a] Number of patients needed to respond to continue into stage 2 or have a positive result at the end of stage 2.
[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of stage 2 in order to claim treatment effect.

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For lymphoma cohorts E and F (Figure 4.a):

The hypotheses for stage 1 are the following:

H_0: ORR < p_0 where p_0 = 45%

H_1: ORR ≥ p_0 where p_0 = 45%

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted) at stage 1, additional patients will be enrolled based on the number of responders in stage 1 and their data will be collected in the second stage.

The hypotheses at the end of stage 2 for a low desirable ORR, p1, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR ≤ p_1 where p_1 = 65%

H_1: ORR > p_1 where p_1 = 65%

The hypotheses at the end of stage 2 for a high desirable response, p2, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR ≤ p_2 where p_2 = 75%

H_1: ORR > p_2 where p_2 = 75%

Similarly, for lymphoma cohorts E and F, assuming a power of 80% for high desirable response and 70% for low desirable response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 6.b).

Table 6.b Sample Size for Each Cohort and Each Stage (Lymphoma Cohorts E and F)

	Stage		Total Number of Patients in Each Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of stage 1				
Number of patients	10	28	28	0.1/70%
Number of responses [a]	≥6 & ≤7	≥16		
High response at the end of stage 2				
Number of patients	10	16	16	0.1/80%
Number of responses	≥8	≥9		

[a] Number of patients needed to respond to continue into stage 2 or have a positive result at the end of stage 2.
[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of stage 2 in order to claim treatment effect.

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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.

In general, the summary tables for efficacy endpoints will be provided by escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase; the summary tables for non-efficacy endpoints (disposition, baseline and demographics, medical history, medication history, exposure, safety analysis) will be provided by escalation cohort, overall for dose escalation phase, by expansion cohort and overall for expansion phase, 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 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.

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

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  - 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 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.

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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.

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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 all Cycle 1 doses of TAK-981 without experiencing a DLT or who have a DLT during Cycle 1 of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Tumor 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 was 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 at least 1 on-treatment 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]

7.3 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each population, and will be presented by dose escalation cohort and overall for dose escalation phase, by dose expansion cohort and overall for dose expansion phase, and overall for both phases combined. 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.

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7.4 Demographic and Other Baseline Characteristics

Demographics will be summarized for each dose escalation cohort, overall in dose escalation phase, and for each expansion cohort, overall in expansion phase, and overall for both phases combined.

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. No inferential statistics will be generated.

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

Baseline characteristics including baseline disease primary diagnosis (lymphoma vs. solid tumor), time since initial diagnosis, staging, Eastern Cooperative Oncology Group (ECOG) performance status, will be summarized. For lymphoma patients, evidence of bone marrow involvement, evidence of extranodal involvement, and number of extranodal sites will be summarized for initial diagnosis; history of bone marrow involvement will be summarized at study entry. For solid tumor patients, sites of cancer involvement will be summarized.

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 systemic therapy, prior radiation, prior surgery, prior transplant procedure and best response to the last prior systemic 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 WHO drug generic term for the safety population, from ICF signature dose of study treatment and 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.

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7.7 Study Drug Exposure and Compliance

Extent of Exposure:

The exposure to TAK-981 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, ≥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, where duration of treatment (days) is calculated as (last dose date of study drug – first dose date of study drug + 1).

Descriptive statistics for Relative dose intensity (RDI) (%) and categorical summary of RDI (<50%, 50% to <80%, 80% to < 100%, >100%, =100%) will be summarized 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 in cycle)

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

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

Action on 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 dose expansion cohort, and overall in dose expansion phase, and overall for both phases combined.

7.8 Efficacy Analysis

Analysis of efficacy measures will be descriptive for each escalation cohort, overall for dose escalation phase, for each expansion cohort, overall in expansion phase. All efficacy analyses will be based on investigator assessments. Investigators will assess responses using the Lugano classification for lymphomas and RECIST version 1.1 for solid tumors.

7.8.1 Primary Efficacy Endpoint(s)

Phase 1:

Efficacy is not the primary objective for this study in the Phase 1 portion.

In the Phase 1 portion of this study, efficacy parameters such as ORR, DCR, DOR, TTR, TTP, and PFS 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 (CR + PR) as defined by the investigator according to response assessments based on RECIST v1.1 for solid tumors or Lugano classification for lymphomas.

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Overall Response Rate (ORR)

The ORR is defined as the proportion of patients who achieved CR and PR during the study as defined by the investigator according to response assessments based on RECIST v1.1 for solid tumors or Lugano classification for lymphomas. Response evaluations after the start of alternative anti-cancer therapy will not be taken into account in the calculation of ORR.

The primary efficacy analysis will be provided by expansion cohort, and overall in expansion phase using the tumor response-evaluable analysis set.

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

7.8.2 Secondary Efficacy Endpoint(s)

Phase 1:

- ORR, DCR, DOR, TTP, TTR and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS.

Phase 2:

- DCR, DOR, TTP, TTR and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS.

Overall Response Rate (ORR)

Similar to analysis of ORR for phase 2 in Section 7.8.1, analysis of ORR will be provided based on the tumor response-evaluable analysis set by each escalation cohort, overall for dose escalation phase.

Duration of Response (DOR)

The DOR will be calculated for responders with a PR or better in the tumor response-evaluable analysis set. DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better.

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

The Kaplan-Meier method will be used to estimate the distribution of DOR when data allows. 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.

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Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve SD or better (determined by the investigator) >6 weeks during the study in the response-evaluable population.

The DCR will be summarized by frequencies and percentages based on response-evaluable analysis set by escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. Estimates of the CBR will be presented with 2-sided 95% exact binomial confidence intervals.

Progression Free Survival (PFS)

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 RECIST version 1.1 for patients with solid tumor and Lugano classification 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.-Patients with no post baseline response assessment will be censored on date of first dose.

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 the safety analysis set by escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. 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 may be repeated for tumor response-evaluable analysis set.

Time to Response (TTR)

TTR is defined as the time from the date of first study drug administration to the date of first documentation of objective response (PR or better) by the investigator.

Patients with no 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 date of first dose.

TTR (months)= (date of 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 (if data allows) by escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. 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.

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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 assessed by the investigator. 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 safety analysis set by escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. 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.

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 escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. 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 OS 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.

7.8.3 Additional Efficacy Endpoint(s)

Best Overall Response (BOR)

Best overall response is defined as the best response recorded after the first dose of study drug until subsequent anti-cancer therapy or end of treatment, whichever is earlier. Responses assessed after disease progression will not be considered in determination of the best overall response.

Best Overall Response (unconfirmed): This will be the best response reported by the investigator; ordered from best to worst: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

Best Overall Response (confirmed for solid tumor only and unconfirmed for lymphoma): This will be the best response reported by the investigator; ordered from best to worst: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

Confirmation of the response for solid tumor will follow guideline specified in RECIST 1.1 criteria.

The general rules for determining the confirmed BOR for solid tumor per RECIST 1.1 guidelines are as follow:

- **Confirmed CR or PR**: any patterns with two or more CRs, PRs, or PR followed by CR at least 4 weeks apart (>25 days) before progression with an exception of CR-SD-CR which gives a best overall response of SD (assuming minimum time interval criteria for SD is met). The two overall responses of CR and/or PR are not required to be consecutive.
- **SD**: at least one overall response of SD (or better) at least 6 weeks (on or after Day 40) after the first dose date and does not meet the criteria for a confirmed CR/PR.
- **PD**: the best overall response is PD.
- **NE**: does not meet any of the criteria above.

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Table 7.a Examples of best confirmed response derivation

Pattern	Best Confirmed Response
CR-PD	SD
PR-PD	SD
SD-PD	SD
CR-CR	CR
CR-NE-CR	CR
CR-SD-CR	SD
CR-NE-NE-CR	CR
PR-PR	PR
PR-CR	PR
PR-NE-PR	PR
PR-NE-CR	PR

Table 7.a Examples of best confirmed response derivation

Pattern	Best Confirmed Response
PR-SD-PR	PR
PR-SD-CR	PR
PR-NE-NE-PR	PR
PR-SD-SD-PR	PR
PR-NE-SD-PR	PR
PR-SD-NE-PR	PR
PR-NE-NE-CR	PR
PR-SD-SD-CR	PR
PR-NE-SD-CR	PR
PR-SD-NE-CR	PR
CR-PR	PR
CR-SD	SD
CR-PR-PR	PR

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Some special considerations when deriving the confirmed BOR:

- Missing scans are ignored in determination of confirmed BOR. NE and missing are equivalent (e.g. for CR-NE-CR, the confirmed BOR is confirmed CR)
- SD and NE are equivalent in confirmation of PR but not for CR.

Duration of SD (DOSD)

Duration of SD (DOSD) will be summarized for the patients with SD only as BOR.

DOSD is the time from the date of first dose to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment.

DOSD (months) = (date of PD – date of first dose + 1)/30.4375.

The Kaplan-Meier method will be used to estimate the distribution of DOSD when data allows. 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.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic (PK) Analysis

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 analysis set. The following PK parameters will be determined, as permitted by data:

- C_{max}.

- t_{max}.
- AUC_{∞}.
- AUC_{last}.
- Terminal disposition phase half-life ($t_{1/2z}$).
- CL.
- V_{ss}.

Additional PK parameters, such as accumulation ratio (RAC), may be estimated as data permit. Details for additional PK parameters and detailed analysis will be specified in clinical pharmacology analysis plan (CPAP).

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 escalation cohort for dose escalation phase, by expansion cohort for expansion phase. Individual and mean concentration-time profiles will also be plotted by cohort for each phase.

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.

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7.9.2 Pharmacodynamic Analysis

The analysis of [redacted] 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 single agent RP2D. In addition, candidate response biomarkers will be evaluated.

7.10 Other Outcomes

7.10.1 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. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 and for determination of BED.

To determine the appropriateness of the BED/schedule as an RP2D/schedule, a totality of evidence approach will be used that will integrate all available data from the dose escalation and expansion phases of the study including:

1. Multicycle safety/tolerability of TAK-981.
2. Single and multiple dose PK of TAK-981.

3. Single and multiple dose pharmacodynamic biomarkers of TAK-981 (in circulation and in the [redacted], skin, [redacted]) including target engagement (adduct formation) and SUMO2/3 inhibition [redacted].
4. Antitumor response with TAK-981 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 addition, the PK-pharmacodynamic data collected in the study during dose escalation and expansion phase may be used to inform quantitative systems pharmacology (QSP) 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 TAK-981 clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and QSP modeling may not be presented in the clinical study report for this study but will be presented in a separate report.

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7.10.2 [redacted]

[redacted]

[redacted]

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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 population.

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

7.11.1 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 for each dose group.

A by-subject listing of DLTs which occur during the treatment will be presented by schedule and dose level for all subjects enrolled during the dose escalation portion of this study. 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.

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

7.11.2 Adverse Events

7.11.2.1 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 using system organ class and preferred term by escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase. Summary of AEs 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, 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, and once within each preferred term.

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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, and on-study deaths. 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.

In addition, TEAEs will be summarized by each dose group.

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, 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).

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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.

Clinical laboratory test results from 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.

By-patient listings to be presented include hematology, serum chemistry, coagulation (Table 7.b), urinalysis tests(Table 9.b in the protocol), serum tumor markers for phase 2 expansion cohorts (Table 9.c in the protocol), and immunosafety markers (Table 9.d in the protocol).

The actual values of quantitative laboratory test results (hematology, serum chemistry, coagulation, serum tumor markers for phase 2 expansion cohorts, immunosafety markers) and percent change from baseline will be summarized according to the scheduled sample collection time point by escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase. 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 for shift tables are included in Table 7.b: 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).

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Table 7.b Chemistry, Hematology, and Coagulation Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	Activated partial thromboplastin time (aPTT)
Hemoglobin (Hgb)	Alkaline phosphatase	Prothrombin time (PT)
Leukocytes with differential (WBC)	Alanine aminotransferase	Fibrinogen
Neutrophils (ANC)	Aspartate aminotransferase	
CD4/CD8 count and ratio	Bilirubin (total)	
Platelet count	Blood urea nitrogen (BUN)	
	Calcium	
	Bicarbonate (HCO3-) or Carbon dioxide (CO2)	
	Creatinine	
	Standard C-reactive protein	
	Chloride	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Urate	

Mean laboratory values over time will be plotted for key lab parameters, including Hgb, WBC, lymphocytes, ANC, platelets, and liver function tests (ALT, AST, alkaline phosphatase, total bilirubin), LDH, creatinine; CD4, CD8 and CD4/8 ratio as well). The analysis for other lab parameters may be performed as needed.

7.11.4 Vital Signs

The actual values of vital sign parameters (blood pressure and heart rate) and weight will be summarized over time by escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase. 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 Electrocardiograms (ECGs)

Descriptive statistics for the actual values and changes from values at baseline in 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)

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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 study entry 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 study entry assessment over time, and ECOG score frequency table over time will be summarized. Shifts from study entry to the worst post study entry score will be tabulated by escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase.

7.11.7 Other Observations Related to Safety

The assessment of left ventricular ejection fraction (LVEF) measured by echocardiography or MUGA scan will be performed at screening, Cycle 2 Day 1, Cycle 3 Day 1 then repeated every 3 cycles from

C3 onwards and at the end of treatment. The summary of LVEF will be tabulated as appropriate. A by-patient listing will be presented.

7.12 Interim Analysis

The SMC will review accruing data to determine dose escalation and number of patients per cohort in the dose escalation phase (see Section 8.2.2 of the protocol).

For Phase 2 cancer treatment expansion cohorts, an IDMC will be established to monitor safety and assess benefit/risk throughout the conduct of these portions of the study (see Section 11.2 of the protocol).

7.13 Changes in the Statistical Analysis Plan from the Protocol

Not applicable.

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8.0 REFERENCES

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