Statistical Analysis Plan

NCT Number: NCT05976334

Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [14C]Subasumstat in Patients With Advanced or Metastatic Solid Tumors

Study Number: TAK-981-1004

Document Version and Date: Final 1.0 , 08 JUN 2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-981-1004

A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [^{14}C]Subasumstat in Patients with Advanced or Metastatic Solid Tumors

PHASE 1

Version: **Final 1.0**

Date: 08 Jun 2023

Prepared by:

[redacted], MS

Oncology Statistics

Based on:

Protocol Version: Initial Protocol

Protocol Date: 25 April 2023

1.1 Approval Signatures

Study Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [^{14}C]Subasumstat in Patients with Advanced or Metastatic Solid Tumors

Approvals:

[redacted], PhD [redacted], Oncology Statistics	Date

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
Ae_{urine}	cumulative amount excreted in urine
ANC	absolute neutrophil count
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomical therapeutic chemical
AUC_{∞}	area under the plasma/blood/serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BIW	twice weekly
BUN	blood urea nitrogen
CL	clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
ICF	informed consent form
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QTc	corrected QT interval
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	first time to reach maximum (peak) plasma concentration

Abbreviation	Term
TEAE	treatment-emergent adverse events
TRA	total radioactivity
V_{ss}	volume of distribution at steady-state
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

- To assess the mass balance (ie, cumulative excretion of TRA in urine and feces) of subasumstat following a single 1-hour infusion of 90 mg [^{14}C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

4.2 Secondary Objectives

- To characterize the PK of subasumstat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 90 mg [^{14}C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.
- To evaluate the safety and tolerability of subasumstat in patients with advanced or metastatic solid tumors during Part A and Part B.
- To collect samples for characterization of the metabolic profile of subasumstat in plasma, urine, and feces following a single 1-hour infusion of 90 mg [^{14}C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

4.3 Exploratory Objectives

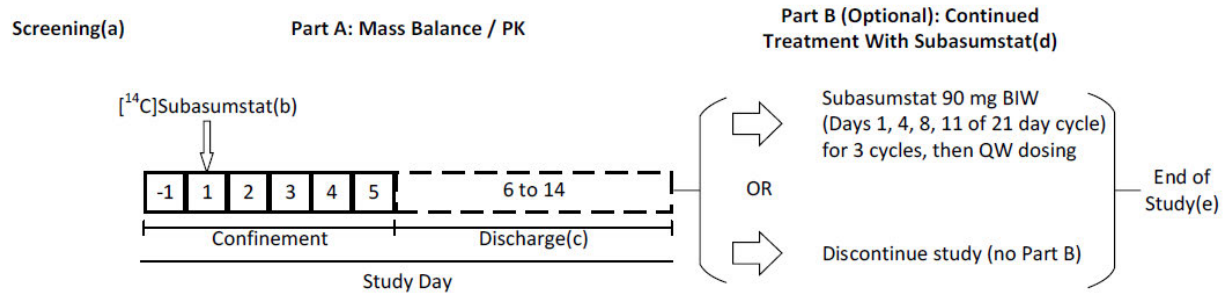
- To evaluate efficacy of subasumstat in patients with advanced or metastatic solid tumors during Part B.

4.4 Study Design

This is a 2-part, open-label, mass balance and absorption, distribution, metabolism, excretion (ADME) study in patients with advanced or metastatic solid tumors.

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

Figure 4.a Schematic of Study Design



BIW: twice weekly; EOS: end of study; IV: intravenous; PK: pharmacokinetic; QW: once weekly.

[a] Screening assessment will be performed within 28 days before administration of [^{14}C]subasumstat.

[b] Patients will receive a single dose of subasumstat 90 mg as a 1-hour IV infusion on Day 1. The clinic will be supplied with vials containing approximately 100 µCi (approximately 3.7 MBq) of [^{14}C] subasumstat as the radioactive tracer.

[c] Discharge criteria for Part A are in Section 6.1.1.1 (Protocol). Patients will be discharged between Days 6 and 14, given that the discharge criteria have been met. Discharge assessments are done only once on the day of discharge. Since up to a 3-day time lag is anticipated for radioactivity counting of samples, actual patient discharge from the study site may occur 3 days after the discharge criteria are met.

[d] Part B treatment will be 1 year. Patients will have 3 cycles (21 days) on a BIW schedule on days 1, 4, 8, and 11 followed by maintenance with the QW schedule.

[e] Patients will attend an EOS visit 30 days after the last dose of study drug in Part B or before the start of subsequent therapy for the patient's indication, if that occurred sooner.

4.4.1 Part A: Mass Balance/ADME Assessment of Single Agent Subasumstat

Part A is the period assessing the mass balance, PK, metabolism, and excretion of subasumstat in this population.

The study will enroll patients diagnosed with locally advanced or metastatic solid tumors with measurable disease. If patients drop out, they may be replaced, to ensure approximately 6 PK evaluable patients complete Part A assessments. Patients can be released from the study site 5 days postdose when the discharge criteria are met. Otherwise, the patient may have to stay at the site for a maximum of 14 days postdose. Samples will be collected and patients will be confined until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples (combined) or until <1% of the dosed radioactivity is collected in 2 consecutive intervals from both urine and feces. Patients who sign an informed consent form (ICF) will be assigned a patient identification number, and those who meet all inclusion criteria and none of the exclusion criteria will be admitted to the study site on Day -1 for predose assessments. On Day 1, patients will receive 90 mg [^{14}C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq; equivalent to 2.74 mrem or 0.0274 mSv whole body effective dose for human male subjects and 1.41 mrem or 0.0141 mSv whole body effective dose for human female subjects) via a 1-hour IV infusion. All samples being assessed for TRA will be tested in batches.

All samples from Day 1 to Day 5 will be assessed at the same time. For patients who do not meet the discharge criteria, the samples collected from Day 6 until the time when the TRA is available will be used for TRA determination. This process of batch measurement will continue until the discharge criteria are met. Since up to a 3-day time lag is anticipated for radioactivity counting of samples, actual patient discharge from the study site may occur 3 days after the discharge criteria are met.

Patients' safety will be closely monitored, and AEs will be collected throughout the study. Vital signs, physical examinations, ECGs, and clinical laboratory tests will be captured during the confinement (predose, during study, before discharge from study site).

In this clinical study, blood samples will be collected at prespecified time points to analyze subasumstat, TRA in blood and plasma, and metabolite profiling in plasma over the confinement. Complete urinary and fecal output will be collected throughout the confinement period until discharge; urine samples will be analyzed for PK, TRA, and metabolite profiling and fecal samples will be analyzed for TRA and metabolite profiling. For patients experiencing emesis after drug administration, the full vomitus will be collected as much as possible and assayed for TRA. If a subject vomits more than once during a period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. More detailed information will be provided in the study manual. Patients may be provided treatment for constipation if needed, as determined by the investigator.

4.4.2 Part B: Continued Treatment with Single Agent Subasumstat

After completion of Part A, patients will have the opportunity to participate in Part B. Participation in Part B is voluntary, and a consent is included in the main study consent form. The patient can withdraw from Part B at any time during the study, or the patient can be withdrawn from the study if there is toxicity or there is no evidence of clinical benefit to the patient at the discretion of the investigator.

During Part B, the patient will receive subasumstat 90 mg twice weekly (on days 1, 4,8, and 11 of the 21-day cycle) for 3 cycles, followed by weekly maintenance dosing (on days 1 and 8 of the 21-day cycle). The treatment will be up to 1 year. For patients who have completed 1 year of treatment with subasumstat, the investigator(s) may discuss treatment options with the sponsor.

Safety and disease assessments will be collected in Part B. Investigators will use RECIST 1.1 criteria to assess the clinical response. Disease assessments will be conducted using radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI]).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are:

- Cumulative percentage of urinary recovery, fecal recovery, and combined recovery, and percentage of recovered TRA in urine and feces for each interval over the entire period of collection.

5.2 Secondary Endpoints

The secondary endpoints are:

- PK parameters of subasumstat and TRA in plasma and whole blood: maximum observed concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), and area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}), and as permitted by data, terminal disposition phase half-life ($t_{1/2z}$), clearance (CL), volume of distribution at steady-state (V_{ss}), and area under the concentration-time curve from time 0 to infinity (AUC_{∞}), calculated using the observed value of the last quantifiable concentration.
- PK parameters of subasumstat in urine: cumulative amount of unchanged drug excreted into the urine (Ae_{urine} and percentage of dose) and renal clearance (CL_R).
- Safety parameters: AEs, SAEs, electrocardiogram (ECG) and abnormality of laboratory values.
- Metabolite profiling and identification in plasma, urine, and feces.

5.3 Exploratory Endpoints

Efficacy parameters will be evaluated: overall response rate (ORR), progression-free survival (PFS), best response (CR, partial response [PR], etc.) and duration of response (DOR) as assessed by the investigator according to RECIST v1.1 criteria for solid tumors [1] (Eisenhauer et al. 2009).

6.0 DETERMINATION OF SAMPLE SIZE

The sample size for this study is not based on statistical considerations. On the basis of the As Low (radioactive burden) As Reasonable Achievable (ALARA) principle set forth in the 96/29/EURATOM directive, a sample size of approximately 6 PK-evaluable patients has been selected to provide adequate characterization of the mass balance, PK, metabolism and excretion of subasumstat in cancer patients. Approximately 10 patients will be enrolled in this study to get approximately 6 PK-evaluable patients.

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. Missing/partial dates may be imputed as appropriate.

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

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

The summary tables will include overall for both part A and part B as appropriate.

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 efficacy 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.

All safety data will be reported from the signing of informed (e)consent through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after administration of the last dose of study drug and recorded in the eCRFs.

7.1.2 Conventions for Missing/Partial Dates in Screening Visit

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

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.3 Conventions for Missing Adverse Event Dates

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

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

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the 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 same as the 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 impute.d
- 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 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 month and year are known, but day is missing, then impute day to first of the month.
- 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 at least 1 PK parameters will be used for PK analyses.

Tumor response-evaluable analysis set: Patients who have received at least 1 dose of study drug, have measurable disease at Baseline, and at least 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.

7.3 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each population. 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.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions (ie, number and percentage of patients) for categorical data and summary descriptive statistics (ie, n, mean, SD, median, minimum, and maximum) for continuous data. Demographic data will also be presented in a by-patient listing. Demographic will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate. Age will be calculated from date of birth to date of informed consent.

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

Baseline characteristics include disease assessment by imaging, Eastern Cooperative Oncology Group (ECOG) score, and other parameters will be summarized as appropriate.

7.5 Medication History and Concomitant Medications

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).

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by ATC Pharmacological Subgroup and WHO drug generic term for the safety population, 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.

7.6 Study Drug Exposure and Compliance

Extent of Exposure:

A patient is considered to have been treated in a cycle as long as this patient receives any amount of study drug. A treatment cycle is defined as a cycle in which the patient receives any amount of study drug. A treated cycle for a specific drug is defined as a cycle in which the patient receives any amount of the specific drug.

The extent of exposure to subasumstat will be summarized by Part A, and Part B.

In Part A, the extent of exposure will be summarized by dose taken in [14C]subasumstat, total amount of dose taken in subasumstat on days 1, and total number of dose taken.

In Part B, the extent of exposure will be summarized based on the number of treatment cycles, total amount of dose taken (in mg), total number of doses taken, numbers and percentages of patients who receive ≥1, ≥2, ≥3 etc treatment cycles.

In addition, the treatment duration in total will be summarized. The treatment duration in days is calculated as last dose date – first dose date +1.

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

7.7 Efficacy Analysis

7.7.1 Primary Efficacy Endpoint(s)

Efficacy is not the primary objective for this study.

7.7.2 Secondary Efficacy Endpoint(s)

Efficacy is not a secondary objective for this study.

7.7.3 Exploratory Efficacy Endpoint(s)

All efficacy analyses will be performed based on data availability.

Exploratory efficacy endpoints include ORR, DOR, Best response, and PFS as assessed by the investigator according to RECIST, Version 1.1. Response related efficacy endpoints by RECIST Version 1.1 are defined and analyzed as below.

Overall Response Rate (ORR)

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study and estimates of the ORR (CR + PR) will be presented with 2-sided 90% exact binomial CIs.

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.

Best Response

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

Best responses ordered from best to worst are as follows: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

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. 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.

7.8 Pharmacokinetic/Pharmacodynamic Analysis

7.8.1 Pharmacokinetic (PK) Analysis

The PK of subasumstat will be characterized in this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. The following PK parameters will be calculated by noncompartmental analysis and tabulated for each individual:

- TRA in plasma and whole blood: C_{max}, t_{max}, AUC_{last}, and as permitted by data, $t_{1/2z}$ and AUC_{∞}.

- TRA in urine: amount of [^{14}C]-radioactivity excreted into urine per sampling interval ($Ae_{urine,^{14}C,t1\text{-}t2}$ in ng-eq and percentage of dose) and cumulative amount of [^{14}C]-radioactivity excreted in urine up to the last sampling interval ($Ae_{urine,^{14}C}$ in ng-eq and percentage of dose).
- TRA in feces: amount of [^{14}C]-radioactivity excreted into feces per sampling interval ($Ae_{feces,^{14}C,t1\text{-}t2}$ in ng-eq and percentage of dose) and cumulative amount of [^{14}C]-radioactivity excreted in feces up to the last sampling interval ($Ae_{feces,^{14}C}$ in ng-eq and percentage of dose).
- The total cumulative excretion of [^{14}C]-radioactivity per interval and over the total collection period will be calculated as the sum of the cumulative excretion in urine and feces: total cumulative excretion of [^{14}C]-radioactivity from the body ($Ae_{total,^{14}C} = Ae_{urine,^{14}C} + Ae_{feces,^{14}C}$) (in ng-eq and percentage of dose).
- Subasumstat in plasma and whole blood: C_{max}, t_{max}, AUC_{last}, and as permitted by data, $t_{1/2z}$, AUC_{∞}, CL, and V_{ss}.
- Subasumstat in urine (per sampling interval and total): cumulative amount excreted in urine (Ae_{urine} and percentage of dose) and CL_R.

Plasma, urine, and feces for metabolite profiling and identification are collected. While the results of the PK of subasumstat and TRA, time course of excretion of TRA in urine and feces, and overall mass balance will be included in the clinical study report, the metabolite profiling and identification results will be reported separately.

7.9 Safety Analysis

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

All safety analyses will be performed based on data availability.

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

7.9.1 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 (TEAEs) 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:

- TEAEs.
- Study drug-related TEAEs.
- Grade 3 or higher TEAEs.

- Grade 3 or higher study drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs.
- Study drug-related SAEs.
- On-study deaths (ie, death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug).
- TEAEs leading to study drug modification and discontinuation.

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

TEAEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, except cytokine release syndrome (CRS) that will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS. Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high-level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10%) 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 TEAE table will include numbers and percentages of patients who had any TEAE, drug-related TEAE, grade 3 or higher TEAE, grade 3 or higher drug-related TEAE, SAE, study drug-related SAE, TEAE resulting in discontinuation, and on-study deaths.

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

7.9.1.1 Serious Adverse Events

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

7.9.1.2 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 TEAE 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.

7.9.1.3 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).

7.9.2 Clinical Laboratory Evaluations

Laboratory test results from the local laboratory will be used.

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

Shift tables will be constructed for selected laboratory parameters to tabulate changes in NCI CTCAE v5.0 for toxicity from baseline to post baseline worst on study CTCAE grade or abnormality, if available. Parameters to be considered may include in the Table 7.a and Table 7.b, but not limited.

Table 7.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	Activated partial thromboplastin time (aPTT)
Hemoglobin	Alkaline phosphatase	Prothrombin time (PT)
Leukocytes with differential	Alanine aminotransferase	Fibrinogen
ANC	Aspartate aminotransferase	
Platelets (count)	Bilirubin (total)	
	(Blood) Urea nitrogen (BUN)	
	Corrected calcium	
	Bicarbonate ($HCO3^-$) or Carbon dioxide (CO_2)	
	Creatinine	
	Chloride	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Protein (total)	
	Urate	

ANC: absolute neutrophil count.

Table 7.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

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

Mean laboratory values over time will be plotted for key lab parameters, including but not limited to hemoglobin, leukocytes with differential, neutrophils, platelet count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and standard C-reactive protein. The analysis for other lab parameters may be performed as needed.

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

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

7.9.3 Vital Signs

The actual values of vital sign parameters (blood pressure and heart rate) and weight will be summarized over time. Change of vital signs from baseline values will also be summarized over time. Vital sign values will also be presented in a by-patient listing.

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

7.9.4 12-Lead ECGs

Descriptive statistics for the calculated QTc interval values and the values changed from the end of infusion to baseline (ΔQTc) will be listed by time point.

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

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

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

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTc intervals will be performed for each time point. The number and percentage of patients in each QTc interval (<450 msec, 450-480 msec, >480-<500 msec, and ≥500msec) will be summarized at study entry 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.

7.9.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Group Performance Status and shifts from study entry 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.

7.10 Interim Analysis

Not applicable

7.11 Changes in the Statistical Analysis Plan

To be update as needed.

8.0 REFERENCES

1. Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., et al. 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version1.1). Eur J Cancer, 45(2), 228-47.

Signature Page for TAK981-1004 SAP v1.0_20230605

Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism

Approval	[redacted] Statistics 08-Jun-2023 19:59:41 GMT+0000

Document Number: TDN-000183275 v1.0