Protocol C3441049

AN OPEN-LABEL, SINGLE-ARM, PHASE 1 STUDY OF PHARMACOKINETICS, SAFETY AND ANTI-TUMOR ACTIVITY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan (SAP)

Version: 1

Date: 18-Mar-2020

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3441049 is based on the protocol dated 27January2020.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 14 Feb 2020	Original 27 Jan 2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3441049. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Any deviations from this analysis plan will be described in the Clinical Study Report.

The primary analysis will include all data up to a data cutoff date which will be determined by the completion of the first cycle, i.e., cycle 1 for the last patient dosed (37 days since last patient first dosed). All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the single and steady-state pharmacokinetics (PK) of single-agent talazoparib.	Not applicable	• Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{½}$, and AUC_{inf} as data permit. • Multiple Dose (MD) - C_{max}, T_{max}, C_{min}, AUC_{τ}, CL/F, R_{ac} ($AUC_{\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{\tau}/AUC_{sd,inf}$) as data permit.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the overall safety profile. • To assess preliminary evidence of anti-tumor activity of single agent talazoparib.	Not applicable	Safety • Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to talazoparib. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital signs and ECG • Concomitant medication use Efficacy • Unconfirmed ORR • DOR

2.2. Study Design

This is an open-label, single arm, Phase 1 study of talazoparib monotherapy to primarily evaluate the PK and safety of single agent talazoparib 1 mg Once Daily (QD) in chinese participants with advanced solid tumors who are resistant to standard therapy or for whom no standard therapy is available.

Approximately 15 participants will be enrolled to obtain about 12 evaluable participants to support metastatic castration resistant prostate cancer (mCRPC) and other future potential indication registrations in China.

Study treatment will be given once daily in 28-day cycles. To understand the single-dose safety and single-dose PK assessments of talazoparib, a lead-in period preceeding the continuous daily doses will be included. In the 9-day lead-in period, a single lead-in dose will be given on Day -9 and PK samples will be collected at pre-dose and 0.50, 1, 2, 4, 8, 24, 48, 96, 168 and 216 hours post dose. No talazoparib will be administered during the interval between the lead-in single dose and Day 1 of the first cycle. Additionally, to characterize the steady state PK profile, serial PK samples after multiple doses will be collected on Day 22 of

the first cycle at pre-dose, 0.50, 1, 2, 4, 8, 24 hours post dose. Pre-dose samples will be collected on C1D21, C1D23.

Tumor assessments are to be done on D29 (±7 days window) and every 8 weeks (±7 days window) thereafter for the initial 12 cycles regardless of any dose interruptions or dose delays. After completion of Cycle 12 (at the beginning of week 45), tumor assessment will be done per local standard practice. Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation.

Pharmacokinetic parameters and plasma concentration data will be summarized as the primary analysis for this study. In addition, safety data including adverse events (AE), laboratory abnormalities and electrocardiogram measurements (ECG), as well as efficacy information reflected by objective response (OR) and duration of response (DOR) will also be summarized and estimated.

This study will not use a data monitoring committee (DMC).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

PK parameters of talazoparib following single dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of determination
C_{max}	Maximum plasma concentration	Observe directly from data
T_{max}	First time at which C_{max} is observed	Observe directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{τ}	Area under the plasma concentration versus time curve from time zero to the time τ(=24 hr)	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration versus time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis; k_{el} is the terminal phase

	curve from time zero extrapolated to infinite time	rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL/F	Apparent oral clearance	$Dose/AUC_{inf}$
V_z/F	Apparent volume of distribution	$Dose/(AUC_{inf} * k_{el})$
$t_{1/2}$	Terminal plasma half-life	$Log_e(2)/k_{el}$

PK parameters of talazoparib following multiple dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	**Definition**	**Method of determination**
C_{max}	Maximum plasma concentration observed during the dosing interval	Observe directly from data
T_{max}	First time at which C_{max} is observed	Observe directly from data as time of first occurrence within τ at steady state
C_{min}	Minimum plasma concentration observed during the dosing interval	Observe directly from data
AUC_τ	Area under the plasma concentration versus time curve within a dosing interval of τ (=24 hr) at steady state	Linear/Log trapezoidal method
CL/F	Apparent clearance	$Dose/AUC_\tau$
R_{ac}	Observed accumulation ratio	$R_{ac}=AUC_\tau /AUC_{sd,\tau}$, where $AUC_{sd,\tau}$ is AUC_{24}
R_{ss}	Steady-state accumulation ratio	$R_{ss}=AUC_\tau /AUC_{inf}$, where AUC_{inf} is from single dose.

Actual PK sampling times will be used in the derivation of PK parameters.

3.2. Secondary Endpoint(s)

3.2.1. Efficacy

Objective response (OR)

Objective response by investigator assessment is defined as a complete response (CR) or partial response (PR) according to the RECIST version 1.1 recorded from Cycle 1 Day 1 (C1D1) until disease progression, start of subsequent anti-cancer therapy or death due to any cause.

Given the exploratory nature of the efficacy endpoint, confirmation of response is not required. A participant will be considered to have achieved an OR if the participant has a complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the participant will be considered a non-responder in the OR rate analysis. Additionally, participants with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis. If participants with non-measurable disease are enrolled, they are included in the aforementioned calculation of OR rate as well, however, a subgroup calculation of OR rate will be conducted among participants who are with measurable disease at baseline.

Duration of response (DOR)

For participants with a objective response (CR or PR), duration of response (DOR) is the time from first documentation of CR or PR to date of first documentation of objective progression or death. Date of first documentation of PD and date of first documentation of CR or PR will be based on investigator assessment of response. DOR data will be censored on the date of the last tumor assessment on study for participants who do not have objective tumor progression and who do not die due to any cause while on study. DOR will only be calculated for the subgroup of participants with an objective response.

3.3. Exploratory Endpoint(s)

Not applicable.

3.4. Baseline Variables

Start and end dates of study treatment:

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug, which is in the lead-in period.

The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.

Definition of baseline:

No windowing will be applied when defining baseline.

For efficacy analyses and baseline characteristics associated with tumor assessments (e.g. number of sites of disease at baseline), the last assessment prior to the first dose will serve as the baseline assessment.

For safety (including Eastern Cooperative Oncology Group (ECOG) performance status) analysis the last assessment performed on or prior to date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

Participants who start treatment and discontinue from the study on the same day may have two different sets of data collected on the start date (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

Triplicate ECGs will be collected on lead in visit and a single ECG will be collected at all other scheduled visits; therefore the baseline for each ECG measurement is the average of the pre-dose measurements on the start date. If the triplicate ECG are incomplete (only 2 or single), the average of the 2 or the single will be used as baseline. Unscheduled assessment on the start date will not be included in the calculation of the average. If the triplicate ECGs were not collected, the single ECG closest but prior to the start date will be used.

3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment is defined as the time from the first dose date of study treatment through minimum (28 days after last dose/start day of new anti-cancer drug therapy – 1 day). The start of new anti-cancer drug therapy after the first dose of study treatemtn is derived as outlined in Section 5.2.5. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study treatment will be considered baseline assessments (see Section 3.4 for the definition of baseline).

Safety data collected outside the on-treatment period as described above will be listed but not summarized.

3.5.1. Adverse Events

Adverse events (AEs) will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. An adverse event is considered treatment emergent relative to a given treatment, i.e., Treatment-Emergent Adverse Events (TEAEs), if the event start date is during the on-treatment period (including on the date of first dose). The focus of AE summaries will be on TEAEs.

An event will be considered treatment related if the investigator considered the event related to the study drug.The number and percentage of participants who experienced any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs on the entire study period as well as by relatedness to study treatment.

Adverse Events of Special Interest (AESI)

AESIs include Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), and second primary malignancies events.

3.5.2. Laboratory Data

Hematology and chemistry result will be programmatically graded according to the NCI CTCAE version 4.03 for relevant parameters. Additional details are provided in Section 6.6.3.

3.5.3. Electrocardiogram measurements

All ECGs obtained during the study will be evaluated for safety. Except for Day -9, single ECG measurement is taken for all other visits.The average of the triplicate ECG measurements at baseline if not single measurement will be used for the statistical analysis and all data presentations.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Only participants who signed informed consent will be included in the analysis sets below.

Population	Description
PK concentration population	Defined as all participants enrolled and treated who have at least 1 PK concentration in the single-dose and/or multiple-dose PK part.
PK parameter analysis population	Defined as all participants enrolled and treated who have at least 1 of the PK parameters of primary interest in the single-dose and/or multiple-dose PK part.
PK evaluable analysis set	Defined as all participants in the PK parameter analysis set who complete both the single dose PK and multiple dose PK parts without major protocol deviations.
Safety	Includes all enrolled participants who receive at least one dose of study medication.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

To support registration of mCRPC and other future potential indications in China, 12 evaluable participants will be needed to characterize Chinese PK profile based on available talazoparib PK data globalwise and with the intention to satisfy regulatory requirement by China National Medical Products Administration (NMPA) in terms of PK evaluation in Chinese population. Considering non-evaluable participants, it is estimated that approximately 15 patients are needed.

All analyses will be descriptive and no hypothesis testing will be conducted.

5.2. General Methods

5.2.1. Data Handling after the Cutoff Date

Data after the cutoff date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the limited sample size in this study and the relatively high number of participating centers in contrast to the anticipated small number of participants enrolled at each center.

5.2.3. Definition of Study Day

The study day for assessments occurring on or after the first dose of study treatment (e.g., adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start date of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (e.g., baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event –start date of study treatment.

The study day will be displayed in all relevant data listings.

5.2.4. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant and not per study treatment.

Study treatment will be given once daily in 28-day cycles; therefore the nominal cycle length is 28 days.

- For Cycle X, the actual cycle start date for each participant is:
  - the earliest start date of dosing in the Cycle X day 1 visit CRF exposure page, if the participant received study treatment on that visit (i.e., any study drug with dose>0 at that visit).
  - the first day of assessments in the Cycle X day 1 visit, if the participant did not receive study treatment on that visit (i.e., all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.
- For all but the last cycle:
  - actual cycle stop date is calculated as the start date of the next cycle minus one day.
  - actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows:

    Actual Cycle Duration (weeks) = (cycle stop date – cycle start date + 1) / 7
- For the last cycle, actual cycle duration is the planned cycle duration and actual cycle stop date is calculated as actual cycle start date + 28 – 1 day.

The cycle day will be calculated as:

Cycle day = Date of the assessment/event – cycle start date + 1.

5.2.5. Definition of Start of New Anti-cancer Drug Therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 3.5) in safety analysis.

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy 'and 'Follow-up Surgery' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy 'and 'Follow-up Surgery' eCRF pages.

5.2.6. Definition of Start of New Anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for efficacy analyses (see Section 6.1).

The start date of new anti-cancer therapy is the earliest date after first dose of talazoparib amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages.

- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'.

- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Date of Last Contact

The date of last contact will be derived for participants not known to have died at the data cutoff date using the latest complete date (i.e. imputed dates will not be used in the derivation) among the following:

- All assessment dates (e.g. blood draws (laboratory, Pharmacokinetics (PK)), vital signs, physical exam, performance status, ECG, tumor assessments);

- Start and stop dates of concomitant therapies including non-drug treatments or procedures;

- Start and end dates of anti-cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries;

- AE start and end dates;

- Last date of contact collected on the 'Survival Follow-up' CRF (do not use date of survival follow-up assessment unless status is 'alive');

- Study treatment start and end dates;

- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed or dates data were entered into the CRF will not be used. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.8. Tumor Assessment Date

The Date of Tumor Assessment at each nominal timepoint as provided by the investigator on the IOTA CRF will be utilized for the respective analyses.

5.2.9. Adequate Baseline Tumor Assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dosing date.
- All documented lesions must have non-missing assessments (i.e. non missing measurements for target lesions and non missing lesions status at baseline for non-target lesions).

5.2.10. Adequate Post-baseline Tumor Assessment

An adequate assessment is defined as an assessment where a response of CR, PR, Stable Disease (SD), non-CR/non-PD, or PD has been provided by the investigator. Timepoints where the response is not evaluable or no assessment was performed will not be used for determining the censoring date.

5.2.11. Nominal and Unscheduled Visits

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal timepoint (i.e. assessment will not be slotted).

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety (except where noted for baseline ECGs). Additionally, unscheduled assessments will be used for efficacy analyses (e.g. defining date of progression/censoring, best overall response, date of last contact).

5.2.12. Standard Deviations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]: year of given informed consent - year of birth;
- Body Mass Index (BMI, kg/m^2) = weight (kg) / [height (m)]^2.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point

between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.13. Analyses for Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified

5.2.14. Analyses for Time-to-Event Endpoints

If data permits, Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median time with two-sided 95% CIs. Probabilities of an event at particular timepoints will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at particular timepoints will be derived using the log(-log) method .

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all data listings imputed values will be presented and flagged as imputed.

Missing statistics, e.g. when they cannot be calculated, should be presented as ‘ND’ for not done, ‘NR’ for not reached or ‘NA’ for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as ‘ND’ or ‘NA’.

5.3.1. Missing Pharmacokinetic Data

Concentrations below the limit of quantification

For all calculations, figures, and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their confidence intervals. A statement similar to ‘All values reported as BLQ have been replaced with zero’ should be included as a footnote to the appropriate tables and figures. In listings BLQ values will be reported as below lower limit

of quantification ("<LLOQ"), where LLOQ will be replaced with the corresponding value from the analytical assay used.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a patient's concentration data due to insufficient sampling, the parameter will be coded as NC (ie, not calculated). If PK parameter cannot be derived from a patient's concentration data due to discontinuation of treatment, the parameter will be coded as NS (ie, no sample).

In summary tables of concentration-time profiles or PK parameters, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are not collected, not calculated, or below LLOQ. For statistical analyses (i.e. analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation for the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Missing ECG Data

For QTc analyses, no values will be imputed for missing data. For triplicate measurements taken at baseline, if one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing for an ECG parameter, no values will be imputed.

5.3.3. Handling of Incomplete or Missing Dates

5.3.3.1. Adverse Events

AE Onset Date:

The following imputation rules apply if the event is unique for a participant or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

If the AE start date is missing, and if the date of first dose is less than AE end date, then the start date will be assigned as the date of first dose. Otherwise if the date of first dose is after the AE end date then the AE start date will be imputed as the earliest of non-missing AE end date or informed consent date.

AE Stop Date:

Ongoing events will have the AE Stop Date set to one of the following values: if the AE end date is missing then the end date will be imputed as the latest of the Subject Withdrawal/Completion date, death date, last dose of study treatment, or AE start date.

Imputation will only occur if event is unique for the participant, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. Adverse Events are deemed similar if they have the same verbatim term.

5.3.3.2. Exposure

No imputation will be done for first dose date. Date of last dose of study treatment, if unknown or partially unknown, will be imputed as follows:

- If the last date of study treatment is completely missing and there is no End of Treatment (EOT) CRF page and no death date, the participant should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or

- If the last date of study treatment is completely or partially missing and there is EITHER an EOT CRF page OR a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date),

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date), or

  = min (EOT date, death date), for all other cases.

5.3.3.3. Date of Death

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact

- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

  - Missing day: 1st day of the month and year of death

  - Missing day and month: January 1st of the year of death

5.3.3.4. Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is:
  - completely missing then it will be ignored in the imputations below;
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy;
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For participants who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is derived as follows:
  - <u>Start date of new anti-cancer therapy is completely missing</u>

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - <u>Only year (YYYY) for start of anti-cancer therapy is available</u>

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - <u>Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available</u>

    IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY ;

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

5.3.3.5. Other Dates

Imputation methods for other partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date.

- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.
- If the date is completely missing, no imputation will be performed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Pharmacokinetic parameters

Summary of pharmacokinetic parameters will be conducted in PK parameter analysis population and PK evaluable analysis set. Actual PK sampling times will be used in the derivation of PK parameters.

The following PK parameters following single dose administration of talazoparib for lead-in phase will be listed and summarized descriptively.

PK parameters	Summary statistics
AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, CL/F, Vz/F	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean and geometric CV%
T_{max}	N, median, minimum, maximum
$t_{1/2}$	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum

The following PK parameters following multiple dose administration of talazoparib will be listed and summarized descriptively.

PK parameters	Summary statistics
AUC_{24}, C_{max}, C_{min}, CL/F, R_{ac}, R_{ss}	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean and geometric CV%
T_{max}	N, median, minimum, maximum

6.1.2. PK concentrations

To assess the single dose and multiple dose PK profiles of talazoparib mono therapy, PK concentrations will be listed, summarized and plotted for subjects in the PK concentration population, where missing and BLQ values will be handled as detailed in Section 5.3.1.

Presentations for talazoparib will include:

- A listing of all concentrations sorted by subject ID, cycle, study day, and nominal time postdose for single dose and multiple dose PK, respectively. The listing of concentrations will include the actual times. Deviations from the nominal time will be also listed.

- A summary of concentrations by nominal postdose time points for single dose and multiple dose PK, respectively, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (CV), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose (based on the summary of concentrations by time postdose) for single dose and multiple dose PK, respectively

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose (based on the summary of concentrations by time postdose) for single dose PK and multiple dose PK, respectively..

- Overlay individual concentration time plots on both linear and semi-log scales against actual time postdose (there will be separate spaghetti plots per scale) for single dose PK and multiple dose PK, respectively.

- Individual concentration time plots by patient on linear and semi-log scales against actual time postdose (there will be separate plots for each patient per scale) for single dose PK and multiple dose PK, respectively.

- Individual and descriptive summary of talazoparib trough concentrations versus study day will also be plotted.

6.2. Secondary Endpoint(s)

6.2.1. Objective response (OR)

The number of patients, with measurable or non-measurable disease at baseline, achieving OR (CR or PR) will be summarized. The OR rate (ORR) will be estimated by dividing the number of patients with OR by the number of patients in the efficacy analysis set. An exact 95% confidence interval calculated using Clopper-Pearson method will be provided for ORR.

Confirmed OR rate based on confirmed CR/PR a minimum of four weeks apart will also be calculated within efficacy analysis set, associated 95% CI from Clopper-Pearson will be provided as well.

In addition, the best overall response for each patient will be summarized

6.2.2. Duration of Response (DOR)

DOR will only be calculated for the subgroup of patients with an objective response. If data permits, DOR will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and the 95% CI for the median calculated using Brookmeyer and Crowley method will be provided. If otherwise only a few responses are observed, the participants with responses and their associated information including the BOR, date of response, date of progression/death/censoring will be listed.

6.3. Other Endpoint(s)

Not applicable.

6.4. Subset Analyses

A subgroup calculation of OR rate would be conducted among participants who are with measurable disease at baseline.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Analyses of baseline data will be based on the Safety Set.

6.5.1.1. Demographic Characteristics

The following demographic and baseline characteristics will be summarized by number and percentage:

- Gender (male, female);
- Age (18-<45; 45- <65; ≥65);
- Race;
- Ethnicity;
- Eastern Cooperative Oncology Group (ECOG) Performance status:

  will be summarized by category (number and percent).

Age (continuous), height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

6.5.1.2. Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's System Organ Class (SOC) and PT from the 'Medical History' eCRF page. Each participant will be counted only once within each PT or SOC. Summaries will be

ordered by primary SOC and PT in descending order of frequency by the experimental treatment arm. Separate summaries will be provided for past and present conditions.

6.5.1.3. Disease Characteristics

The following baseline disease characteristics will be summarized by number and percentage:

- primary diagnosis (coded by MedDRA preferred term. if all participants have the same diagnosis this may be omitted);
- Measurable disease at baseline (yes/no);
- Involved tumor sites at baseline;
- Number of target tumor sites at baseline (1, 2,3, ≥4);
- Number of non-target tumor sites at baseline (1, 2,3, ≥4).

Time since diagnosis (months), defined as (date of first dose – date of diagnosis)/30.4375, will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum).

Involved tumor sites at baseline will be derived from target and non target lesions at baseline. Each participant will be counted once per organ. Similarly, number of sites of disease at baseline will be derived by counting the number of unique organ sites from target and non target lesions at baseline. "Other" will be counted as one organ site.

6.5.1.4. Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer treatment;
- Participants with at least one prior anti-cancer drug therapy;
- Participants with at least one prior anti-cancer radiotherapy;
- Participants with at least one prior anti-cancer surgery.

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants:

- Number of prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / ≥4;

- Type of prior anti-cancer therapy;
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Advanced – Metastatic.

The prior anti-cancer drugs will be coded in the WHO Drug coding dictionary and will be summarized based on the number and percentage of participants by preferred term. A participant will be counted only once within a given preferred term, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency. In case of equal frequency, alphabetical order will be used.

Specific details on surgeries and radiotherapy will be listed.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Disposition

The percentages below will be calculated based on the overall number of participants.

- Number of participants enrolled overall and by site;
- Number of participants who discontinued from the study prior to first dose overall and by the main reason for discontinuation;
- Number and percentage of participants in each of the analysis sets defined in Section 4;
- Number and percentage of participants with study drug ongoing;
- Number and percentage of participants who discontinued study drug overall and by the main reason for discontinuation of study drug;
- Number and percentage of participants who entered follow-up;
- Number and percentage of participants who discontinued follow-up overall and by the main reason for discontinuation.

6.5.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and will be summarized by category (n(%)) for the safety set for treatment arm. Categories will be assigned by the study Clinician.

6.5.3. Study Treatment Exposure

Exposure will be summarized for the safety analysis set.

6.5.3.1. Exposure to talazoparib

The summary of treatment exposure for talazoparib will include the following information (by dose level for safety population):

- Treatment duration (months): For each patient, treatment duration is defined as (date of last dose – date of first dose + 1) / 30.4375. Treatment duration will be summarized both as a continuous measure and a categorical measure (≤ 3 months, 3 to < 6 months, 6 to < 12 months, ≥ 12 months).

- Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by acutal number of days on treatment, where cumulative dose is the sum of the actual dose levels that patient received.

- Dose intensity (DI, mg /week)

- Relative dose intensity (RDI, %).

The dose intensity (DI, mg /week) of talazoparib during the study will be defined as follows:

- Overall DI (mg /week) = [overall cumulative dose (mg)] / [treatment duration in weeks].

The RDI of talazoparib will be defined as the ratio of the DI and planned dose intensity and expressed in percentage as follows:

- Overall RDI (%) = 100 × [overall DI] / [planned dose intensity per week, i.e., 7 mg/week].

6.5.3.2. Dose Reductions, Interruptions

A dose reduction is defined as a non-zero dose that is less than the prior dose.

The number and percentage of participants with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3) will be summarized for safety set.

Reasons for dose reductions will also be summarized. Participants can contribute to more than one reason if multiple dose reductions occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of participants in safety analysis set.

An interruption is defined a 0 mg dose administered on one or more days for continuously dose medications, in this case talazoparib. (Note: A dose interruption is not considered a dose reduction). The number and percentage of participants with dose interruptions and the corresponding reasons will be summarized for safety set. Participants can contribute to more than one reason if multiple dose interruptions occurred for different reasons, but will only be

counted once per reason. Percentages will be calculated based on the total number of participants in safety analysis set.

6.5.4. Concomitant Medications and Nondrug Treatments

The following analyses will be based on the safety analysis set.

Concomitant medications are medications, other than study medications, which started prior to first dose date of study treatment and continued on on-treatment period as well as those started during the on-treatment period.

Summary of concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of concomitant medications will be created with the relevant information collected on the corresponding eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the safety Set.

Anti-cancer treatment will be provided in a data listing with data retrieved from related eCRF pages.

6.6. Safety Summaries and Analyses

Summaries of AEs and other safety parameters will be based on the safety analysis set.

6.6.1. Adverse Events

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.5.1. AEs not considered treatment emergent will be flagged in data listings.

A high level summary of adverse events will include the number and percent of participants with:

- Any Adverse Event;
- Serious AE;
- Adverse Events with CTCAE Grade 3-4;
- Grade 5 events;
- AEs leading to dose interruptions of talazoparib;
- AEs leading to dose reductions of talazoparib;
- AEs leading to discontinuation of talazoparib.

Additionally, the number of events reported for each of the categories above will be provided. Each unique adverse event at the PT level for a participant is included in the count.

Seriousness, toxicity grade, action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries, SOC and PT in decreasing frequency based on the frequencies observed will be provided for:

- Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
- Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related);
- Serious Treatment Emergent Events by Maximum Toxicity (All Causality);
- Serious Treatment Emergent Events by Maximum Toxicity (Treatment Related);

An event will be considered treatment related if the investigator considered the event related to study drug.

The following summaries will be provided by PT only (i.e. summaries will not include SOC) in decreasing frequency based on the frequencies observed in the treatment arm for:

- Treatment Emergent Events (All Causality) by Preferred Term and Maximum Toxicity Grade;
- Treatment Emergent Grade 3-5 Events (All Causality) by Preferred Term and Maximum Toxicity Grade;
- Treatment Emergent Adverse Events Leading to Dose Interruptions of Study Drug talazoparib (All Causality);

- Treatment Emergent Adverse Events Leading to Dose Reductions of Study Drug talazoparib (All Causality);
- Treatment Emergent Adverse Events Leading to Permanent Withdraw of Study Drug talazoparib (All Causality);
- Serious Treatment Emergent Events (All Causality).

Each participant will be counted only once within each SOC and PT.

In case a participant has events with missing and non missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a participant and the grade is missing.

6.6.1.1. Adverse Events of Special Interest

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), and second primary malignancies are the AEs of special interest in this study.

Complete blood counts should be obtained at baseline and monitored for signs of hematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.

Any diagnosis of MDS or AML for any participant enrolled will be reported as an SAE.

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died and who died within 28 days after last dose of study treatment as well as the primary reason for death, will be tabulated based on information from the 'Notice of Death' CRFs.

The frequency (number and percentage) of participants in the safety analysis set who died within 42 days of first dose of study treatment will also be provided.

The frequency (number and percentage) of participants in the safety analysis set who died due to TEAE will be provided as well.

Date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first / last administration, the latest dose).

6.6.3. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying toxicity grades and for all summaries.

A shift summary of baseline grade by maximum post-baseline grade will be presented.

Quantitative data will be summarized using simple descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (i.e. unscheduled assessments will be excluded). Summary will only include data from central laboratories. The total number of participants for change from baseline will include all participants in the treatment arm who have both a baseline and a value at the nominal visit.

As described in section 3.4, baseline will defined as the last assessment performed on or prior to date of the first dose of study treatment. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade. Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Results collected as strict inequalities (e.g., >10, <10) will be converted to numeric values by adding or subtracting a factor of <0.001>, for example '<10' will be converted to 9.999. Expressions of the form" ≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities, but will not be included in calculations of summary statistics.

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 4.03 grade. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (e.g. hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of participants corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (e.g. CTCAE grading criteria for Creatinine Increased – a value can fall into one range based on comparison to ULN and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically by in the CTCAE guidance. However, programmatically this is used as a category to represent those participants who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Abnormalities will be described using the worst grade overall. Worst case overall will be determined using local laboratory results from scheduled and unscheduled visits. Several

laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum post-baseline grade for a given participant and CTCAE term will be the maximum across all possible laboratory tests.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the following categories overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (e.g., > Upper Limit of Normal (ULN) and < Lower Limit of Normal (LLN)), then both abnormalities are counted. Summaries at schedule timepoints will consider only central laboratory data; however summaries overall will consider both central and local laboratory data.

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over the ULN will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized:

- ALT ≥ 3×ULN, ALT ≥ 5xULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN;
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN;
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN;
- TBILI ≥ 2×ULN;
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN;
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN;
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN;
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN;
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing.

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment arms, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN.

- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

6.6.4. Vital Signs

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The number and perentage of participants with the following potentially clinically significant vital sign changes at any point while on treatment will be presented. The definitions of potentially clinically significant abnormalities are shown as:

Parameter	Criteria for potentially clinically significant abnormalities
Systolic blood pressur	Absolute result > 180 mmHg and increase from baseline ≥ 40 mmHg
	Absolute result < 90 mmHg and decrease from baseline >30 mmHg
Diastolic blood pressure	Absolute result > 110mm Hg and increase from baseline ≥ 30 mmHg
	Absolute result < 50 mmHg and decrease from baseline > 20 mmHg
	≥ 20 mmHG increase from baseline
Pulse rate	Absolute result > 120 bpm and increase from baseline > 30 bpm

	Absolute result < 50 bpm and decrease from baseline > 20 bpm
Weight	>10% decrease from baseline

All assessments, including unscheduled assessments will be considered. A participant can be included in multiple categories if different criteria are met at different timepoints.

6.6.5. Electrocardiograms

Triplicate ECGs is required for baseline assessment, and a single ECG is required at screening and each scheduled ECG evaluation on treatment. A mean score is calculated for any replicate measurements having the same nominal visit. The mean measurement is reported.

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate.

Fridericia's correction (QTcF) will be programmatically derived using the following formula:

$$QTcF(msec) = QT(msec)/\sqrt[3]{RR(sec)}$$

and Bazett's correction (QTcB) will be programmatically derived using the following formula:

$$QTcB(msec) = \frac{QT(msec)}{\sqrt{RR}(sec)},$$

where RR represents the RR interval of the ECG, in seconds.

Use an ECG machine that automatically calculates the heart rate and measures PR, RR, QT intervals, QTc, QTcF (if available) and QRS complex. If HR are not collected,Baseline heart rate (HR) will be derived from RR measured in seconds as 60/RR if RR is collected, and QT/QTc interval assessments will be derived from the visit where both HR and QT are not missing. QTcF (Fridericia's correction) and QTcB (Bazett's correction) will be derived based on RR and QT as aforementioned.

Data will be summarized using QTcB and QTcF.

Additionally QTcB and QTcF will be summarized by maximum on-treatment values using the following categories

- ≤ 450 msec;
- > 450 msec but ≤ 480 msec;
- > 480 msec but ≤ 500 msec;
- > 500 msec.

List participants with maximum on-treatment QTc values ≥500 msec including the time that value is observed.

Unscheduled assessments will be utilized in addition to planned assessments.

Shift tables will be provided for baseline value versus worst on-treatment value.

Additionally maximum increases from baseline (including scheduled and unscheduled assessments) will be summarized based on the following categories*:*

- Change > 60 msec;
- Change >30 msec but ≤ 60 msec;
- Change ≤ 30 msec.

6.6.6. Performance Status

The ECOG shift from baseline to the highest score during the on-treatment period will be summarized. The paticipants with baseline ECOG=0 or 1 but shift to ECOG 2 or higher post treatment will also be presented in a data listing.

6.6.7. Physical Examination

Number and percentage of participants with abnormal findings in physical examination will be summarized by body system.

6.6.8. Medication errors

Medication errors for study treatment include lack of dose reduction, continuation of treatment after discontinuation criteria met, and incorrect dosage taken. Medication errors will be listed.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study.

8. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse events of special interest
ALP	Alkaline Phosphatase
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-Time Curve
AUC_{inf}	area under concentration-time curve from time 0 to infinity
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of C_{last}
$AUC_{sd,inf}$	Area under the plasma concentration versus time curve from time zero to infinity at steady state
$AUC_{sd,\tau}$	Area under the plasma concentration versus time curve within a dosing interval of τ (=24 hr) at steady state
AUC_{τ}	Area under the plasma concentration versus time curve from time zero to the time τ
BLQ	below the level of quantification
BMI	Body mass index
C1D1	Cycle 1 Day 1
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
C_{min}	Minimum Plasma Concentration
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DI	Dose intensity
DOR	Duration of response
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EOT	End of treatment
HR	heart rate
IOTA	Investigator Overall Tumor Assessment
k_{el}	Constant of elimination rate
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
mCRPC	metastatic castration resistant prostate cancer

MedDRA	Medical Dictionary for Regulatory Activities
MD	multiple dose
MDS	Myelodysplastic Syndrome
N/A	not applicable
NC	Not calculated
NCI	National Cancer Institute
ND	Not done
NMPA	National Medical Products Administration
NS	No sample
OR	Objective response
ORR	objective response rate
OTR	outside toxicity reference
PD	disease progression
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QD	Once Daily
OR	objective response
QTc	corrected QT
QTcB	Bazett's correction
QTcF	corrected QT (Fridericia method)
R_{ac}	observed accumulation ratio
RDI	Relative dose intensity
R_{ss}	steady-state accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	single dose
SD	stable disease
SD	Standard deviation
SOC	system organ class
$t_{1/2}$	Terminal Half-Life
TBili	total bilirubin
TEAEs	treatment-emergent adverse events
T_{max}	Time to Reach Maximum Plasma Concentration
ULN	upper limit of normal
V_z/F	Apparent volume of distribution
WHO	World health organization