Integrated Analysis Plan

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Approval Page

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Phase I study to evaluate the mass balance, pharmacokinetics (PK), metabolism and excretion of berzosertib (intravenous) containing microtracer [^{14}C]berzosertib in participants with advanced solid tumors

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

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2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
BMI	Body Mass Index
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DI	Dose Intensity
ECG	Electrocardiogram
ECOG PS	Eastern Co-operative of Oncology Group (Performance Status)
EDS	Early Development Services
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FU	Follow-up
GBS	Global Biostatistics
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IRR	Infusion Related Reactions
ISR	Infusion Site Reactions
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NA	Not Applicable

NC	Not Calculated
Nd	Not done
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PRO	Patient-Reported Outcomes
PT	Preferred Term
PK	Pharmacokinetics
PR	Partial Response
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	06.12.2022	PPD	This is the first version of the IAP

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the analysis of data collected for CSP MS201923_0008. Results of the analyses described in this IAP will be included in the CSR. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9 (Statistical considerations) of the CSP and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the CSP and protocol amendments.

The wording used in this IAP is chosen to best match the respective wording in the CSP template, the CSR template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term “participant” will be used instead of “subject” or “patient”. However, in tables and listings the term “subject” will be used to match CDISC requirements, except for in-text tables where “participant” will be used to match the CSR and CSP templates. Similarly, the term “study intervention” will be used in this document instead of “treatment” to match CSP and CSR templates, however, tables and listings will use “treatment” for brevity reasons. Exceptions from this rule are commonly used terms like “on-treatment”, “treatment-emergent”, “treatment policy”, “subject-years”, “by-subject”, or names of CRF pages like “Treatment Termination” page.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Period 1		
Primary		
To determine the rates and routes of excretion and mass balance of berzosertib following single intravenous administration of 210 mg/m^2 of [^{14}C] berzosertib to participants with advanced solid tumors.	• Percent urinary recovery (fe_{urine}) of total radioactivity over the entire period of collection. • Percent fecal recovery (fe_{feces}) of total radioactivity over the entire period of collection. • Percent total recovery in urine and feces (fe_{total}) combined of total radioactivity over the entire period of collection.	16
To characterize the PK of berzosertib in plasma and urine; and of drug-related material (total radioactivity) in plasma and whole blood to participants with advanced solid tumors.	• Plasma C_{max} of berzosertib • Plasma $AUC_{0\text{-}tlast}$ of berzosertib • Plasma $AUC_{0\text{-}\infty}$ of berzosertib • Plasma $t_{1/2}$ of berzosertib • Plasma CL of berzosertib • Plasma V_z of berzosertib • Plasma V_{ss} of berzosertib • Plasma C_{max} of total radioactivity • Plasma $AUC_{0\text{-}tlast}$ of total radioactivity • Plasma $AUC_{0\text{-}\infty}$ of total radioactivity • Plasma $t_{1/2}$ of total radioactivity • Blood C_{max} of total radioactivity • Blood $AUC_{0\text{-}tlast}$ of total radioactivity • Blood $AUC_{0\text{-}\infty}$ of total radioactivity • Cumulative amount of berzosertib excreted in urine ($Ae_{0\text{-}\infty}$ urine) • Fraction of administered berzosertib that is excreted unchanged in urine: fe(%) = $Ae_{0\text{-}\infty}$urine/Dose • Renal clearance (CLR)	16
Secondary		
To evaluate the safety and tolerability of berzosertib in participants with advanced solid tumors.	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs)	15

Objectives	Endpoints (Outcome Measures)	IAP section
	• Occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings.	
CCI		
Period 2		
Secondary		
To evaluate the safety and tolerability of berzosertib + topotecan in participants with advanced solid tumors.	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) • Occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings.	15
CCI		

6 Overview of Planned Analyses

All final, planned analyses identified in the CSP and in this IAP will be performed only after the last subject has completed the last visit, i.e., end of trial visit/early termination visit with all trial data in-house, all data queries resolved, and the database locked for EDC (ICON terminology) or

integrated lock (Merck terminology). There would only be one integrated final analysis at the end of the study.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Study Protocol

- For the objective of identifying and quantifying berzosertib and its metabolites in excreta (urine and feces) and plasma in order to elucidate key biotransformation pathways and clearance mechanisms of berzosertib in participants with advanced solid tumors, % of drug-related material will serve as an endpoint (outcome measure) instead of Metabolite AUC in plasma.

The Following objectives will not be pursued although planned in the CSP:

CCI

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

For purposes of analysis, the following populations are defined:

Screening	The screening analysis set (SCR) will include all participants who provided signed informed consent, regardless of study intervention status in the trial. This set will be used for subject disposition.
Safety	The Safety Analysis Set (SAF) will include all participants who have received any dose of any study intervention. Participants will be analyzed according to the actual study intervention they receive.
Pharmacokinetic	The Pharmacokinetic (PK) Analysis Set is a subset of the SAF will consist of all participants who receive at least one dose of IMP, in Period 1 and provide at least one measurable post-dose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. All PK analyses will be based on this analysis set. A participant who has any missing urine or feces samples that impact assessment of mass balance or does not have sufficient PK sampling to derive the primary PK parameters, is not considered evaluable. Participants will be analyzed according to the actual study intervention they received. If a subject takes any medication likely to affect the PK of Berzosertib. Subject will be included in PK Analysis Set , but may be excluded from summary statistics.

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set		
Analyses	**Screening**	**Safety Set**	**PK**
Disposition summaries	✓	✓	✓*
Demographic summaries		✓	✓*
Compliance and Exposure		✓	
Safety Assessments		✓	
PK Concentrations		✓	
PK Parameters			✓
Safety and Tolerability		✓	
Efficacy Analyses		✓	

*only to be created if there is a difference between Safety Analysis Set (SAF) and PK

8.2 Subgroup Definition and Parameterization

Not applicable.

9 General Specifications for Data Analyses

Statistical analyses will be performed using the computer program package SAS® System for Windows™ (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this clinical study will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by study intervention and/or scheduled time point, as appropriate.

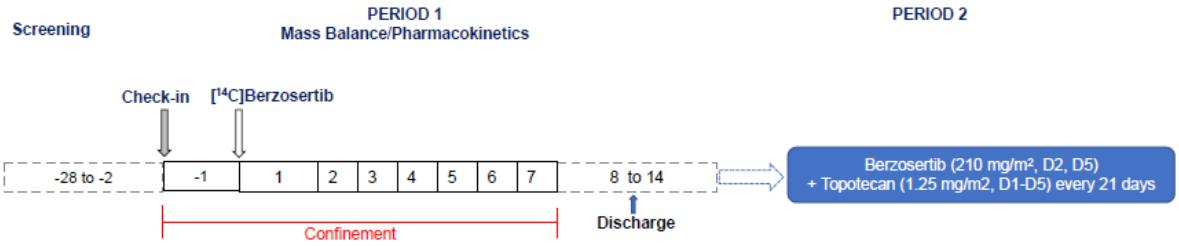
For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (i.e., number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, minimum, and maximum) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise. Mean, Median, Min, Max will have the same precision as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean. For subject disposition and demographic tables, the denominator will be the number of subjects in the analysis set. Counts of missing observations will be included as a separate category.

Repeated laboratory assessments will be flagged as repeats in the subject data listings and not included in summary tables statistics (unless the scheduled measurement was considered unreliable, e.g., due to technical reasons, and needed to be replaced by an unscheduled repeat measurement).

The following study intervention label will be used in the tables, figures and listings (TLFs):

- Period 1: [^{14}C]Berzosertib
- Period 2: Berzosertib + Topotecan

The following Figure depicts the actual Treatment Schema for Period 1 and 2:



9.1 Definition of Baseline and Change from Baseline

If not otherwise specified, “baseline” refers to the last scheduled measurement before administration of the first study intervention. However, if a participant is missing the baseline

collection, the previous non-missing evaluation predose could become the baseline value. If no baseline or previous to baseline evaluations exist, then the baseline value will be treated as missing. The last observation can be an unscheduled / repeated measurement. Unscheduled assessments post treatment start will not be used for analysis by timepoint, but are to be considered for analysis like identifying maximum on- treatment value.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.2 Study Day / Study Intervention Day

Day 1 is the day of start of study intervention, the day before is Day -1 (no Day 0 is defined). Study day / Study intervention day is defined relative to Day 1.

9.3 Definition of Duration and "Time Since" Variables

Durations in days will be calculated by the difference of start and stop date + 1 (if not otherwise specified).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event

9.4 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.5 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study intervention day in period 1 to the last administration day of study intervention + 30 days, or death, whichever occurs first. The on-treatment period consists of two distinct periods:

- Period 1 is defined as the time from the first dose of study intervention day in period 1 to until start of the subsequent administration of any study drug intervention in Period 2 or 30 days after period 1 dosing if there is no further dosing in period 2.

- Period 2 is defined as time from end of Period 1 (administration of study intervention in Period 2) to the last administration day of study intervention + 30.

The attribution of AEs during Period 1 and 2 and overall is added in Section 15.

9.6 Exposure time

Analysis will be performed for the total on-treatment period only. Duration will be calculated differently based on the dosing days and frequency as follows.

Participants will receive 2 infusions of Berzosertib on Days 2 and 5 in each 21-day cycle. Hence, duration of Berzosertib therapy is calculated as follows:

$$Duration\ of\ Berzosertib\ (weeks) = \frac{(date\ of\ last\ dose - date\ of\ first\ dose + 18)}{7}$$

Participants will receive 5 infusions of Topotecan on Days 1 through Day 5 in each 21-day cycle. Hence, duration of Topotecan therapy is calculated as follows:

$$Duration\ of\ Topotecan\ (weeks) = \frac{(date\ of\ last\ dose - date\ of\ first\ dose + 17)}{7}$$

9.7 Imputation of Missing Data

In this Phase I PK study, missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

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

Missing statistics, e.g. when they cannot be calculated, should be presented as "nc" (not calculated). For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nc".

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing).

- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

Incomplete dates for disease history (e.g. initial diagnosis date) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study intervention, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is the same as the year of the first study intervention, the month and day will be imputed as January 1st.

Incomplete prior/concomitant medication and concomitant procedures start and stop dates will be imputed as in Table 1.

For the derivation of previous and concomitant medications and Concomitant Procedures following rules will be applied:

Previous Medication:

- Start date ≤ Start of study medication OR
- Start date = Missing

Concomitant Medication and Concomitant Procedures:

- End date ≥ Start of study medication AND (Start date ≤ End of study medication +30 days OR Start date=Missing) OR
- End date = Missing AND (Start date ≤ End of study medication +30 days OR Start date = Missing)

The derivation is based on the following principles

- Imputation leads to maximum reasonable duration
- Worst case: If medication is administered the same day as start of study medication, medication is classified as concomitant and previous

Table 1 Imputation rules for missing/incomplete start/end dates of medication/ procedures

	Start Date	End Date
Day missing only	Day = 1	Day = Last day of month
Month missing	Day = 1 Month = Jan	Day = 31 Month = Dec
Year missing	Date = Missing No imputation	
All	if imputed date > date of death: imputation by date of death	

9.8 Age at Time of an Event

If Age at the Time of an Event is derived, the following algorithm will be used for the derivation

- Year of Event minus Year of Birth

10 Study Participants

10.1 Disposition of Participants and Discontinuations

This following will be presented in a summary table, by period:

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of screened participants who discontinued from the trial prior to dosing overall and grouped by the main reason for discontinuation:
  - Subject did not meet all eligibility criteria (including which criterion)
  - Withdrawal by subject
  - Progressive Disease
  - Adverse Events
  - Lost to follow-up
  - Other
- Number and percentage of treated subjects
- Number and percentage of Subjects that received no treatment (per end of treatment status)
- Number and percentage of Subjects Treatment ongoing (per end of treatment status)
- Number and percentage of Subjects completed (per end of treatment and end of study status)

- Number and percentage of treated participants who discontinued the study or treatment, with the primary reason of discontinuation by end of treatment and end of study status:
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Withdrawal by subject
    - Other [(COVID-19 related and COVID-19-non-related)]

A listing of discontinued participants will be provided along with a listing for eligibility determination - in-/exclusion criteria.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing in the relevant period. A distinction will be made between important protocol deviations due to COVID-19 versus not due to COVID-19. The respective important protocol deviations will be flagged accordingly.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a subject from an analysis set will be listed based on the safety set.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing based on the safety analysis set.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be given for both the safety and the PK set, if different.

Demographic characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit case report form (CRF) pages.

Demographic characteristics:

- Sex: male

- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, White + Black or African American, White + Asian, Asian + Black or African American, Other
- Ethnic origin: Hispanic or Latino, Not Hispanic or Latino
- Age (years)
- Age categories {< 65 years, ≥ 65 years (65-74, 75-84, ≥85 years)}

11.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), using Version 25.0 or later, and listed.

11.3 Other Baseline Characteristics

Other baseline characteristics will be listed by participants and only height, weight and BMI summarized using the following information from the Screening/Baseline Visit CRF pages.

Other baseline characteristics:
- Height (cm) at Baseline
- Weight (kg) at Baseline
- Body Mass Index (BMI) (kg/m²) at Baselines
- BSA (Body Surface Area) (m²)
- Medical History
- Disease History
- Serum and urine human chorionic gonadotropin (β-hCG) pregnancy test,
- Follicle stimulating hormone (FSH) and estradiol test

BMI will be re-derived (i.e., not taken directly from the database) according to the following formula:

BMI (kg/m²) = weight (kg) / (height (m) * height (m))

BSA will be derived according to the following formula:

$$\text{BSA } [m^2] = \sqrt{\frac{height[cm] \times weight[kg]}{3600}}$$

11.4 Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details" CRF pages

The listings of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding CRF pages.

- Listing of prior anti-cancer drug therapies
- Listing of prior anti-cancer radiotherapy
- Listing of prior anti-cancer surgeries

12 Previous or Concomitant Therapies/Procedures

Medications will be presented for the Safety Analysis Set.

Previous medications are defined as any medication discontinued prior to the administration of study intervention. Concomitant medications are defined as any medication taken during the course of the study, with a starting date greater than or equal to the administration of the first study intervention, or with a starting date prior to the administration of the first study intervention and ongoing at the time of the administration of study intervention.

The World Health Organization Drug dictionary (WHO-DD), latest version, will be used for coding of prior and concomitant medications and they will be described using Preferred Term (PT) as applicable.

Previous and concomitant medications will be listed. Concomitant procedures, if any, will also be listed.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the SAF by treatment group as needed.

A listing of date and time of each drug administration sorted by participant and date of drug administration including information on total absolute planned dose, percent of total planned volume given and if the infusion was fully administered. In addition to this a listing will be

provided for exposure duration, number of infusions, cumulative actual treatment dose and actual dose intensity per Subject.

The summary of study intervention exposure (dosing) of each drug administration will be presented including the following information:

- Exposure duration (weeks): overall distribution and by categories of ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 – 18 weeks, >18 – 24 weeks, >24 – 30, >30 – 36, and every 9 weeks after 36 weeks

- Total number of infusions received: For each study intervention, total number of infusions is calculated as the sum of the actual number of infusions that a participant received across cycles, regardless of infusion delays, interruptions, or any other types of deviations from the protocol required schedules. An infusion is regarded to be administered if either the actual dose received is > 0 or the duration of the infusion is > 0.

- Cumulative Actual Treatment dose (mg/m^2): Cumulative dose (mg/m^2) will be presented for each Drug as the sum of the BSA-adjusted actual dose amount that a participant received. This will be calculated for each 21 day period/cycle, e.g. Day 1-21, 22-42, 43-64, etc. and also over the entire treatment period.

  BSA-adjusted actual dose amount (mg/m^2) = actual dose amount (mg) / BSA (m^2)

  The actual dose amount (mg) is taken at each dosing day from "Actual dose" on the relevant CRF pages at each dosing day. BSA will be derived as mentioned in Section 11.3 using the most recent height and weight entries. In case the BSA is missing the latest BSA available will be used for calculation following the Last Observation Carried Forward principle. If BSA cannot be derived due to missing weight and/or height data, data from the last available visit will be used instead.

- Actual Dose Intensity (DI): The DI per week is calculated for each study intervention as follows:

$$Actual\ DI\ (mg/m^2/week) = \frac{total\ cumulative\ dose\ (mg/m^2)}{treatment\ duration\ (weeks)}$$

- Relative Dose Intensity (RDI): The RDI (%) is calculated for each study intervention by dividing the DI by the planned dose intensity per week of the appropriate study intervention. Planned dose intensity per week will be derived by dividing planned dose (mg/m^2) by duration of therapy (weeks).

14 Efficacy Analyses (Period 2 only)

The following analyses on efficacy estimands will be performed based on the SAF except when otherwise stated.

14.1 Tertiary/ ExploratoryObjective: Objective Response

14.1.1 Tertiary/ Exploratory Estimand

Endpoint

Derivation of BoR and a corresponding listing according to RECIST 1.1, Eisenhauer EA, et. al., as assessed by the Investigator.

OR is defined as a confirmed BOR of complete response (CR) or partial response (PR). Confirmation of the response according to RECIST 1.1 is required no sooner than 4 weeks after the initial documentation of CR or PR. Patients with BOR of NE are considered as non-responders for OR.

Confirmed BOR is derived as follows:

- CR = at least two determinations of CR at least 4 weeks apart (with no PD in between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR), with no PD in between
- SD (applicable only to participant with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after start date (and not qualifying for CR or PR), i.e. Study Day 42 or later.
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks (42 days) after start date (and not qualifying for CR or PR).
- PD = PD ≤ 12 weeks (84 days) after start date (and not qualifying for CR, PR, non-CR/non-PD or SD). The condition PD in or out of the respective timeframe addresses a missing data situation in view of determining best overall response as PD or NE, respectively. Clinical deterioration will not be considered as documented disease progression.
- Not Evaluable (NE): all other cases.

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met.

The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

Population

Patients with advanced solid tumors.

Treatment

Berzosertib + topotecan

Intercurrent Event Strategy

- Discontinuation of treatment: Treatment-policy strategy, i.e., regardless of the intercurrent event
- Start of subsequent anticancer treatment: while not treated with subsequent anticancer therapy strategy; i.e., ignoring tumor assessments after the intercurrent event. If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.
- Progression according to RECIST 1.1: While not progressed strategy, i.e., considering assessments up to the intercurrent event

Population Level Summary

Overall response and BoR will be derived and provided via listings. Additionally, no summary tables are planned..

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

All safety analyses will be performed for the Safety Analysis Set and will be presented by study intervention (period). An additional column for all active doses of study intervention may be presented when specified.

Safety analyses will be done on the Safety Analysis Set and according to the as-treated principle.

15.1 Adverse Events

All AEs recorded during the course of the study will be coded with the MedDRA, version 25.0 or later and assigned to a System Organ Class (SOC) and a Preferred Term (PT).

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the first administration of study intervention. Any AE occurring before the administration of study intervention on Day 1 and resolved before administration of study intervention or not worsening after administration of study intervention will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as "pre-treatment" AEs. An AE occurring after administration of study intervention will be counted towards the last treatment received before the onset, even if the event is not resolved at the beginning of the following intervention period. An AE that worsens during a later intervention period will be counted towards both treatments.

TEAEs will be presented by respective Periods and Overall. TEAE flags will be created in line with the attribution of TEAEs as follows:

Period 1: Any AE that starts in Period 1, i.e. any AE with onset after start of first drug administration and before the start of further drug administration in Period 2

Period 2: Any new AE that was not existent in Period 1 and started in Period 2. Any AE that starts in Period 1 and worsens in Period 2.

Overall: An AE will be counted only once in the Overall attribution even if it is existent in Period 1 and worsens in Period 2.

In case AE-related dates are partial, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent as described in Section 9.

All analyses described in this section will be based on TEAEs if not otherwise specified.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, as well as the number of events, by study intervention (period), primary SOC sorted alphabetically and PTs within each SOC in decreasing frequency (based on the total column).

15.1.1 All Adverse Events

Treatment-emergent AEs and participants experiencing TEAEs will be summarized by study intervention or period and overall in the following tables. Additionally, for Period 2 these tables will also provide relevant information on individual drug Topotecan or Berzosertib related events:

- Overall Overview table, showing the number and percentage of participants with

  Any TEAE

  Any Study Drug related TEAE

  Any Berzosertib related TEAE

  Any Topotecan related TEAE

  Any serious TEAE

  Any Study Drug related serious TEAE

  Any Berzosertib related serious TEAE

  Any Topotecan related serious TEAE

  Any Grade >=3 (severe) TEAE

  Any Grade >=4 (life-threatening) TEAE

  Any Study Drug related Grade >=3 (severe) TEAE

  Any Berzosertib related Grade >=3 (severe) TEAE

  Any Topotecan related Grade >=3 (severe) TEAE

  Any Study Drug related Grade >=4 (life-threatening) TEAE

  Any Berzosertib related Grade >=4 (life-threatening) TEAE

  Any Topotecan related Grade >=4 (life-threatening) TEAE

  Any TEAE leading to Study discontinuation

  Any Related TEAE leading to Study discontinuation

  Any Berzosertib Related TEAE leading to Study discontinuation

  Any Topotecan Related TEAE leading to Study discontinuation

  Any TEAE leading to death

  Any Study Drug related TEAE leading to death

  Any Berzosertib related TEAE leading to death

Any Topotecan related TEAE leading to death

Any TEAE leading to temporary discontinuation of at least one study drug

Any TEAE leading to temporary discontinuation of Berzosertib

Any TEAE leading to temporary discontinuation of Topotecan

Any TEAE leading to permanent discontinuation of at least one study drug

Any TEAE leading to permanent discontinuation of Berzosertib

Any TEAE leading to permanent discontinuation of Topotecan

Any TEAE leading to dose reduction of at least one study drug

Any TEAE leading to dose reduction of Berzosertib

Any TEAE leading to dose reduction of Topotecan

- .The number and percentage of participants with at least one TEAE by SOC and PT by Periods and Overall
- The number and percentage of participants with at least one TEAE by Trial Drug Relationship, SOC and PT by Periods and Overall
- The number and percentage of participants with at least one TEAE by Trial Drug Relationship, SOC and PT by Drugs for Period 2
- The number and percentage of participants with at least one TEAE by Worst Severity Grade, SOC and PT by Periods and Overall
- The number and percentage of participants with at least one related TEAE by Worst Severity Grade, SOC and PT by Periods and Overall
- The number and percentage of participants with at least one related TEAE by Worst Severity Grade, SOC and PT by Drugs for Period 2

Additionally, listings will be provided for TEAEs, pre- treatment AEs and TEAEs Leading to Trial Treatment Discontinuation

Within each level of TEAE term, if a participant experiences more than one occurrence, the participant will only be counted once for that TEAE.

If an AE is reported for a given participant more than once during treatment, the worst severity and the worst relationship to study intervention will be tabulated.

Adverse events related to any study intervention are those events with relationship missing, unknown or related.

In case a participant had events with missing and non-missing severity, the maximum non-missing severity will be displayed.

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

A listing of TEAEs leading to permanent discontinuation of a trial treatment will be provided.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Listing of deaths, if any, will be provided displaying date and cause of death (including TEAE leading to death and relatedness to trial treatment, when applicable), and date and time of treatment administration.

15.2.2 Serious Adverse Events

A listing of SAEs, if any, will be provided.

15.2.3 Other Significant Adverse Events

For this study, no Adverse Events of Special Interest (AESI(s)) have been identified other than Infusion Related Reactions (IRR) and Infusion site reactions (ISR). IRRs are identified based on a list of MedDRA PTs, see Appendix 2 in Section 18.2 and divided into reactions versus signs and symptoms.

Reactions of IRR: should be considered when onset is during berzosertib and/or topotecan infusion or within 24 hours of infusion and resolution on the same day or the day after onset for any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.

Signs and symptoms of IRRs and hypersensitivity/allergic reactions: should be considered when onset is during berzosertib and/or topotecan infusion or within 24 hours of infusion and resolution on the same day or the day after onset.

The listing of all IRRs will be provided with the relevant information.

Infusion site reactions (ISR) are considered identified risks (non-important) and are likely associated with berzosertib treatment if the infusion site reaction develops during infusion or within 24 hours of berzosertib administration (with resolution on the same day or the day after onset).

ISR have been reported using a variety of terms to describe the same biologic event, including catheter site pain, catheter site pruritus, catheter site rash, catheter site-related reaction, infusion site discomfort, infusion site erythema, infusion site extravasation, infusion site pruritus, infusion site rash, infusion site reaction, injection site rash, and injection site reaction. See Appendix 17.2 for the detailed MedDRA PTs.

The same listings described above for IRR will be provided for ISR.

15.3 Clinical Laboratory Evaluation

Listings and summary statistics at each assessment time will be presented using the Système International (SI) units. Normal ranges will be provided by the central laboratory, and out of range flags will be calculated based on the normal ranges. Laboratory data not transferred from the central laboratory in SI units will be converted to SI units before processing. Both original units and SI units will be provided in the SDTM domain.

Continuous clinical laboratory data for hematology and clinical chemistry will be summarized by study intervention and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation.

Listings of all clinical laboratory data for each participant will be provided, with values outside the normal ranges indicated. Listings of abnormal test results (low and high) will be provided.

15.4 Vital Signs

Vital signs data will be summarized by study intervention and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of vital signs data will be provided.

Vital signs assessments will include:

- Blood Pressure including position (Standing, Supine, Sitting, Semi-recumbent):
    - Systolic Blood Pressure

  - Diastolic Blood Pressure
- Supine pulse rate
- Respiratory rate
- Tympanic or body temperature
- Weight (at Screening only)
- Height (at Screening only)

15.5 Other Safety or Tolerability Evaluations

ECG data will be summarized by study intervention and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of ECG data and of clinically significant ECG findings for individual participant will be provided.

The time intervals (PR, QRS, RR, QT and corrected QT intervals [based on Fridericia's formula, QTcF]) will be summarized descriptively by study intervention.

The Fridericia's Correction (QTcF) is derived as follows:

Fridericia's Correction (QTcF) $QTc_f = \frac{\mathrm{QT}}{\sqrt[3]{RR}}$

where: RR = RR-interval measured in seconds.

All ECG measurements will be listed, with abnormalities indicated. Investigator reported interpretation results will be listed, in addition to a listing for ECOG.

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by ICON plc EDS.

All statistical analyses and descriptive summaries of PK data will be performed on the PK analysis set (PKAS).

Accelerator mass spectrometry (AMS) analysis is used to determine total radioactivity (TR) and perform metabolite profiling. Depending on the excretion profile of [^{14}C]berzosertib, traditional radioactivity detection methods such as liquid scintillation counting will also be explored for recovery of TR and mass balance determination.

16.1.1 Descriptive Statistics of PK Concentration Data

16.1.1.1 Plasma and Whole Blood

PK concentrations will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics will only be calculated for n>2 in which a measurement of BLQ represents a valid measurement and will be taken as zero for summary statistics of PK concentration data. In case n ≤2, individual data will be presented (min, max) in summary tables.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. PK concentrations will be carried over with full precision as provided in the source data without any rounding applied to CDISC SDTM PC and ADaM PC domains

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

n	: 0 decimal place
Mean, Min, Median, Max, SD	: 3 significant digits
CV%	: 1 decimal place

16.1.1.2 Free fraction (% unbound) of berzosertib

Free fraction (%unbound) of berzosertib in plasma may be summarized by time points and pool of time points as permitted by the data.

16.1.1.3 Urine and Feces

Individual berzosertib (urine) and total radioactivity (urine and feces) excretion data (concentrations, volumes (urine), weights (feces)) will be listed per collection interval. Berzosertib and total radioactivity (cumulative) amount, % of dose and excretion rate data per collection interval will be tabulated together with summary statistics. Summary statistics (number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max)) will be provided by analyte and collection interval. In addition, for the metabolites from the pooled metabolite profiling sample the percentage of the dose (%) will be calculated.

16.1.1.4 Vomitus

In case vomitus is collected, total radioactivity will be assayed and results listed.

16.1.2 Descriptive Statistics of PK Parameter Data

16.1.2.1 Plasma and Whole Blood

PK parameter data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For PK parameters related to time (e.g. t_{max}, t_{lag}, t_{last}), only n, Min, Median, and Max may be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2. In case n ≤2, individual data will be presented (min, max) in summary tables.

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. Descriptive statistics of PK parameter data will be calculated using full precision and rounded for reporting purposes only.

PK parameters will be provided with full precision, without any rounding applied to CDISC SDTM PP and ADaM PP domains.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI, SD:	3 significant digits
CV%, GeoCV%:	1 decimal place

16.1.2.2 Urine and Feces

PK parameter data will be descriptively summarized: number of observations (n), arithmetic mean, SD, CV%, Min, Median, Max.

Descriptive statistics of cumulative amount excreted and excretion rate will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK excretion data:

Mean, Min, Median, Max, SD	: 3 significant digits
CV%	: 1 decimal place

The % of the dose will be reported with 1 decimal place.

16.1.3 General Specifications for PK Concentration and PK Parameter Data

Predose samples that occur before the first drug administration per period will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration.

Predose samples which have been taken after the subsequent dosing will be reported as a protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation.

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g. AUC) and for graphical presentations.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as “N.R.”. A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from summary statistics and PK parameter calculation if agreed by the Sponsor. In this case the rationale for exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

If important protocol deviations occurred likely to affect the PK profile of participants as specified in Section 10.2, the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participants listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets (ADAM and SDTM).

PK concentrations and PK parameters excluded from summary statistics will not be included in mean/median figures. Mean/median plots will only contain values where n>2. In case ≤2, individual participant profiles may be included in mean/median plots.

In case of missing or incomplete urine/feces samples, affected urine/feces PK parameters might not be calculated.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 8.1, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.4 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

16.1.4.1 Estimation of Pharmacokinetic Parameters in Plasma and Whole Blood

PK parameters will be calculated using the actual elapsed time since dosing. In cases where the actual sampling time is missing, calculations may be performed using the nominal time. Details (e.g. number of samples, participants affected) will be described in the CSR. In cases actual dosing

time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rational should be included in the CSR.

The following PK parameters will be calculated for berzosertib and MSC2699092A (M11) and total radioactivity in plasma and whole blood when appropriate:

Symbol	Definition
$AUC_{0\text{-}tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (tlast) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at tlast, as estimated using the linear regression from λz determination. $AUC_{0\text{-}\infty}$ = $AUC_{0\text{-}tlast}$ + $C_{last\ pred}$/ λz, where Clast pred is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for λz determination at which the measured plasma concentration is at or above LLOQ
$AUC_{0\text{-}t}$	The partial area under the concentration-time curve (AUC) from time zero (= dosing time) to a defined time 't'. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). Timepoint 't' will be defined upon receipt of the metabolite profiling data.
$AUC_{0\text{-}96}$	The partial area under the concentration-time curve (AUC) from time zero (= dosing time) to 96 hours after dosing, calculated using the mixed log-linear trapezoidal rule (linear up, log down). In cases where the actual observation time is not equal to the scheduled observation time, $AUC_{0\text{-}96}$ will be calculated based on the estimated concentration at 96 hours, and not the concentration at the actual observation time.
C_{max}	Maximum observed concentration of Berzosertib, MSC2699092A or total radioactivity
C_{eoi}	The observed concentration at the end of the infusion period.
CL (berzosertib only)	The total body clearance of study intervention following intravenous administration, CL = Dose/ $AUC_{0\text{-}\infty}$
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval.
$t_{1/2}$	Terminal half-life of Berzosertib, MSC2699092A or total radioactivity, calculated as ln(2)/λz
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
λz	Terminal rate constant determined from the terminal slope of the log- transformed concentration curve of Berzosertib, MSC2699092A or total radioactivity using linear regression on terminal data points of the curve
V_Z (berzosertib only)	The volume of distribution during the terminal phase following intravenous administration. VZ = Dose/($AUC_{0\text{-}\infty}$*λz).
V_{SS} (berzosertib only)	An estimate of the volume of distribution at steady-state based on the last predicted concentration, calculated as CL * MRTiv.
MRT_{iv} (berzosertib only)	The mean residence time extrapolated to infinity, calculated as ($AUMC_{0\text{-}\infty}$/$AUC_{0\text{-}\infty}$)-T/2, where T is the infusion duration. AUMC is the total area under the first moment curve.

Symbol	Definition
M/P($AUC_{0-\infty}$)	Molecular weight-corrected ratio of MSC2699092A $AUC_{0-\infty}$ to parent $AUC_{0-\infty}$. M/P($AUC_{0-\infty}$) = ($AUC_{0-\infty}$metabolite × MWparent) / ($AUC_{0-\infty}$parent × MWmetabolite). Ratios are presented in %.
MRTR($AUC_{0-\infty}$)	Molecular weight-corrected metabolite ratio of $AUC_{0-\infty}$ to total radioactivity. $AUC_{0-\infty}$ for parent and for MSC2699092A divided by the total radioactivity $AUC_{0-\infty}$ (corrected by MW of parent). Ratios are presented in %.

Total radioactivity will be given in ng eq/mL. Metabolite profiling data will be given in % ROI (% of drug-related exposure) for plasma and % of dose for excreta.

Additional PK parameters may be calculated where appropriate. Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

In cases where the actual observation time is not equal to the scheduled observation time, e.g. AUC_{0-24}, the parameter will be calculated by extrapolation to the given time point, e.g. 24 h, provided λz is estimable. In case suitable regression cannot be performed, partial areas may be calculated using the concentration at given time point, e.g. 24 h if actual sampling time is within 10% of the nominal sampling time.

In cases BLQ concentrations occur at the end of the collection interval, these concentrations might be set to missing for calculations of partial AUCs after agreement with the Sponsor. This is an exemption to the general BLQ handling rule and should be applied in case its application would result in estimation of implausible partial AUC values. Implausibility is considered in cases partial AUCs were greater than $AUC_{0-\infty}$.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- First (λz low) and last (λz up) time point of the time interval of the log-linear regression to determine λz.
- Number of data points (Nλ) included in the log-linear regression analysis to determine λz.
- Goodness of fit statistic (adjusted Rsq) for calculation of λz.

- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. ($AUC_{extra\%}$)
- Span ratio of interval over which $t_{1/2}$ was estimates/$t_{1/2}$

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin "best fit" methodology will be used as standard. If warranted, further adjustment may be made by the pharmacokineticist, after agreement with the Sponsor. The last quantifiable concentration >LLOQ should always be included in the regression analysis, while the concentration at t_{max} and any concentrations BLQ which occur after the last quantifiable data point >LLOQ should not be used.

If $AUC_{extra\%}$>20%, the coefficient of correlation (Rsq adj) of λz is <0.8 or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL etc.) will be listed, flagged and included in the parameter outputs descriptive statistics.

The molecular weights of berzosertib and metabolite(s) to be used in the calculation of M/P and MRTR ratios are as follows:

Analyte	Molecular Weight
M6620	463.55 g/mol
MSC2699092A (M11)	464.79 g/mol

The parameter $AUC_{0-tlast}$ or other common partial area may be used to determine M/P(AUC) and MRTR AUC if $AUC_{0-\infty}$ or AUC_{τ} cannot be reliably calculated for the majority of participants.

16.1.4.2 Estimation of Pharmacokinetic Parameters in Urine and Feces

For samples such as urine or feces which are collected within a time range the nominal midpoint may be used for PK evaluation, in case where the actual sampling time is missing. Otherwise, there will be no further imputation of missing data. Where available, actual collection intervals will be used in the calculation of urine PK parameters. Urine concentrations which are BLQ will be set to zero. The following urine PK parameters will be calculated where appropriate:

Symbol	Definition
Ae_{t1-t2}, urine	Amount excreted in urine between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.

Symbol	Definition
Ae_{t1-t2}, feces	Amount excreted in feces between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.
Ae_{total}	Total (cumulative) amount radioactivity recovered in urine and feces over the entire collection period.
CL_R (berzosertib only)	The renal clearance of study intervention. CLR= Ae0-t_urine/AUC0-t
fe (%) (berzosertib only)	Percent of dose excreted as an unchanged berzosertib in urine.
fe_{t1-t2}, urine %	Fraction of administered drug that is excreted in urine between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.
fe_{t1-t2}, feces %	Fraction of administered radioactivity that is excreted in feces between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.
fe_{total} %	Total (cumulative) fraction of administered radioactivity recovered in urine and feces over the entire collection period.

16.1.5 Statistical Analysis of PK Parameter Data

PK and mass balance TLFs will be presented with the following subtitles:

Period 1 – ADME:

- Berzosertib in plasma and urine
- Selected metabolites (see Section 16.1.4.1) in plasma
- Total radioactivity in plasma, whole blood, urine, feces, total (urine + feces)
- Metabolite profiling in plasma, urine and feces

16.1.6 Presentation of PK Concentration and PK Parameter Data – Period 1 ADME

16.1.6.1 Listings and Tables

The following PK tables as also mentioned in section 18.1 will be produced (PK Analysis Set):

- Descriptive statistics (presented together with individual values) of concentrations by analyte, matrix, and nominal timepoint
- Descriptive statistics (presented together with individual values) of PK parameters by analyte, matrix, and nominal timepoint

The following PK Listings as also mentioned in section 18.1 will be produced (Safety Analysis Set):

- PK Sampling date, actual time, nominal time, deviation from time and concentration by participant, analyte, matrix sorted in chronological order. The listing will include the whole blood to plasma ratio of total radioactivity at each timepoint. Calculated as follows from the concentration in whole blood ($C_{whole\ blood}$) and plasma (C_{plasma}):
    - Ratio = $C_{whole\ blood}$ / C_{plasma}
- Individual PK parameters by analyte, matrix, and nominal timepoint
- Start and end time and date of collection interval, urine volume/ feces weight, concentration, excreted amount by participant, analyte, matrix and group sorted in chronological order
- Radioactivity parameters in Urine, Feces and total will be listed in addition to their total and Cumulative Recovery in Urine and Feces
- Phoenix WinNonlin NCA Core Output

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

- Individual concentration versus time plots overlaying berzosertib and its metabolites in plasma; linear and semi-log; using the actual time points by participant; if any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots
- Individual concentration versus time plots overlaying berzosertib (plasma), the sum of berzosertib and metabolites measured (total SUM of berzosertib and metabolite concentration (molecular weight adjusted) in plasma) and TRA in whole blood and plasma. Linear and semi-log; using the actual time points by participant; if any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.
- Individual Total Radioactivity, Berzosertib and its Metabolite (s) Plasma Concentrations Versus Time Profiles (Linear and Semi Logarithmic Scale); using the actual time points by participant; if any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.
- Arithmetic mean plasma concentration-time profiles overlaying berzosertib and its metabolites on linear scale (±SD for arithmetic mean) and semi-logarithmic scale using scheduled (nominal) time points; if any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots.
- Arithmetic mean plasma and whole blood concentration-time profiles overlaying berzosertib, the sum of berzosertib and metabolites measured (total plasma) and total radioactivity in plasma and whole blood. On linear scale (±SD for arithmetic mean) and semi-logarithmic

scale. If any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.

- Arithmetic mean whole blood to plasma ratios versus time on linear scale.
- Arithmetic Mean Profiles of Cumulative Total Radioactivity Excretion in Urine, Feces and Total Recovery (Linear Scale)
- Individual Profiles of Cumulative Total Radioactivity Excretion in Urine, Feces and Total Recovery (Linear Scale)
- Individual Radioactivity Excretion Rate Profiles, Including Excretion and Plasma Profiles.

16.1.6.3 Metabolite Profiling (Period 1)

For the metabolite profiling, where the plasma samples from different time points are pooled using Hamilton pooling method and then analysed individually per subject or pooled over selected or all subjects or timepoints. Metabolite and ^{14}C-berzosertib will be presented as % ROI over the sampling interval of the Hamilton pool, corresponding to the % of drug-related material in the analyzed pool.

The results of the metabolite profiling excretion data in urine and feces will be listed. The % of dose per collection interval will be tabulated.

16.2 Further Other Endpoint(s)

Not Applicable

17 References

Not Applicable

18 Appendices

18.1 Appendix 1 List of Tables, Figures and Listings

A list of tables, figures and listings are presented below.

No.	Tables/ Figures
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Table 8.1.1.1	Subject Disposition Status
Table 8.1.1.2	Analysis Sets
8.1.2	**Demographic Characteristics**
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8.1.3	**Other Baseline Characteristics**
Table 8.1.3.1	Height, Weight, and Body Mass Index at Baseline
8.1.4	**Treatment Compliance and Exposure**
Table 8.1.4.1	Exposure Duration, Total Infusions, Cumulative Dose and Dose Intensity
8.2	Efficacy Data (Not Applicable)
8.3	**Safety Data**
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Table 8.3.1.1	Overall Overview of Treatment Emergent Adverse Events (TEAEs)
Table 8.3.1.2	TEAE by Primary System Organ Class (SOC) and Preferred Term (PT) by Periods and Overall
Table 8.3.1.3	TEAEs by Trial Drug Relationship, SOC and PT by Periods and Overall
Table 8.3.1.4	TEAEs by Trial Drug Relationship, SOC and PT by Drugs for Period 2
Table 8.3.1.5	TEAE by Worst Severity Grade, SOC and PT by Periods and Overall

Table 8.3.1.6	Related TEAE by Worst Severity Grade, SOC and PT by Periods and Overall
Table 8.3.1.7	Related TEAE by Worst Severity Grade, SOC and PT by Drugs for Period 2
8.3.2	**Deaths, Other Serious and Significant Adverse Events**
Table 8.3.2.1	Listing of Deaths
Table 8.3.2.2	Listing of Serious TEAEs
8.3.3	**Clinical Laboratory Evaluations**
Table 8.3.3.1	Hematology – Summary Statistics over Time
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8.3.4	**Other Safety Evaluations**
Table 8.3.4.1	Vital Signs Summary Statistics over Time
Table 8.3.4.2	ECG Results Summary Statistics over Time
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18.2 Appendix 2 Criteria for infusion related reactions (IRRS) and infusion site reactions (ISRs)

Infusion related reactions	**Reactions - Considered when onset is during berzosertib and/or topotecan infusion or within 24 hours of infusion and resolution on the same day or the day after onset:** • Infusion related reaction • Drug hypersensitivity • Anaphylactic reaction • Hypersensitivity • Type 1 hypersensitivity **Signs and Symptoms - when onset is during berzosertib and/or topotecan infusion or within 24 hours of infusion and resolution on the same day or the day after onset** • Erythema • Rash • Rash erythematous • Rash macular • Rash pruritic • Pruritus • Pruritus allergic • Flushing • Chills • Urticaria • Headache • Bronchospasm • Dyspnoea • Hypotension • Hypertension
Infusion site reactions	**Infusion site reactions - if develop during infusion or within 24 hours of Berzosertib administration with resolution on the same day or the day after onset.** • Catheter site pain • Catheter site pruritus • Catheter site rash

	• Catheter site-related reaction • Infusion site discomfort • Infusion site erythema • Infusion site extravasation • Infusion site pruritus • Infusion site rash • Infusion site reaction • Injection site rash • Infusion site reaction