Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	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
Study Number:	MS201923_0008
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Merck Compound:	Berzosertib
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase I
Short Title:	Berzosertib Human Mass Balance Study
Acronym:	**DDR**iver Solid Tumors 208
Principal Investigator:	PPD , MD, PhD PPD [redacted]
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany
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Keywords	Unique terms not already on the Title Page: • Topotecan • Ataxia telangiectasia mutated and Rad3-related (ATR) protein • ATR inhibitor • M6620

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1 Protocol Summary

1.1 Synopsis

Protocol Title: 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

Short Title: Berzosertib Human Mass Balance Study

Rationale: The mass balance study will determine drug-related entities present in circulation and provide a comprehensive understanding of biotransformation pathways and clearance mechanisms in humans. The mass balance study may identify potential contributors to interparticipant variability. In this respect, the performance of a mass balance study is recommended by guidance documents such as the European Medicines Agency (EMA) drug interaction guideline on the investigation of drug interactions, the International Council for Harmonisation (ICH) M3 and the Food and Drug Administration (FDA) Metabolites in Safety Testing (MIST) guidance.

Objectives and Estimands:

Objectives	Estimand Attributes
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 (Period 1).	**Endpoint:** Percent urinary recovery (fe_{urine}), percent fecal recovery (fe_{feces}), percent total recovery in urine and feces (fe_{total}) of total radioactivity over the entire period of collection. **Population:** Participants with advanced solid tumors. **Treatment:** Single dose berzosertib.
To characterize the PK of berzosertib in plasma and urine; and of drug-related material (total radioactivity) in plasma and whole blood (Period 1).	**Endpoint:** PK parameters: C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL, V_z, and V_{ss} of berzosertib and C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$ of total radioactivity in plasma; PK parameters (C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$) of total radioactivity in blood. PK parameters of berzosertib in urine: cumulative amount excreted in urine (Ae and fe_{urine} (%)), renal clearance (CL_R). **Population:** Participants with advanced solid tumors. **Treatment:** Single dose berzosertib.

Objectives	Estimand Attributes
Secondary	
To evaluate the safety and tolerability of berzosertib (Period 1) and berzosertib + topotecan (Period 2).	**Endpoint:** Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) and occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead electrocardiogram (ECG) findings. **Population:** Participants with advanced solid tumors. **Treatment:** Single dose berzosertib and berzosertib in combination with topotecan.

Overall Design: This is a single group, sequential period, unblinded study with treatment of berzosertib single dose (Period 1 Mass Balance), followed by berzosertib in combination with topotecan (Period 2 Extension) in participants with advanced solid tumors.

Brief Summary:

The purpose of Period 1 of this study is to provide a definitive quantitative characterization of the mass balance, rates and routes of elimination, and metabolic pathways after a single intravenous administration of [^{14}C]berzosertib. The purpose of Period 2 is to assess safety and efficacy of berzosertib in combination with topotecan.

Number of Participants: A total of approximately 6 participants (or more) will be treated with study intervention such that approximately 4 to 6 PK evaluable participants are anticipated to be obtained. If the initial group of 6 leads to fewer than 4 evaluable participants, the cohort will be increased up to a maximum of 12 participants, until 4 participants have completed all study procedures for Period 1 and are evaluable.

Study Intervention Groups and Duration: Period 1 represents the period for assessment of the mass balance, PK, metabolism, and elimination of berzosertib. During Period 1, admission to the CRU is required until the discharge criteria are met, with a maximum confinement period of 15 days (Day -1 plus 14 days).

After completing Period 1, within 7 days of discharge from the clinical research unit (CRU), if no study withdrawal criteria are met, participants may enter Period 2 Extension of the study and will continue with 21-day cycles of berzosertib in combination with topotecan until disease progression or other criteria for study intervention discontinuation are met, an End-of-Treatment Visit, and a Safety Follow-up Period of 30 days (± 7 days) after last study intervention dose. Berzosertib will be administered at a dose of 210 mg/m^2 intravenous (IV) on Day 2 and Day 5 and topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

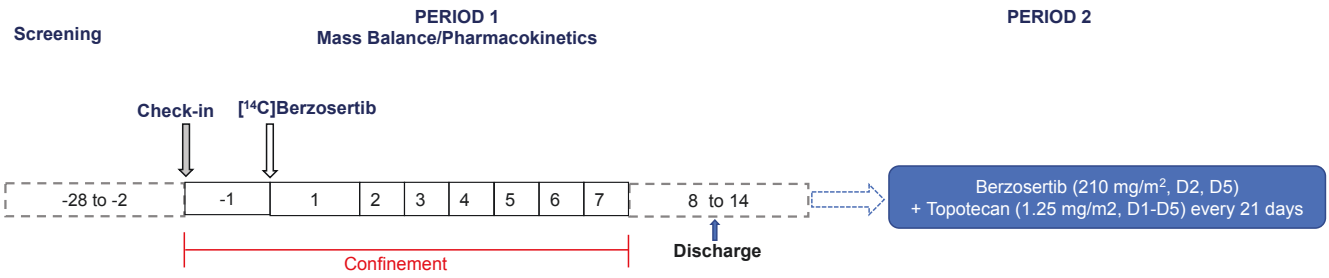
Involvement of Special Committee(s): No

1.2 Schema

The study will consist of 2 periods (1 and 2; see Figure 1):

- Period 1: Mass balance inpatient period, with single dose [^{14}C]berzosertib in 4 to 6 PK evaluable participants with advanced solid tumors
- Period 2: Extension period. After completion of Period 1, participants from Period 1 will continue with berzosertib in combination with topotecan.

Figure 1 Schema



Note: for details, see the Section 1.3, Section 4.1, Section 4.1.1.1, and Sections 6.1.1 and 6.1.2.

1.3 Schedule of Activities

The schedule of activities (SoA) for Period 1 for the mass balance study is presented in Table 1.

The Period 1 schedule of blood and plasma samples is provided in Table 2. The Period 1 schedule of urine and fecal samples is provided in Table 3.

The SoA for Period 2 for the berzosertib and topotecan combination is presented in Table 4.

Table 1 Period 1 Schedule of Activities: Mass Balance Study

Activity	Screening	Period 1										Notes
	D-28 to -2	D-1	D1 Predose	D1	D2	D3	D4	D5	D6	D7	Discharge D8 to D14	Safety Follow-up (only if not continuing to Period 2; 30 days after single dose)	
Informed Consent	X												
Confinement to CRU		X	X	X	X	X	X	X	X	X	X		Note: D8 to D14 assessments are obtained once, prior to discharge from the CRU -Discharge occurs once criteria are met (see details in Section 4.1.1.1) -Maximum stay up to 15 days (D-1 plus 14 days)
Inclusion and Exclusion Criteria; Medical History	X	X											-Should be checked during Screening and either at D-1 or D1 Predose -Medical history includes collection of prior therapy
Demographics	X												
Physical Examination	X	X									X	X	Symptom-directed physical examinations performed as clinically indicated per Investigator's judgment.
Height	X												
Weight	X	X	X								X	X	Obtain weight either at D-1 or D1 Predose.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	Obtain vital signs either at D-1 or D1 Predose.
Standard 12-lead ECG	X	X	X								X	X	Obtain ECG either at D-1 or D1 Predose
Urine Cotinine	X	X											At Screening and D-1

Activity	Screening	Period 1											Notes
	D-28 to -2	D-1	D1 Predose	D1	D2	D3	D4	D5	D6	D7	Discharge D8 to D14	Safety Follow-up (only if not continuing to Period 2; 30 days after single dose)	
Covid 19 PCR Testing		X											If test is positive, discussion with Medical Monitor is required.
Hematology	X	X									X	X	
Serum Chemistry	X	X									X	X	
Coagulation	X										X	X	
Plasma for Radioactivity	X												Screening for ^{14}C levels by AMS
FSH and Estradiol	X												Serum test at Screening, as needed if not a WOCBP only
β-HCG, Serum/Urine (WOCBP only)	X	X									X		Serum test at Screening and D8 to D14, urine test on D-1
Imaging Disease Assessment	X												
ECOG PS	X	X									X	X	
Single Dose ^{14}C-berzosertib IV				X									Dose: berzosertib 210 mg/m^2 IV solution containing ~3 µCi of [^{14}C]berzosertib over 60 minutes
Oral Laxative Administration				X									If not medically contra-indicated, oral laxative(s) of osmotic properties with short onset of action, such as magnesium hydroxide and lactulose may be administered to ensure fecal output is complete for mass balance assessment

Activity	Screening	Period 1											Notes
	D-28 to -2	D-1	D1 Predose	D1	D2	D3	D4	D5	D6	D7	Discharge D8 to D14	Safety Follow-up (only if not continuing to Period 2; 30 days after single dose)	
Concomitant Medications, Therapies and Procedures	X											X	
AEs and SAEs													
Blood Sample Collection			See Table 2, Period 1 for Blood Sampling Collection Schedule										
CCI [redacted]		[redacted]											[redacted]
Urine Sample Collection		See Table 3, Period 1 for Urine Collection Sample Schedule											For TR, berzosertib PK and metabolite profiling
Fecal Sample Collection		See Table 3 Period 1 for Fecal Collection Sample Schedule											For TR and metabolite profiling
Vomitus				X									Collect vomitus if event occurs any time after dosing on Day 1 and/or Day 2

AE = adverse event; AMS = accelerator mass spectrometry; β-HCG = β-human chorionic gonadotropin; CRU = Clinical Research Unit; D = Day(s); ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; FSH = follicle-stimulating hormone; IV = intravenous; PCR = polymerase chain reaction; PK = pharmacokinetic; SAEs = serious adverse events; TR = total radioactivity; WOCBP = woman of childbearing potential.

Table 2 Period 1 Blood and Plasma Samples

Timepoint (min / hour)	Blood Samples[a]	Plasma Samples[b]	Plasma Samples for Metabolite Profiling	Plasma Samples for ex vivo Plasma Protein Binding
D1 Predose (60 min before BOI)	X	X	X	
0.5 hours post BOI (± 5 min)	X	X		
EOI[c] (– 5 min before EOI to + 1 min after EOI)	X	X	X	X
0.5 hours post EOI[d] (± 5 min)	X	X		
1 hours post EOI[d] (± 15 min)[d]	X	X	X	
2 hours post EOI[d](± 15 min)[d]	X	X		
3 hours post EOI[d] (± 30 min)[d]	X	X		
4 hours post EOI[d] (± 45 min)[d]	X	X	X	
8 hours post EOI[d] (± 1 hour)[d]	X	X	X	
12 hours post EOI[d] (± 1 hour)[d]	X	X	X	X
24 hours after BOI (± 1 hour)[e]	X	X	X	X
48 hours after BOI (± 2 hours)[e]	X	X	X	
72 hours after BOI (± 3 hours)[e]	X	X	X	X
96 hours after BOI (± 4 hours)[e]	X	X	X	
120 hours after BOI (± 4 hours)[e]	X	X	X	
144 hours after BOI (± 4 hours)[e]	X	X		
168 hours after BOI (± 4 hours)[e,f]	X	X	X	

BOI = beginning of infusion; EOI = end of infusion; IV = intravenous; PK = pharmacokinetics; TR = total radioactivity.

a For determination of TR.

b For determination of TR and berzosertib PK.

c The window for collection of the EOI time point is between 5 minutes before completion of infusion to 1 minute after completion of infusion. In the event that the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped, and 1 sample drawn when the infusion is restarted) should be collected so that the participant may be considered evaluable.

d Samples are to be collected after completion of berzosertib IV infusion on Day 1.

e Samples are to be collected after beginning of berzosertib IV infusion on Day 1.

f Samples will continue to be collected in 24-hour intervals until discharge criteria are met, for metabolite profiling samples in 48-hour intervals.

Table 3 Period 1 Urine and Fecal Samples

Time Interval (hour)	Urine Collection[a]	Feces Collection[b]
Predose (-24 to 0 hours) (before BOI)	X	X
0 (BOI)-4 hours post EOI[c]	X	X (0-24 hours after BOI)
4-12 hours post EOI	X	
12 post EOI-24 hours after BOI	X	
24-48 hours after BOI	X	X
48-72 hours after BOI	X	X
72-96 hours after BOI	X	X
96-120 hours after BOI	X	X
120-144 hours after BOI	X	X
144-168 hours[d] after BOI	X	X

BOI = beginning of infusion; EOI = end of infusion; PK = pharmacokinetics; TR = total radioactivity

a For determination of TR, berzosertib PK, and metabolite profiling

b For determination of TR and metabolite profiling.

c Collection of urine should start from BOI and until 4 hours post EOI for this collection interval.

d Samples will continue to be collected in 24-hour intervals until discharge criteria are met.

Table 4 Period 2 Schedule of Activities: Treatment, End of Treatment, and Follow-up Period

Assessments and Procedures	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up 30 days after last dose (± 7 days)	Notes
	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)			C1D1 up to 7 days after discharge in Period 1 Cycle start may be delayed up to 7 days to accommodate scheduling conflicts
Review Inclusion and Exclusion Criteria; Medical History	X									
Physical Examination	X							X	X	
Weight	X							X	X	
Vital Signs	X	X	X	X	X			X	X	Predose on all visits
Standard 12-lead ECG								X	X	
Hematology	X					X	X	X	X	Recommended at D8 and D15 at Cycle 1 only, optional at subsequent cycles. Baseline neutrophils should be ≥ 1,500/µL and platelets ≥ 100,000/µL prior to C1; for subsequent cycles, neutrophils should be > 1,000/µL, platelets > 100,000/µL, and hemoglobin ≥ 9 g/dL

Assessments and Procedures	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up 30 days after last dose (± 7 days)	Notes
	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)			C1D1 up to 7 days after discharge in Period 1 Cycle start may be delayed up to 7 days to accommodate scheduling conflicts
Serum Chemistry	X							X	X	
Coagulation	X							X		
β-HCG, Urine (WOCBP only)	X							X	X	
Imaging Disease Assessment	At the end of every 6 weeks (± 1 week) after first dose (C1D1) until Week 24, then every 9 weeks (± 2 weeks) until disease progression, start of new anticancer therapy, death, withdrawal of consent, lost to follow-up, or End-of-Study, whichever comes first, regardless of study intervention modifications/discontinuation									
ECOG PS	X							X	X	

Assessments and Procedures	**Cycle Duration = 21 Days**							**EOT (within 7 days after last dose)**	**Follow-up 30 days after last dose (± 7 days)**	**Notes**
	D1 (± 3)	**D2**	**D3**	**D4**	**D5**	**D8** (± 3)	**D15** (± 3)			C1D1 up to 7 days after discharge in Period 1 Cycle start may be delayed up to 7 days to accommodate scheduling conflicts
Concomitant Medications and Procedures	X									
AEs and SAEs										
Berzosertib		X			X					Dosing: 210 mg/m^2 IV on D2 and D5 every 21 days
Topotecan	X	X	X	X	X					Dosing: 1.25 mg/m^2 IV on Days 1 through 5 every 21 days

AEs = adverse events; β-HCG = β-human chorionic gonadotropin; C = Cycle; D = Day(s); ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; IV = intravenous; SAEs = serious adverse events; WOCBP = woman of childbearing potential.

2 Introduction

Berzosertib (formerly known as M6620) is a free base drug substance that acts as a potent inhibitor of the ataxia telangiectasia mutated and Rad3-related (ATR) protein that is being developed for the treatment of malignancies as a single agent or in combination with chemotherapy and/or ionizing radiation or other anticancer agents.

Detailed information on the chemistry, pharmacology, efficacy, and safety of berzosertib is in the Investigator's Brochure (IB) and details regarding topotecan are in the topotecan product information.

2.1 Study Rationale

Mass balance study in humans is part of a standard clinical development program and its results will be included in the submission package for the marketing authorization applications. The mass balance study will determine drug-related entities present in circulation and provide a comprehensive understanding of biotransformation pathways and clearance mechanisms in humans. The mass balance study may identify potential contributors to inter-participant variability. In this respect, the performance of a mass balance study is recommended by guidance documents such as the European Medicines Agency (EMA) drug interaction guideline on the investigation of drug interactions, the International Council for Harmonization (ICH) M3 and the Food and Drug Administration (FDA) Metabolites in Safety Testing (MIST) guidance.

The berzosertib human mass balance study will consist of 2 periods (Periods 1 and 2). Period 1 will evaluate mass balance and metabolism after a single intravenous administration of [^{14}C]berzosertib. Period 2 consists of an extension of the study where participants will receive berzosertib in combination with topotecan until disease progression or other criteria for study intervention discontinuation are met.

The purpose of Period 1 of this study is to provide a definitive quantitative characterization of the mass balance, rates and routes of elimination, and metabolic pathways after a single intravenous administration of [^{14}C]berzosertib. Such definitive characterization will help guide understanding of the potential for patient-specific (e.g., renal function, hepatic function) or extrinsic (e.g., concomitant medications with potential to affect drug metabolism) factors to affect berzosertib pharmacokinetics (PK) and thereby, is important to inform the need for future clinical pharmacology studies (e.g., special population studies in patients with organ impairment, drug-drug interaction [DDI] as a victim, etc.).

The purpose of Period 2 is to assess safety and efficacy of berzosertib in combination with topotecan. The results from a Phase I/II study of berzosertib + topotecan demonstrated clinical activity across different tumor types, particularly in participants with platinum-resistant small cell lung cancer (SCLC), high grade neuroendocrine tumors, or tumor with DNA damage response (DDR) deficiencies. In addition, topotecan has clinical activity in several other malignancies such as gynecological, soft tissue, and brain tumors (topotecan product information), which can be potentialized with the combination with berzosertib. In terms of safety, comparison with historical data of single agent topotecan, the berzosertib and topotecan

combination has a toxicity profile that largely mirrored that of topotecan as single agent (Thomas 2018; Thomas 2021). Thus, the berzosertib and topotecan combination has the potential of providing clinical benefit in advanced solid tumor patients with poor outcomes and high unmet medical need.

2.2 Background

Chemotherapeutic agents that induce DNA damage are an effective and common treatment option for patients with many types of solid tumors; however, many cancers, despite displaying initial sensitivity and clinical response to these agents, ultimately progress. One mechanism that has been proposed to protect tumor cells from DNA damage is the DDR pathway regulated by the ATM and ATR kinases. Theoretically, small molecule-mediated inhibition of ATR should enhance the effect of DNA damaging chemotherapy on cancer cells.

Berzosertib is a potent inhibitor of ATR that blocks ATR activity in cells, with a concentration resulting in 50% maximal inhibition of 20 nM. Based on nonclinical and clinical data (refer to the latest IB), berzosertib has the potential to have a substantial therapeutic impact on a number of malignancies, particularly in combination with chemotherapeutic agents such as gemcitabine, platinum agents, and topotecan (Konstantinopoulos 2020; Thomas 2018, Thomas 2021).

Following intravenous (IV) dosing of ^{14}C-labeled berzosertib to rats, means of 10.4% and 81.1% of the administered radioactivity were excreted in urine and feces, respectively, by 96 hours postdose. The high percentage of radioactivity eliminated in feces after IV dosing indicates biliary excretion was the major route of elimination of ^{14}C-berzosertib-derived radioactivity. The overall mean recovery of radioactivity after IV dosing to rats was 94.3% (Study 8302826 Final Report 2015). After IV administration to bile duct-cannulated dogs (Vertex Study I135 Nonclinical Study Report 2012), little unchanged berzosertib was detected in dog urine and bile (3.59% and 6.46%, respectively). These data indicated that berzosertib was eliminated primarily through metabolism in nonclinical species.

In a subsequent study in human hepatocytes and liver microsomes, biotransformation of ^{14}C-berzosertib revealed multiple metabolites. Exploratory metabolite profiling performed on pooled plasma samples from 6 participants revealed 3 circulating metabolites i.e. a carboxylic acid metabolite (M11) and 2 glucuronides, the likely acyl glucuronide of M11 (M17) and the direct glucuronide of parent (M14). In humans, the mean percentage of berzosertib excreted unchanged in the urine was approximately 5% to 6%, indicating minimal renal clearance of the unchanged drug. Overall, human in vitro and in vivo data indicated metabolism is the primary clearance mechanism of berzosertib.

The plasma PK of berzosertib are characterized by a moderate to high clearance (approximately 60 L/h), high distribution volume (approximately 1250 L) and a mean terminal elimination half-life of approximately 17 hours across all dose groups (18 to 480 mg/m^2). Systemic exposures of berzosertib (C_{max} and $AUC_{0-\infty}$) tended to increase proportionally with increasing dose after IV administration of the drug as monotherapy. Mean berzosertib plasma exposures, when berzosertib was given 1 day after administration of gemcitabine, cisplatin, carboplatin, carboplatin plus avelumab, or in combination with irinotecan were largely comparable to the corresponding values of berzosertib when administered alone at equivalent doses. In Parts A and

B of Study MS201923-0001, the mean percentage of berzosertib excreted unchanged in the urine was approximately 5% to 6%, indicating minimal renal clearance of the unchanged drug. Exploratory metabolite profiling was performed on pooled plasma samples from 6 participants administered berzosertib at a dose of 72 mg/m^2 (Study MS201923-0001). Three circulating metabolites were detected: M11 (MSC2699092A), a de-alkylation product (major), M14, a direct glucuronide (minor), and M17, a glucuronide of M11 (minor). No clinical DDI studies to assess the victim or perpetrator potential of berzosertib have been conducted.

Berzosertib was extensively metabolized via oxidative metabolism pathways, cytochrome P450 (CYP)3A4 as the principal isozyme based on preliminary in vitro assessment. Berzosertib is a P-glycoprotein (P-gp) substrate but not a Breast Cancer Resistance Protein (BCRP) substrate. Using both basic and static mechanistic modeling prediction, berzosertib is in general not expected to elicit clinically meaningful DDI as a perpetrator based on in vitro assessment (potential for CYP induction, inhibition of CYPs, uridine diphosphate glucuronosyltransferases (UGTs), P-gp, organic anion transporting polypeptide (OATP)1B1, and OCT1 inhibition) at maximum unbound berzosertib concentrations observed in humans. A weak DDI risk is predicted for inhibition of CYP3A4 and according to EMA criteria, a possible DDI risk is predicted for BCRP and OATP1B3. As berzosertib is primarily metabolized by CYP3A4, strong inhibitors and inducers of CYP3A4 are expected to impact berzosertib exposure.

The berzosertib + topotecan combination has shown promising clinical activity and a favorable safety profile in participants with solid tumors. A Phase I/II study with the berzosertib + topotecan combination established the recommended Phase II dose, with topotecan at 1.25 mg/m^2 administered from Day 1 to Day 5, and berzosertib at 210 mg/m^2 administered on Day 2 and Day 5, in cycles of 21 days. The toxicity profile of this regimen largely mirrored that of topotecan as single agent. The most common Grade 3 and 4 toxicities were hematological, such as anemia, leukopenia, and neutropenia (40% to 50% each) and thrombocytopenia (25%); however, with most participants having received granulocyte colony-stimulating factor (G-CSF) prophylactically, complications such as febrile neutropenia were uncommon, and no treatment-related deaths occurred (Thomas 2018; Thomas 2021). In the Phase I portion, in terms of efficacy, there were 2 partial responses (PRs) of ≥ 18 months, and ≥ 7 months, and 7 stable disease (SD) responses lasting ≥ 3 months (median: 9 months; range, 3 to 12 months). Three of 5 participants with SCLC, all of whom had platinum-resistant disease, had a PR or prolonged SD of ≥ 6 months (Thomas 2018). In the subsequent Phase II portion of the study of berzosertib in combination with topotecan in participants with relapsed SCLC, there was an overall response rate of 36%: 30% in participants with platinum-resistant disease (n = 20) and 60% in participants with platinum-sensitive disease (n = 5) (Thomas 2021). These results suggest a potential benefit of the combination in patients with platinum-resistant SCLC, defined by disease recurrence within 90 days from the last dose of platinum given in prior lines; thus, the berzosertib and topotecan combination is being further investigated in this patient population with poor outcomes (NCT04768296).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of berzosertib (and topotecan) may be found in the respective IBs.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment

The planned intravenous infusion of 210 mg/m^2 of berzosertib will contain approximately ~0.111 MBq (~3 µCi) of radioactivity (^{14}C) per participant. The radioactive burden due to low amounts of radioactivity (approximately ~3 µCi) planned to be administered per participant is considered to pose negligible risk above the background cosmic radiation. The estimated radiation burden is far below the recommended dose limit for public of 1 mSv per year (Study No. MSI2047A-2047AX, M6620 – Radiation Burden Calculation Report 2020). The safety profile of berzosertib from clinical studies performed to date suggests that berzosertib is well tolerated when administered as single agent.

In the Phase I (Thomas 2018) and Phase II (Thomas 2021) berzosertib and topotecan combination studies, the toxicity profile of berzosertib + topotecan was similar to that of topotecan when given as a single agent. The combination of berzosertib with topotecan will be further assessed and evaluated for exacerbated toxicities or unforeseen adverse events (AEs), as compared with historical data from berzosertib and topotecan as single agents, and from berzosertib in combination with topotecan.

Identified and potential risks of the study intervention and procedures are presented in Table 5.

Table 5 Berzosertib and Topotecan – Identified and Potential Risks with Mitigation Strategies

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Berzosertib		
Identified risks for berzosertib in combination with chemotherapy		
Gastrointestinal disorders such as nausea and vomiting	Refer to the berzosertib IB.	Continuous safety monitoring is performed during the study per the SoA (Sections 1.3 and 8.3).
Hypersensitivity, including infusion-related reactions[a]	Refer to the berzosertib IB	Exclusion criteria are in place to prohibit enrollment of participants with known hypersensitivity to the study interventions, a similar structural compound, or to 1 or more excipients used. Continuous safety monitoring is performed during the study. Premedication is permitted for participants who have experienced an infusion-related reaction (Section 6.1).

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks for berzosertib in combination with chemotherapy		
Risks associated with DDIs	No formal drug interaction studies have been conducted with berzosertib in humans; however, in a Phase I/II study of berzosertib in combination with topotecan, no drug interactions were reported with authorized concomitant medications and/or with topotecan. The toxicity profile of the study drugs combination largely mirrored that of topotecan as single agent. Refer to the berzosertib IB.	Concomitant administration with potent inhibitors or inducers of CYP3A4 is prohibited in this study. In Period 1, moderate inhibitors and inducers of CYP3A4 and inhibitors of P-gp are also prohibited. Clinical protocol-specific instructions should be closely followed (see Section 6.8.3).
Pregnancy, fertility, and lactation	There is a potential risk, based on its mechanism of action, that administration of berzosertib during pregnancy could cause fetal harm. Refer to the berzosertib IB.	A negative serum pregnancy test is required for inclusion. Participants who get pregnant during the study must discontinue the study intervention (see Section 7.1). Refer to the berzosertib IB for guidance regarding pregnancy, lactation, contraception and fertility and see protocol Section 5.1 and Appendix 3 for contraception and barrier requirements. Further, strict use of contraception is required; participants should be informed that fertility might be impaired long term and may opt to cryopreserve sperm or ova prior to treatment. Male participants must also use a condom with pregnant female partners during the study, since exposure to the study intervention through the ejaculate could harm an existing fetus.
Increased toxicity in patients with Li Fraumeni Syndrome or ataxia telangiectasia	Based on non-clinical findings, increased toxicity in patients with Li-Fraumeni Syndrome or ataxia telangiectasia was classified as an important potential risk.	Exclusion of patients with Li_Fraumeni Syndrome or ataxia telangiectasia
Study Intervention: Topotecan (SmPC 2019)		
Anemia	Moderate to severe (Hb ≤ 8.0 g/dL) in 37% of patients (14% of courses).	AEs are continually monitored during the study (see Section 8.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Leukopenia (including neutropenia)	Abnormally low white blood cell count (leukopenia, neutropenia) that may be accompanied with fever and signs of infections (febrile neutropenia). Severe neutropenia (neutrophil count < 0.5 × 10^9/L) during Course 1 in 55% of patients, with duration ≥ 7 days in 20% and overall, in 77% of patients (39% of courses). In association with severe neutropenia, fever or infection occurred in 16% of patients during Course 1 and overall, in 23% of patients (6% of courses). Median time to onset of severe neutropenia was 9 days and the median duration was 7 days.	AEs are continually monitored during the study (see Section 8.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.
Thrombocytopenia	Severe (platelets < 25 × 10^9/L) in 25% of patients (8% of courses); moderate (platelets between 25.0 and 50.0 × 10^9/L) in 25% of patients (15% of courses). Median time to onset of severe thrombocytopenia was Day 15 and the median duration was 5 days.	AEs are continually monitored during the study (see Section 8.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.
Study Procedures		
Blood sampling	Blood sampling is required for participants as detailed in the SoA and is considered essential for the study's scientific objectives. Blood sampling carries a risk of AEs including pain, bruising, bleeding, redness and swelling of the site/vein, and infection.	Minimization of blood sampling was thoughtfully considered during protocol development weighing risk to participants versus achievement of the study's scientific objectives. Blood samples will be taken by qualified professional and every effort will be made to minimize any discomfort.
Imaging procedures	Imaging disease assessments are required for all participants as detailed in the SoA to monitor disease progression. These are associated with a risk of allergic reactions to contrast agents, exposure to ionizing radiation for some types of imaging (e.g. CT scans, bone scintigraphy), nephrogenic systemic fibrosis, and intracranial gadolinium deposition for gadolinium and contrast-induced renal damage for iodinated contrast.	Imaging procedures in this study will be conducted at a similar frequency to that in routine clinical practice. Participants will be monitored for allergic reactions, as per routine clinical practice. Selection of imaging modality will be guided by any identified risk factors, as described in the Imaging Manual.

AEs = adverse events; CT = computed tomography; CYP3A4 = cytochrome P450 3A4; DDI = drug-drug interaction; Hb = hemoglobin; IB = Investigator's Brochure; SoA = Schedule of Activities.

a Infusion-related reactions have been reported using a variety of terms to describe the same biologic event, including erythema, eyelid edema, face edema, flushing, hypersensitivity, infusion-related reaction, pruritus, pruritus allergic, rash, rash erythematous, rash macular, rash pruritic, and rhinitis allergic.

2.3.2 Benefit Assessment

- All participants in the current study will receive [^{14}C]berzosertib in Period 1 and berzosertib in combination with topotecan in Period 2, which has the potential to improve their treatment outcome (see Section 2.2).
- Participants in this study will be contributing to the process of developing new therapies in areas of unmet needs.
- The medical evaluations and assessments in the current study protocol, with regular physical examinations, monitoring of AEs, imaging disease assessments, and laboratory assessments, in many instances go beyond the local standard of care.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, as outlined in Table 5, the risks (potential and identified) associated with berzosertib (and in combination with topotecan) are justified by the anticipated benefits that may be afforded to participants with advanced solid tumors.

3 Objectives and Estimands

Table 6 Periods 1 and 2: Objectives and Estimand Attributes

Objectives	Estimand Attributes
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 (Period 1).	**Endpoint:** Percent urinary recovery (fe_{urine}), percent fecal recovery (fe_{feces}), percent total recovery in urine and feces (fe_{total}) of total radioactivity over the entire period of collection. **Population:** Patients with advanced solid tumors. **Treatment:** Single dose berzosertib.
To characterize the PK of berzosertib in plasma and urine; and of drug-related material (total radioactivity) in plasma and whole blood (Period 1).	**Endpoint:** PK parameters: C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL, V_z, and V_{ss} of berzosertib and C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$ of total radioactivity in plasma; PK parameters (C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$) of total radioactivity in blood. PK parameters of berzosertib in urine: cumulative amount excreted in urine (Ae and fe_{urine} (%)), renal clearance (CL_R). **Population:** Patients with advanced solid tumors. **Treatment:** Single dose berzosertib.

Objectives	Estimand Attributes
Secondary	
To evaluate the safety and tolerability of berzosertib (Period 1) and berzosertib + topotecan (Period 2.)	**Endpoint:** Occurrence of TEAEs and treatment-related AEs and occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings. **Population:** Patients with advanced solid tumors. **Treatment:** Single dose berzosertib and berzosertib in combination with topotecan.
CCI	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
To assess efficacy of intervention in terms of objective response of berzosertib + topotecan therapy (Period 2).	**Endpoint:** Objective response according to RECIST 1.1 as assessed by the Investigator. **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. • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event.

AE = adverse event; DME = drug-metabolizing enzyme; ECG = electrocardiogram; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TEAE = treatment-emergent adverse event

4 Study Design

4.1 Overall Design

Study Design	Single group; see Section 1.2 for Study Schema
Control Method	None (i.e., uncontrolled)
Single or Multicenter	Multicenter
Control Group	Not applicable
Study Population Type	Patients with advanced solid tumors
Level and Method of Blinding	Open-label study
Bias Minimalization Method(s)	See Section 6.3
Study Intervention Assignment Method	Not applicable, open-label study
Involvement of Special Committee(s):	No
Total Duration of Study Participation per Participant	Screening: 27 days (from D-28 to D-2) Period 1 ([^{14}C]berzosertib single dose): confinement maximum up to 15 days (D-1 plus 14 days) Safety Follow-up (if not entering Period 2): 30 days after single dose administered Period 2 (berzosertib in combination with topotecan): Study Intervention consisting of 21-day cycles until disease progression or other criteria for study intervention discontinuation are met. Safety Follow-up (at the end of Period 2): 30 days (± 7 days) after last dose of study intervention Participants who discontinue study intervention for reasons other than disease progression or death will continue with regular imaging assessments until disease progression, addition of subsequent anticancer therapy, death, withdrawal of consent, lost to follow-up, or End of-Study.
Provisions for Study Extension or Entry into Roll-Over Studies	See Section 6.6
Adaptive Aspects of Study Design	Not applicable

This is a single group, sequential period, unblinded study with treatment of berzosertib single dose (Period 1 Mass Balance), followed by berzosertib in combination with topotecan (Period 2 Extension) in participants with advanced solid tumors.

4.1.1 Period 1: Berzosertib Mass Balance Study

Period 1 represents the period for assessment of the mass balance, PK, metabolism, and elimination of berzosertib.

During Period 1, admission to the clinical research unit (CRU) is required until the discharge criteria are met (see Section 4.1.1.1), with a maximum confinement period of 15 days (Day -1 plus 14 days). Patients who meet all inclusion criteria and none of the exclusion criteria will be admitted to the clinical facility on the morning of Day -1 for predose samples collection. Following the collection of Day 1 predose assessments and samples (if any), participants will receive a single dose of 210 mg/m^2 of [^{14}C]berzosertib IV solution (containing approximately ~3 µCi of [^{14}C]berzosertib) via an intravenous infusion for 1 hour. The actual amount of administered radioactivity will be documented for each participant.

Participants will be closely monitored for AEs throughout the period. Safety will be assessed by monitoring vital signs, physical examinations, electrocardiogram (ECGs), and clinical laboratory tests.

Blood will be collected at prespecified time points for analyses of berzosertib and drug-related material, and metabolite profiling over the confinement period. The mean terminal elimination half-life ($t_{1/2}$) of berzosertib as parent drug is approximately 17 hours (range 14.2 to 17.6 h) in adults with advanced solid tumors. The human $t_{1/2}$ of metabolites of berzosertib is not known; therefore, the $t_{1/2}$ of total drug-related material (parent drug + metabolites) cannot be accurately estimated. The estimated confinement period of 7 days (approximately 5 $t_{1/2}$) takes into account potential metabolites that may have $t_{1/2}$ that are up to 2 times that of parent drug for characterizing the PK of total radioactivity (TR) and excretion of drug-related material in urine and feces.

Complete urinary and fecal output will be collected until discharge from the clinical unit and analyzed for total drug-related material and products of berzosertib biotransformation. To ensure defecation prior to release from the clinical facility, oral laxatives of osmotic properties (e.g., magnesium hydroxide, lactulose) may be administered as needed.

For those not participating in Period 2, a Safety Follow-up Visit should be performed 30 days after the single dose of berzosertib in Period 1.

4.1.1.1 Period 1: Clinical Research Unit Discharge Criteria

Admission to the CRU is required, with a maximum confinement period of 15 days (Day -1 plus 14 days), until the following discharge criteria are met:

- At least 85% of the total dose of radioactivity has been collected
  OR
- The excretion of radioactivity in the urine and feces combined has declined to ≤ 1% of the total administered radioactivity for at least 2 consecutive days

4.1.2 Period 2: Extension with Berzosertib in Combination with Topotecan

After completing Period 1, within 7 days of discharge from the CRU, if no study withdrawal criteria are met, participants may enter Period 2 Extension of the study and will continue with 21-day cycles of berzosertib in combination with topotecan until disease progression or other criteria for study intervention discontinuation are met, an End-of-Treatment Visit, and a Safety Follow-up Period of 30 days (± 7 days) after last study intervention dose. Berzosertib will be administered at a dose of 210 mg/m^2 IV on Day 2 and Day 5 and topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

4.2 Scientific Rationale for Study Design

The study design is based on the regulatory guidance (FDA and EMA) to characterize rates and routes of elimination, mass balance and clearance pathways. The PK and disposition of any drug is governed by several processes, including organ distribution, and elimination by metabolism and/or transport processes, and ultimately excretion. Period 1 of this study is designed to elucidate these processes, a [^{14}C]-radiotracer of berzosertib will be used, which allows the detection, tracking, and quantification of parent drug and metabolites in biological samples.

Since a berzosertib mass balance study can only be performed in patients with cancer, and only a single-dose administration of berzosertib is required, the Period 2 Extension will consist of a combination of berzosertib with topotecan, which is a regimen potentially active in several solid tumors, particularly SCLC, high grade neuroendocrine tumors, or tumor with DDR deficiencies.

4.3 Justification for Dose

Berzosertib will be administered in Period 1, the mass balance portion of this study, as a single 1-hour IV infusion of 210 mg/m^2 containing approximately ~3 µCi of [^{14}C]berzosertib as the radioactive tracer to allow mass balance evaluation and quantitative metabolite profiling in plasma, urine, and feces. Since radioactivity used in this study is approximately ~3 µCi, accelerator mass spectrometry (AMS) analysis, a highly sensitive method for the detection of radioactive ^{14}C, will be used to assess the recovery and PK of 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.

The radioactive burden due to low amounts of radioactivity (approximately ~3 µCi) planned to be administered per participant is considered to pose negligible risk above the background cosmic radiation. The estimated radiation burden is far below the recommended dose limit for public of 1 mSv per year (Study No. MSI2047A-2047AX, M6620 – Radiation Burden Calculation Report 2020).

The selected 210 mg/m^2 of berzosertib is based on the reported Phase I study, which determined the combination of berzosertib and topotecan to be safe and tolerable (Thomas 2018). The starting study intervention doses for the combination in the Period 2 are as follows:

- Berzosertib by IV administration at a dose of 210 mg/m^2 on Day 2 and Day 5 of each 21-day cycle
- Topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

Section 6.5 provides the dose selection and modification information for this study.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study periods, including the Safety Follow-up Visit, as shown in Section 1.3 (SoAs for Periods 1 and 2) and fulfilled at least 1 of the following criteria:

- Withdrawal of consent from the study
- Lost to Follow-up
- Died.

The end of the study is defined as the date of last contact (related to this study) with the last participant who participates in this study (Safety Follow-up Visit).

The Sponsor may terminate the study at any time once access to berzosertib or topotecan for participants still benefiting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Category	Criterion
Age	1. Are ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Histologically proven advanced solid tumors that are considered appropriate for treatment in Period 2 of this study, for which no effective standard therapy exists, or standard therapy has failed or cannot be tolerated 3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 (see Appendix 5) 4. Evaluable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) at Screening. 5. Have adequate hematologic function as indicated by: • Platelet count ≥ 100,000/mm^3 • Hemoglobin ≥ 9.0 g/dL. Prior red blood cell transfusions are allowed • Absolute neutrophil count ≥ 1,500/µL with no growth factor treatment within 14 days of obtaining the Screening blood sample • Total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase (AST) and an alanine aminotransferase (ALT) level ≤ 3.0 × ULN or ≤ 5 × ULN in presence of liver metastases • Adequate renal function defined as creatinine clearance ≥ 60 mL/min by calculation using the Cockcroft-Gault formula or measured by 24-hour urine collection. The Cockcroft-Gault formula is: (l40 – age) × weight [kg]) / (72 × serum creatinine [mg/dL]) × 0.85 (if female) • Suitable venous access for the study-required blood sampling (including PK sampling)

Sex and Contraception/Barrier Requirements	6. All sexes allowed The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. 7. Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies <u>Male participants:</u> Agree to the following during the Study Intervention Period and for at least 6 months after the last study intervention dose: • Refrain from donating sperm • PLUS, either: o Abstain from any activity that allows for exposure to ejaculate OR o Use a male condom: When having sexual intercourse with a woman of childbearing potential (WOCBP), who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak. Male participants must use a condom with pregnant female partners <u>Female participants:</u> Are **not** pregnant or breastfeeding, and at least 1 of the following conditions applies: • Not a WOCBP OR • If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods: o Before the first dose of the study intervention, if using hormonal contraception:

Category	Criterion
	▪ Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses OR ▪ Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay AND A barrier method, as described in Appendix 3. o During the Study Intervention Period o After the Study Intervention Period (i.e., after the last study intervention dose is administered) for at least 6 months after the last study intervention dose and agree not to donate eggs (ova, oocytes) for reproduction during this period The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. o Have a negative serum pregnancy test, as required by local regulations, within 24 hours before the first study intervention dose. Additional requirements for pregnancy testing during and after study intervention are in Appendix 3.
Informed Consent	8. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Category	Criterion
Medical Conditions	1. Clinically relevant (i.e., active), uncontrolled intercurrent illness including, but not limited to, severe active infection including, acute respiratory syndrome coronavirus-2 infection/coronavirus disease 2019 (Covid 19), immune deficiencies, uncontrolled diabetes, uncontrolled arterial hypertension, symptomatic congestive heart failure (New York Heart Association

Category	Criterion
	Classification ≥ Class III), unstable angina pectoris, myocardial infarction, uncontrolled cardiac arrhythmia, and cerebral vascular accident/stroke. Calculated QTc average (using the Fridericia correction calculation) of > 450 msec for males and > 470 msec for females. Any psychiatric illness/social situations that would limit compliance with study requirements, including required inpatient confinement. Known hepatic cirrhosis or severe pre-existing hepatic impairment. The following exceptions apply: a. Participants with human immunodeficiency virus infection are eligible if they are on effective antiretroviral therapy with undetectable viral load within 6 months, provided there is no expected DDI. Human immunodeficiency virus testing is not mandated for study inclusion. If performed, the participant must be consented for testing as per local standard guidance. b. Participants with evidence of chronic hepatitis B virus (HBV) infection are eligible if the HBV viral load is undetectable on suppressive therapy (if indicated), and if they have ALT, AST, and total bilirubin levels < ULN, and provided there is no expected DDI with berzosertib due to treatment medication (see Table 11). c. Participants with a history of hepatitis C virus (HCV) infection are eligible if they have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load, and if they have ALT, AST, and total bilirubin levels < ULN, and provided there is no expected DDI with berzosertib due to treatment medication (see Table 11).
	2. Unstable brain metastases; however, participants with known brain metastases may be enrolled in this clinical study if they are clinically stable (without evidence of progression by imaging for at least 2 weeks prior to the first study intervention administration and any neurologic symptoms have returned to baseline), have no evidence of new brain metastases, and are on a stable or decreasing dose of steroids for at least 14 days prior to study intervention. Participants with carcinomatous meningitis are excluded regardless of clinical stability. Screening central nervous system imaging is not mandatory.

Category	Criterion
	3. Participants not recovered from AEs Grade > 1 from prior anticancer therapies, including surgeries. Exception: Grade 2 AEs not constituting a safety risk (e.g., alopecia), based on the Investigator's judgment; must consult with the Medical Monitor prior to enrollment.
	4. Participants with known history of Li-Fraumeni Syndrome and ataxia telangiectasia.
	5. Irregular defecation patterns (< 1 defecation/2 days or excessive diarrhea).
	6. Persistent diarrhea (≥ Grade 2) lasting > 3 days within 2 weeks before the first dose of study intervention.
	7. History of urinary and/or fecal incontinence.
	8. Major surgery within 14 days before the first dose of study intervention or scheduled surgery during Period 1 of the study.
	9. Participation in a trial involving administration of 14C labeled compound(s) within last 6 months prior to start of study intervention.
	10. Total ^{14}C radioactivity measured by AMS in plasma (during screening) exceeding $^{14}C/^{12}C$ ratio $1.1E^{-12}$
	11. Radiotherapy within 14 days before the first dose of study intervention
	12. Prior treatment with an ATR inhibitor
	13. Prior or concurrent treatment with a nonpermitted drug/intervention from the first dose of study intervention administration: • Participants who may have received any of the following anticancer therapy(ies) within the following time windows from the first day of study interventions administration:

Category	Criterion
	a. Small molecule inhibitor therapy (including investigational) within 2 weeks or 5 half-lives, whichever is longer b. Any type of anticancer antibody or antibody drug conjugates within 3 weeks c. Systemic chemotherapy within 4 weeks (within 6 weeks for nitrosoureas/ mitomycin C) d. Prior curative-intent high-dose radiotherapy within 4 weeks. Prior palliative radiotherapy to metastatic lesion(s) is permitted provided it was completed at least 1 week prior to first day of study interventions administration and toxicities recovered to Grade ≤ 1. e. Any other type of anticancer therapy, not listed above, within 4 weeks. • Concomitant use of medication or supplements that are known strong and moderate inhibitors (Period 1 only) of CYP3A4 enzymes that cannot be discontinued within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or 7 days prior to administration of study intervention and for the duration of study intervention. • Concomitant use of medication or supplements that are known strong and moderate CYP3A4 inducers that cannot be discontinued 4 weeks prior to administration of study intervention and for the duration of study intervention. • Concomitant use of medication or supplements that are known inhibitor of P-gp that cannot be discontinued within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or for 7 days prior to administration of study intervention and for the duration of study intervention (Period 1 only). • Food and beverage containing grapefruit within 7 days before the first dose of study interventions. Note that food and beverages containing grapefruit, Seville orange, and star fruit are not permitted during the study (Period 1 only). • No history of amiodarone use in the 6 months before the first dose of berzosertib. • Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Category	Criterion
	• Other prohibited concomitant medications as listed in Section 6.8.3
Prior/Concurrent Clinical Study Experience	14. Concurrent participation in another interventional clinical study is not permitted. There are no restrictions on prior clinical study participation provided the above washout periods are followed.
Other Exclusions	15. Known hypersensitivity to the study interventions, a similar structural compound, or to one or more excipients used. 16. Smokers (use of tobacco products or nicotine-containing smoking cessation agents in the previous 1 month). Urine cotinine levels will be measured during screening and admission on Day -1 for all participants (Period 1 only). Smokers will be defined as any participant who reports tobacco use and/or who has a urine cotinine ≥ 500 ng/mL. 17. Donation or loss of more than 450 mL of blood in the 60 days prior to screening. 18. Is not willing to comply with dietary and fluid restrictions.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

During Period 1 only, abstain from consumption of the following from 7 days before the start of study intervention: Seville oranges, grapefruit or grapefruit juice, and star fruit.

There are no dietary restrictions for Period 2.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- No restrictions on caffeine or modest alcohol use apply during this study.
- Use of tobacco products will not be allowed from 1 month prior to screening until after the final follow-up visit.

5.3.3 Activity

Participants will abstain from strenuous exercise for 2 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

Based on in vitro and in vivo assays, berzosertib has a phototoxic potential as it absorbs in the UV-visible radiation spectrum, and is widely distributed in tissues, including skin. Therefore, participants should be cautioned to minimize exposure to the sun and other sources of visible and UV radiation, and to take protective measures when necessary.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within 7 days, after the reason for the screening failure has been addressed. Rescreened participants will be assigned a new participant number and will undergo Screening procedures as planned in the protocol. Any previous screening tests can be used for rescreening, provided they are within the new screening window of -28 days.

5.5 Criteria for Temporarily Delaying the Administration of Study Intervention

See Section 6.5 in this protocol.

6 Study Intervention(s) and Concomitant Therapies

Study intervention is any investigational interventions, marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol. Study intervention is used instead of "study drug, Investigational Medicinal Product, or study treatment".

6.1 Study Intervention(s) Administration

Participants are planned to continue with study intervention until documented disease progression, discontinuation due to AEs, death, or withdrawal from the study, whichever occurs earlier.

Additional details of sourcing, packaging, including quantity per container, anticipated length of supply per container, and labeling of the study interventions will be defined in a separate Pharmacy Manual.

Table 7 Study Interventions

Intervention Name	Berzosertib	Topotecan
Type	Drug	Drug
Dose Formulation	Solution for infusion	Concentrate for solution for infusion
Unit Dose Strength	20 mg/mL	1 mg/mL topotecan free base
Dose Amount	Periods 1 and 2: 210 mg/m^2 Containing ~3 µCi of [^{14}C]berzosertib in Period 1	Period 2 only: 1.25 mg/m^2
Premedication	Suggested premedication regimen: hydrocortisone (200 mg IV) and a locally available antihistamine approximately 60 minutes before study intervention infusions. The regimen may be modified based on local treatment standards and guidelines, as appropriate, as long as not prohibited by the protocol (see Section 6.8.3)	Prophylactic or therapeutic use of antiemetic medication according to the topotecan product information is recommended, unless the specific medication is prohibited for other reasons, e.g., the antiemetic is also a strong CYP3A4 inhibitor (see Table 11)
Frequency	Period 1: Single dose on Day 1 Period 2: On Day 2 and Day 5 of each 21-day cycle	Period 2: Days 1 through 5 of each 21-day cycle
Route of Administration	IV infusion	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	SoC/IMP depending on local law (in Hungary)
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Packaging and Labeling	Study Intervention will be provided in vials. Each vial will be labeled per country requirements.	Depending on the local regulations (in Hungary), topotecan may be either sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider) and will be packaged/labeled according to local requirements.
Current/Former Name(s) or Alias(es)	Substance code MSC2527093A, M6620, VX-970	

CYP = Cytochrome P450; IMP = Investigational Medicinal Product; IV = intravenous; NIMP = non-investigational medicinal product; SoC = standard of care.

6.1.1 Period 1: Study Intervention Administration

Berzosertib will be administered after predose samples and assessments are performed in Period 1, the mass balance portion of this study, as a single 1-hour IV infusion of 210 mg/m^2 containing ~3 µCi of [^{14}C]berzosertib as the radioactive tracer to allow mass balance evaluation and quantitative metabolite profiling in plasma, urine, and feces.

6.1.2 Period 2: Study Intervention Administration

In Period 2, berzosertib at a dose of 210 mg/m^2 will be administered via IV over 60 minutes (± 10 minutes) and start approximately 15 minutes after completion of topotecan administration

on Day 2 and Day 5, of each 21-day cycle. Topotecan at a dose of 1.25 mg/m^2 will be administered via IV over 30 minutes on Days 1 through 5 of each 21-day cycle. Study intervention details are provided in Table 7.

Prior to study intervention administration, baseline neutrophils should be ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3 prior to Cycle 1. For subsequent cycles, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

Investigators should prophylactically premedicate participants with corticosteroid and antihistamine before the first 2 berzosertib infusions. Premedication should be administered for subsequent berzosertib infusions based upon clinical judgment and presence/severity of prior infusion-related reactions to berzosertib. See Table 7 for suggested premedication regimen with corticosteroids and antihistamine.

Prophylactic G-CSF will be administered according to local practice and topotecan label. Its administration as primary or secondary prophylaxis is highly recommended and can be adjusted according to institutional guidelines and clinical judgment. G-CSF may be used from Day 6, at least 24 hours after the last dose of topotecan.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, formulations, and the participant numbers.

- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After obtaining informed consent, participants will receive a subject number. This number will ensure identification throughout the study. Only subjects that pass screening according inclusion and exclusion criteria will be enrolled in the treatment part of the study.

This is a single-arm study, all participants will receive the same study interventions. Administration will be supervised by the Principal Investigator and clinical site staff. The date and time of administration, the volume of the IMP will be documented in the electronic Case Report Form (eCRF).

Trial medication will be prepared and distributed by Good Manufacturing Practice (GMP) pharmacies specialized for that service in compliance with ICH Good Clinical Practice (GCP) and GMP guidance.

6.3.2 Blinding

Not applicable as this is an open-label study.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

There will be no dose modification for the single dose of [^{14}C]berzosertib in Period 1 of this study. If during Period 1 there is a need to interrupt or slow the IV infusion, contact the project clinician or designee as soon as possible for consideration of participant replacement as appropriate.

In Period 2, participants will receive berzosertib in combination with topotecan as per Table 7 until the criteria are met as outlined in Section 4.4 (End of Study Definition) and/or Section 7.1 (Discontinuation of Study Intervention). Berzosertib and topotecan should be administered in combination, including during dose modifications and interruptions, unless one agent is permanently discontinued.

In case a dose reduction is necessary, berzosertib and topotecan will be administered as outlined in Sections 6.5.1 and 6.5.2, respectively. See Section 7 for information regarding discontinuation of study intervention and participant discontinuation/withdrawal.

The justification for study intervention dose is presented in Section 4.3.

6.5.1 Berzosertib Dose Modifications (Period 2 Only)

In Period 2, the dose of berzosertib may be reduced for the occurrence of drug-related toxicity using the following toxicity-dependent guidelines:

- **For Grade 4 hematologic toxicity:** The dose of berzosertib will be reduced by 1 dose level (first dose reduction).
- **For Grade 3 nonhematologic toxicity:** The dose of berzosertib will be reduced by 1 dose level (first dose reduction).
- **For Grade 4 nonhematologic toxicity:** The dose of berzosertib will be reduced by 2 dose levels (equivalent to second dose reduction).

For liver function toxicity, please also see Section 7.1 as it may indicate potential severe liver injury (possible Hy's Law) and study intervention discontinuation.

Based on the criteria above, a maximum of 2 dose reductions will be permitted. Once the berzosertib dose has been reduced, it should not be re-escalated to the starting dose. If a second Grade 4 nonhematologic toxicity were to recur, treatment will be discontinued. Dose reduction levels are provided in Table 8.

Table 8 Berzosertib Dose Modifications

Dose modifications for Grade 4 hematologic and Grade 3 nonhematologic drug-related AEs	
Starting dose	210 mg/m^2
First dose reduction (1 dose level)	160 mg/m^2
Second dose reduction (2 dose levels)	105 mg/m^2
Dose modifications for Grade 4 nonhematologic drug-related AEs	
Starting dose	210 mg/m^2
First dose reduction (2 dose levels)	105 mg/m^2

AE = adverse event.

In case of hematological toxicity during any cycle, treatment may be interrupted. Prior to initiation of the next cycle, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

In addition, in case of non-hematologic Grade 3 or higher toxicity during any cycle, treatment should be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2; resumption may be at the discretion of the Investigator.

Treatment interruptions due to a study intervention-related AE may occur for a maximum of 21 days.

Participants who develop intolerance to berzosertib may continue on single agent topotecan at the discretion of the Investigator, administered every 3 weeks (on Days 1 to 5) at the same dose administered in combination therapy, until disease progression or other criteria for discontinuation are met (Section 7.1).

6.5.2 Topotecan Dose Modifications

The dose of topotecan may be reduced for drug-related toxicity using the toxicity-dependent guidelines in Table 9 and Table 10. Topotecan dose reductions will be accomplished by decreasing the dose of topotecan for each of the 5 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted. Once the topotecan dose has been reduced, it should not be re-escalated to the starting dose.

Table 9 Topotecan Dose Modifications for Hematologic and Nonhematologic Toxicities

	Topotecan 1st Dose Reduction (mg/m^2)	Topotecan 2nd Dose Reduction (mg/m^2)
Dose Modifications for Hematologic Toxicities		
Toxicity		
Grades 1 and 2	No adjustment	Not applicable
Grades 3 neutropenia persisting after Day 21	1	0.75
Grade 4 thrombocytopenia or Grade 4 neutropenia with fever or infection or of duration ≥ 7 days	1	0.75
Dose Modifications for Nonhematologic Toxicities		
Toxicity		
Grades 1 and 2	No adjustment	Not applicable
Grades 3 and 4 (except Grade 3 nausea)	1	0.75

Table 10 Topotecan Dose Modifications for Renal Function (Regardless of Drug Relationship)

Creatinine Clearance (Cockcroft-Gault Formula)	Topotecan 1st Dose Reduction (mg/m^2)
≥ 60 mL/min	No adjustment
40-59 mL/min	1
20-39 mL/min	0.75
< 20 mL/min	Discontinue

For liver function toxicity, please also see Section 7.1 as it may indicate potential severe liver injury (possible Hy's Law) and study intervention discontinuation.

In case of hematological toxicity during any cycle, treatment may be interrupted. Prior to initiation of the next cycle, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

In addition, in case of non-hematologic Grade 3 or higher toxicity during any cycle, treatment should be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2; resumption may be at the discretion of the Investigator.

Treatment interruptions due to a drug-related AE may occur for a maximum of 21 days.

Participants who develop intolerance to topotecan may continue single agent berzosertib at the discretion of the Investigator, administered weekly (on Days 2 and 5 of 21-day cycles) at the same dose administered in combination therapy, until disease progression or other criteria for discontinuation are met (Section 7.1).

6.6 Continued Access to Study Intervention after the End of the Study

The Sponsor will **not** provide any additional care to participants after they leave the study (outside of potential continued treatment as described in Section 4.4) because such care would not differ from what is normally expected for patients with advanced solid tumors.

6.7 Treatment of Overdose

For this study, any dose of berzosertib or topotecan greater than 10% over the planned daily dose included in this study protocol or planned for an individual participant enrolled in the study will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose. The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Even if not associated with an AE or a serious adverse events (SAE), any overdose is recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4.

6.8 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.8.1 Rescue Medicine

There is no specific treatment or medicine available to counteract the inhibition of ATR intended by berzosertib or topotecan. For any unwanted events during treatment with berzosertib and/or topotecan, the oncological standards in supportive care should be applied.

6.8.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Permitted premedications are described in Section 6.1.

6.8.3 Prohibited Medicines

Prohibited concomitant medications during berzosertib treatment are listed in Table 11.

Any inadvertent use of prohibited medications during the Study Intervention Period will be reported as protocol deviations. These will be reviewed by the Sponsor and proportionate action taken. In cases where prohibited medication use is judged to significantly affect the participant's

safety or compromise the study's scientific objectives, study participants will be permanently discontinued from the study.

Participants must not receive concurrent anticancer therapy.

Because berzosertib is primarily metabolized by CYP3A4, inhibitors of CYP3A4 might be expected to decrease berzosertib's clearance and inducers of CYP3A4 might be expected to increase its clearance.

Berzosertib is a substrate of P-gp.

The Investigator should refer to the topotecan summary of product characteristics (SmPC) or Package Insert for guidance on prohibited mediations during treatment.

Table 11 Prohibited Concomitant Medications During Berzosertib Treatment

Restricted Medication/Food	Screening and Treatment Period
Medication: **Strong CYP3A4 inhibitors (Periods 1 & 2)** • Examples of strong CYP3A4 inhibitors include clarithromycin, diltiazem, idelalisib, cobicistat, HIV/HBV/HCV protease inhibitors, itraconazole, ketoconazole, posaconazole, voriconazole and nefazodone. **Moderate CYP3A4 inhibitors (Period 1 only)** • Examples of moderate CYP3A4 inhibitors include Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, isavuconazole (or isavuconazonium), tofisopam, verapamil **P-gp inhibitors (Period 1 only)** • Examples of P-gp inhibitors azithromycin (Zithromax), captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor **Food (Period 1 only)** • Grapefruit, Seville orange, exotic citrus fruits and star fruit or beverages containing these fruits	None allowed within 7 days before the first dose of study intervention and until the permanent discontinuation of berzosertib
Strong CYP3A4 inducers (Periods 1 & 2) • Examples of strong CYP3A4 inducers include apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin and St. John's wort. **Moderate CYP3A4 inducer (Period 1 only)** • Examples of moderate CYP3A4 inducers Bosentan, Efavirenz, Modafinil, Nafcillin, Rifabutin	None allowed within 4 weeks prior to the first dose of study intervention and until the permanent discontinuation of berzosertib

CYP3A4 = cytochrome P450 3A4; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P-gp = P-glycoprotein.

6.8.4 Other Interventions

Radiation therapy is allowed on this study for palliative treatment e.g., for lesions that cause symptoms that cannot be adequately controlled by other means e.g., analgesics; however, the use of radiation therapy during the Study Intervention Period should be discussed with the Medical Monitor on a case by case basis considering the influence on imaging assessments of target/nontarget lesions.

In addition, the Investigator should ensure that tumor assessments are recently obtained and reported as per RECIST 1.1, before initiation of radiation therapy. Berzosertib and topotecan should be withheld at least 1 day before the administration of radiation therapy; both interventions can be resumed after radiation therapy is completed, provided the participant has recovered from potential radiation therapy toxicities (Grade < 2 or back to baseline) and will derive benefit from resuming study treatment, as assessed by the Investigator. In case whole brain radiation therapy is administered, a wash-out period of ≥ 14 days is required before resuming study treatment.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety, 30 days after the last dose of study intervention. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants will be withdrawn from study intervention for any of the following reasons:

- A participant may withdraw from the study intervention at any time at his/her own request, and without giving a reason. The participant will continue follow-up, unless consent to study was withdrawn as well
- Upon documentation of disease progression per RECIST 1.1
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgment of the Investigator
- Unequivocal clinical progression
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- Pregnancy
- Liver injury:

  The Investigator will consider discontinuation of study intervention for abnormal liver function when a participant meets 1 of the conditions outlined in the algorithm or if the Investigator believes that it is in best interest of the participant.

- All events of ALT or AST > 8 × ULN
- All events of ALT or AST > 5 × ULN for more than 2 weeks
- All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT > 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

These may indicate potential severe liver injury (possible Hy's Law) and will be reported as a SAE.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records and the eCRF and inform the Sponsor. The samples will be destroyed.
- Additional participants must be enrolled for each participant who withdraws from the study after signing consent and successfully meeting entry criteria but did not receive study intervention.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.

- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- No more than 400 mL of blood may be drawn in a 2-week period.

  Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the Clinical Study Report (CSR).

  The long-term storage of samples after study completion for future research may be performed with all sample types collected in the study (e.g., PK or pharmacogenomics) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Radiographic images and clinical findings (such as physical assessments and biopsies) will be used by the Investigators for the local determination of disease progression and participant treatment decisions.

Participants will have a chest/abdomen/pelvis imaging scan (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) and, if clinically indicated, imaging scans of other body areas (e.g., neck) or other modalities (e.g., bone scan, positron emission tomography-CT [PET-CT]). A brain scan with contrast (MRI [preferred] or CT, with contrast) should be performed as clinically indicated. Participants should have a repeat imaging scan as described in the SoA in Section 1.3. All imaging scans to assess disease progression should be performed using similar CT/MRI platforms and imaging techniques, including the use or absence of

contrast, and should be of consistent anatomic locations with prior imaging scans, whenever possible.

Imaging scans will be locally read, and the Investigator should continue treatment administration until progressive disease (PD). The applicable overall response category for each visit that includes disease assessment, based on evaluation of imaging scan, will be recorded in the eCRF. Determination of participant study disposition (i.e., discontinuation or extension of therapy) will be based on disease progression as interpreted from the local evaluation of the imaging scan.

Tumor assessments per protocol will be performed until PD or start of subsequent anticancer treatment, whichever comes first, regardless of study intervention discontinuation.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.

8.2.1 Physical Examinations

Physical examinations will be performed and the ECOG PS should be recorded according to the SoA (Table 1 and Table 4). Symptom-directed physical examinations may be performed as clinically indicated per Investigator's judgment.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcB or QTcF.

- ECGs will be recorded after 5 minutes of rest.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the SoA. All samples will be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of the relevant systemic exposure of the study intervention plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1 (Inclusion Criteria).
- Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and a SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or Clinical Research Organization (CRO)-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3). Beyond this reporting period, any new

unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 4.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and file it in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 6 months after the last study intervention dose.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable for cardiovascular events.

For death events refer to Appendix 4 for more information.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with advanced solid tumors and can be serious/life threatening:

- Progressive disease

Because PD is typically associated with the disease under study, it will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the applicable eCRF page.

However, if either of the following conditions applies, then the event will be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.7 Adverse Events of Special Interest

No AEs of special interest have been identified.

8.4 Pharmacokinetics

Whole blood samples of approximately 12 to 24 mL will be collected at each time point for measurement of whole blood (total radioactivity) and plasma concentrations of total radioactivity, and berzosertib and metabolite profiling and identification (MetID). Collection times are specified in the SoA and Table 2. Details of timepoints and required blood volumes will be captured in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Urine and feces samples for measurements of concentrations of total radioactivity, berzosertib (urine only) and for metabolic profiling will be collected as specified in the SoA (Table 3). The actual start and end date and time (24-hour clock time) of each urine and feces fraction as well as the volume (urine) and the weight (feces) of each collection fraction will be recorded. The accepted time deviations from planned whole blood and plasma sampling times that will not be considered a protocol deviation are listed in Table 2.

The quantification of berzosertib in plasma and urine, will be performed using validated assay methods. In addition, known berzosertib metabolites may be measured and samples will be used for metabolic profiling. Concentrations will be used to evaluate the PK of study intervention and TR (and metabolites, if applicable).

Remaining samples collected for analyses of berzosertib, metabolite profiling and TR concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF, according to local regulations.

The following PK parameters will be calculated for berzosertib 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 (t_{last}) 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 t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred}/\lambda_z$
$AUC_{0\text{-}t}$	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.
C_{max}	Maximum observed concentration.
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. $t_{1/2} = \ln(2)/\lambda_z$
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification.
V_Z (berzosertib only)	The volume of distribution during the terminal phase following intravenous administration. $V_Z = Dose/(AUC_{0\text{-}\infty} * \lambda_z)$.
Vss (berzosertib only)	An estimate of the volume of distribution at steady-state based on the last predicted concentration, calculated as CL * MRTiv.

Symbol	Definition
MRT_{iv} (berzosertib only)	The mean residence time extrapolated to infinity, calculated as ($AUMC_{0-\infty}/AUC_{0-\infty}$)-T/2, where T is the infusion duration.

The following PK parameters will be calculated for berzosertib (urine only) and total radioactivity in urine and feces, when appropriate:

Symbol	Definition
$Ae_{t1\text{-}t2,\ urine}$	Amount excreted in urine between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.
$Ae_{t1\text{-}t2,\ feces}$	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. $CL_R = Ae_{0\text{-}t\_urine}/AUC_{0\text{-}t}$
fe (%) (berzosertib only)	Percent of dose excreted as an unchanged berzosertib in urine.
$fe_{t1\text{-}t2,\ urine}$ %	Fraction of administered drug that is excreted in urine between times t1 (= start) and t2 (= end), calculated per collection interval and cumulative.
$fe_{t1\text{-}t2,\ feces}$ %	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.

Free fraction (%unbound) of berzosertib in plasma may be summarized by time points and pool of time points as permitted by the data. In case vomitus is collected, total radioactivity will be assayed and results listed. Details will be provided in the Integrated Analysis Plan (IAP).

Additional PK parameters may be calculated, if appropriate. Methodology for the calculation of PK parameters will be detailed in the IAP.

CCI [redacted]

[redacted]

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Medical Resource Utilization and Health Economics

Not applicable.

9 Statistical Considerations

This section outlines the statistical analysis strategy and procedures for the study. Full details of all planned analyses will be described in the study IAP.

9.1 Statistical Hypotheses

The statistical analysis of study data will be purely descriptive; no hypothesis tests will be performed.

9.2 Sample Size Determination

A total of approximately 6 participants (or more) will be treated with study intervention such that approximately 4 to 6 PK evaluable participants are anticipated to be obtained. If the initial group of 6 leads to fewer than 4 evaluable participants, the cohort will be increased up to a maximum of 12 participants, until 4 participants have completed all study procedures for Period 1 and are evaluable.

The decision to enroll additional participants will be taken on a case-by-case basis, in agreement between the Sponsor and the Investigator.

For participants who experience emesis during the first 48 hours after the end of [^{14}C]berzosertib administration, the vomitus should be collected as much as possible and assayed for total radioactivity.

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.

9.3 Analyses Sets

The analysis sets are specified below.

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
FAS / SAF	All participants, who were administered any dose of any study intervention.
PKAS	The PKAS is a subset of the SAF and will consist of all participants, who receive the single dose of study intervention in Period 1 and provide at least one measurable post-dose concentration. A measurement BLQ is considered a valid measurement. All PK analyses will be based on this analysis set.

BLQ = below lower limit of quantification; FAS = Full Analysis Set; PK = pharmacokinetic; PKAS = Pharmacokinetics Analysis Set; SAF = Safety (Analysis Set); SCR = Screening (Analysis Set)

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS® System (release 9.2 or later version; SAS Institute, Cary NC, US), or R (R Core Team, 2020. R: A Language and Environment for Statistical Computing, Vienna, Austria. https://www.R-project.org/). More details on the statistical analyses will be presented in the IAP prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

The statistical analysis will not be started until all data have been cleaned and checked for plausibility, and until all necessary coding and assessments have been completed.

All data recorded during the study will be presented in individual data listings.

All data will be evaluated as observed, no imputation method for missing values. The handling of concentration values below the limit of quantification will be described in the IAP.

9.4.1 Efficacy Analyses

All analyses on efficacy estimands will be conducted on the Full Analysis Set (FAS). The estimands framework is used in Table 12.

Table 12 Efficacy Analyses and Estimands (Period 2)

Endpoint	Statistical Analysis Methods/Further Estimand Attributes
CCI	
Objective Response	**Endpoint:** Objective Response according to RECIST 1.1 as assessed by the Investigator **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 • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set (SAF).

Medical history and AE terms will be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) (Version 23.0 or later); concomitant medication will be coded with World Health Organization (WHO) Drug Dictionary, WHO Drug Reference List and Anatomical Therapeutic Chemical Classification System, latest versions. Versions of dictionaries used for coding will be defined in the Data Management Plan.

The on-treatment period is defined as the time from first study intervention to the last study intervention date + 30 days.

Table 13 Safety Endpoints

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	
AEs	The definitions, procedures for recording, evaluating, follow-up, and reporting of AEs are described in Appendix 4. AEs will be coded according to the latest available version of the MedDRA. Missing classifications concerning study intervention relationships will be considered related to the study interventions. Analysis will be based on TEAEs, which are events with onset dates during the on-treatment period, or events with onset dates before the on-treatment period and worsening during the on-treatment period. The following TEAEs will be presented in summaries by incidence and type according to MedDRA SOC and Preferred Term: • TEAEs • TEAEs related to study interventions. The following AEs will be listed: • SAEs • NCI-CTCAE Grade ≥ 3 TEAEs

Endpoint	Statistical Analysis Methods
	• TEAEs leading to dose modification or temporary/permanent interruption of study interventions • TEAEs leading to death.
Deaths	Death and primary reason for death will be listed.
Laboratory Values	Baseline values are defined as the last value prior to first administration of study intervention in the respective period. Only on-treatment values will be summarized. Laboratory values will be graded using NCI-CTCAE (Version 5.0), if applicable. Non-gradable parameters will be classified as normal, high, or low. Summary statistics for: • Absolute values • Change from baseline (Period 2 only; baseline is the Day 1 pre-dose value in each cycle) • Worst on-treatment grade (Period 2 only)
Vital Signs	• Summary statistics for baseline and on-treatment values
ECGs	• Summary statistics of all measurements by scheduled time point
Tertiary/Exploratory	Not applicable

AEs = adverse events; ECGs = electrocardiograms; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

9.4.3 Other Analyses

Baseline characteristics will be analyzed on the SAF. Summary statistics will be provided as described for continuous/categorical variables in Section 9.4.

For demographic (e.g., age, sex, race, etc.), 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, the first and third quartile [Q1 and Q3], minimum [Min], and maximum [Max]) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

Analysis of Pharmacokinetics

PK parameters (e.g. C_{max}, AUC, $t_{1/2}$, CL, V_z, and V_{ss} of berzosertib and C_{max}, AUC, $t_{1/2}$ of total radioactivity in plasma; C_{max}, AUC, $t_{1/2}$ of total radioactivity in blood) will be calculated using noncompartmental methods based on the actual sampling times, listed and tabulated with descriptive statistics. The noncompartmental analysis will be outsourced under the supervision of the Sponsor and will be performed by PRA – Early Development Services (EDS) using Phoenix® WinNonlin® version 8.1 or higher (Certara, L.P., Princeton, NJ, 08540 US). Individual plasma concentrations of berzosertib and radioactivity, and amounts excreted in urine/feces will be tabulated using the nominal sampling times with descriptive statistics at all time points. Excretion of total radioactivity will be calculated based on the administered radioactive dose and the relative amount of radioactivity recovered in urine and feces. Graphical displays will be produced where appropriate.

Details on the PK analyses will be in the IAP that will be finalized before database lock.

9.4.4 Sequence of Analyses

After all participants have completed Period 1, the primary report for the study will be generated once all data queries are resolved, and the primary database will be soft-locked for Period 1. The primary analysis will include all data collected in Period 1 and all planned analyses identified in the Clinical Study Protocol, in particular the analysis of the mass balance data. Data from Period 2 will be added to the report as an addendum, upon end of study as described in Section 4.4, with all study data in-house, all data queries resolved, and the database locked.

10 References

Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020;21:957-68.

Thomas A, Redon CE, Sciuto L, et al. Phase I study of ATR inhibitor M6620 in combination with topotecan in patients with advanced solid tumors. J Clin Oncol. 2018;36(16):1594-602.

Thomas A, Takahashi N, Rajapakse VN, et al. Therapeutic targeting of ATR yields durable regressions in small cell lung cancers with high replication stress. Cancer Cell. 2021;39:566-79.

11 Appendices

Appendix 1 Abbreviations

AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related
BCRP	Breast Cancer Resistance Protein
β-HCG	β-human chorionic gonadotropin
BLQ	Below lower limit of quantification
BOI	Beginning of infusion
C	Cycle
CIOMS	Council for International Organizations of Medical Sciences
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome P450
D	Day
DDI	Drug-drug interaction
DDR	DNA damage response
CCI	[redacted]
DRE	Disease-related events
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDS	Early Development Services
EMA	European Medicines Agency
EOI	End of infusion

EORTC	European Organization for the Research and Treatment of Cancer
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRT	Hormonal replacement therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LAM	Lactational amenorrhea method
MedDRA	Medical Dictionary for Regulatory Activities
MetID	Metabolite identification
MIST	Metabolites in Safety Testing
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Noninvestigational Medicinal Product
OATP	Organic anion-transporting polypeptide

PD	Progressive disease
PET-CT	Positron emission tomography computed tomography
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetics Analysis Set
PR	Partial response
PRA	PRA Health Sciences
QTL	Quality Tolerance Limit
RECIST 1.1	Response Evaluation Criteria in Solid Tumor Version 1.1
SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis Set
SCLC	Small Cell Lung Cancer
SCR	Screening (Analysis Set)
SD	Stable disease; standard deviation
SmPC	Summary of product characteristics
SoA	Schedule of Activities
SoC	Standard of care
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent Adverse Event
TR	Total radioactivity
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally-authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- Participants who are rescreened are required to sign a new ICF (see Section 5.4 for details).

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.
- Certain tasks listed above can be delegated to PRA

Study Administrative

The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical

input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

Details of structures and associated procedures will be defined in a separate Project Management Plan.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator, or other relevant study-appointed committees or groups. This task may be delegated to PRA.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Study results will be shared with study participants
- Merck-sponsored study information and tabular study results will be published on www.ClinicalTrials.gov once the drug is approved or the program has been terminated, whichever occurs first.

Data Quality Assurance

- All participant study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF. Details for managing eCRFs are in the Data Management Plan.
- The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Quality Tolerance Limits (QTLs) will not be pre-defined in this study because of the impracticality of applying QTLs in the limited number of planned participants in this trial.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and

monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.

- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the eCRFs.
- Data recorded on eCRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the eCRF guidelines.

Study and Site Start and Closure

The study start date is when the first participant signs the ICF.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

- Discontinuation of further development of the Sponsor's compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
- A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for the his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

All pregnancies occurring during the study and their outcome will be documented on the Pregnancy report form and Parent-Child/Fetus Adverse Event Report form as outlined in Section 8.3.4.

Overdoses associated with an AE or a SAE are recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses not related to an AE/SAE (without signs or symptoms) are recorded in eCRF on treatment forms and are reported to Drug Safety using SAE paper form.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- As needed, Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor/designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the eCRF Completion and Monitoring Conventions.

Assessment of Intensity

Investigators will reference the NCI-CTCAE, Version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours. This applies for this study.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.
- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard eCRF and as a back-up method for an electronic data capture (EDC) system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the eCRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the eCRF.

Reporting of Adverse Events of Special Interest

Not applicable; no adverse events of special interest have been identified.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 6 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

Table 14 Clinical Laboratory Assessments

Laboratory Assessments[1]	Parameters			
Hematology	Platelet count		MCV	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		MCH	
	Hematocrit			
Coagulation	Prothrombin time/INR		Activated partial thromboplastin time	
Biochemistry[2]	BUN or Urea[3]	Potassium	Aspartate aminotransferase	Bilirubin (i.e., total) Direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Protein[4]
	Glucose	Calcium	Alkaline phosphatase	Albumin Magnesium Phosphate
Notes: 1 Laboratory assessments, e.g. hematology, chemistry, etc., will be performed locally. 2 Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. 3 Urea can be performed only when BUN cannot be done; the same test should be performed consistently for each participant for the duration of the study. 4 A measurement of the total protein.				
Other Screening Tests	• FSH and estradiol (as needed if not a woman of childbearing potential only). • Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential). • Covid 19 PCR testing will be performed at D-1 during Period 1. • Urine cotinine testing will be performed at Screening and at D-1.			

BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PCR = polymerase chain reaction

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Appendix 8 Protocol Amendment History

Not applicable

Appendix 9 Sponsor Signature Page

Study Title:	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
Regulatory Agency Identifying Number:	EudraCT: 2021-002226-24
Clinical Study Protocol Version:	15 June 2021/Version 1.0

I approve the design of the clinical study:

PPD

Signature

18JUN2021

Date of Signature

Name, academic degree:	PPD, MD
Function/Title:	PPD
Institution:	PPD, Merck KGaA
Address:	PPD
Telephone number:	PPD
E-mail address:	PPD

Appendix 10 Principal Investigator Signature Page

Study Title:	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
Regulatory Agency Identifying Number:	EudraCT: 2021-002226-24
Clinical Study Protocol Version:	15 June 2021/Version 1.0
Site Number:	001 and 002

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD PPD
Function/Title: Principal Investigator, PPD

Institution: PPD

Address:

Telephone number:
Fax number:
E-mail address: