Clinical Study Protocol

Clinical Study Protocol Number	MS201923-0007
Title	A Rollover Study to Provide Continued Treatment with M6620
Phase	I
IND Number	Not applicable
EudraCT Number	2017-002354-37
Coordinating Investigator	PPD Telephone: PPD Fax: PPD E-mail: PPD
Sponsor Name and Legal Registered Address	Merck KGaA Frankfurter Str. 250, 64293 Darmstadt, Germany **Medical Responsible:** PPD General Merck Phone Number: PPD General Merck Fax Number: Not Applicable
Clinical Study Protocol Version	01 March 2021 / Version 4.0
Replaces Version	17 November 2020 / Version 3.0

- Confidential –

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	17 Aug 2017
2.0	Global	18 Sep 2017
3.0	Global	17 Nov 2020
4.0	Global	01 Mar 2021

Protocol Version 4.0 (01 March 2021)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union: because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The purpose of this amendment is to provide the correct Sponsor name.

Section # and Name	Description of Change	Brief Rationale
Cover Page and Synopsis	Sponsor name modified to: Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany	To provide correct Sponsor name

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List of Abbreviations

AE	Adverse event
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related protein
ATRi	Ataxia telangiectasia mutated and Rad3-related protein inhibitor
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
EDC	Electronic data capture
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DDR	DNA damage response
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	Ionizing radiation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

1 Synopsis

Clinical Study Protocol Number	MS20193-0007
Title	A Rollover Study to Provide Continued Treatment with M6620
Study Phase	I
IND Number	Not applicable
FDA covered study	No
EudraCT Number	2017-002354-37
Coordinating Investigator	PPD
Sponsor	Merck KGaA Frankfurter Str. 250, 64293 Darmstadt, Germany
Study sites/countries	The number and nature of the study sites will be determined by the actual need. At the time of initiation of this protocol, it is expected that participants from a single site in the UK will enter this Safety Follow Up study.
Planned study period (first participant in-last participant out)	Estimated 5 years
Trial Registry	EudraCT

Objective:

Primary Objective:

- To monitor the safety of participants who are on long-term treatment with M6620 (berzosertib).

Methodology: This clinical study enables further treatment with M6620 (referred to as berzosertib henceforth) and safety follow up of participants from Vertex clinical study VX13-970-002, that was terminated. Therefore, this is a multicohort study not requiring any study committees. Participants enrolled in the Merck KGaA-sponsored rollover study will continue treatment with berzosertib on the same dose and schedule as the original study. Participants receiving combinations of berzosertib with other drugs in the study from which the participant is transitioned will continue to receive the same combination drugs in this Safety Follow Up study. Combination drugs will be obtained from the local study site pharmacy. The participants will complete a Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib.

Planned number of participants: This is a rollover study to allow the participants to continue their treatment. Therefore no sample size considerations were undertaken.
Primary endpoints: Occurrence of adverse events (AEs) and treatment-related AEs in participants receiving berzosertib, graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) (Version 4.03).
Secondary endpoints: Not applicable.
Pharmacokinetics: Not applicable.
Diagnosis and key inclusion and exclusion criteria: Participants on ongoing treatment with berzosertib either as monotherapy or in combination with other drugs at the time of transitioning will be enrolled in this study.
Study Intervention: dose/mode of administration/dosing schedule: Berzosertib CCI [redacted] mode of administration: intravenous infusion after dilution in CCI [redacted] before intravenous infusion. Dosage and schedule will be diverse, depending on the details of treatment in the study from which the participant transitioned. Participants will continue receiving treatment at the same dosage and according to the same schedule from which the participant transitioned.
Reference therapy: dose/mode of administration/dosing schedule: Not applicable.
Planned study and treatment duration per participant: Participants can continue treatment until disease progression or unacceptable toxicity is reported. The End of Study is defined by the completion of a Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib.
Statistical methods: CCI [redacted] Safety: All safety data summaries will be based on the safety analysis set. Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE (Version 4.03) toxicity grades. Adverse events will be summarized by frequency and incidence using MedDRA. Safety data measurements will be summarized by dose group and/or time point using descriptive statistics for observed values and change from baseline values (as appropriate).

Table 1 Schedule of Assessments for Participants Transitioned from Part A1: Single Agent Therapy once weekly

Event/Assessment[a]	Enrollment	Treatment Cycle (21 days)			Follow Up[b]
		Day 1	Day 8	Day 15	28 (+7) days after last administration
Safety Assessment					
Informed consent	X				
Demographic and other Baseline Characteristics	X				
Concomitant medication/AEs	Continuous from signing Informed Consent Form through Safety Follow Up visit				
Study Intervention Administration					
Berzosertib dosing		X	X	X	

AE = Adverse event

a Physical examination, weight, vital signs, serum chemistry, hematology and urinalysis will be measured as per Standard of Care and institutional guidelines and as clinically indicated; only clinically significant values should be reported as AEs.

b Follow Up will include a Safety Follow Up Visit to be scheduled 28 (+7) days following the last administration of berzosertib.

2 Sponsor, Investigators and Study Administrative Structure

This clinical study will be sponsored by Merck KGaA (Darmstadt, Germany).

The number and nature of study sites will be determined by the actual need. It is expected that participants from a single site in the UK will enter this Safety Follow Up study. Further sites and countries may be added via amendment(s) to this protocol in the future if new demand for participants transitioning into this transition rollover study emerges.

The Coordinating Investigator will provide expert medical input and advice relating to study design and execution and is responsible for the review and signoff of the clinical study report.

Signature pages for the Medical Responsible and Coordinating Investigator are in Appendix II.

The study will appear 12 months after the last clinical visit of the final study participant, or another appropriate date to meet applicable requirements, in the following clinical trial registry: EudraCT.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Study Leader.

3 Background Information

Chemotherapeutic agents and ionizing radiation 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 DNA damage response (DDR) pathway regulated by the kinases ataxia telangiectasia mutated (ATM) and ataxia telangiectasia mutated and Rad3-related protein (ATR). In many malignant cells, ATR assumes a crucial role in protecting cancer cells from DNA damage and from subsequent cell death after chemotherapy and ionizing radiation (IR). A reliance on ATR can arise from expression of oncogenes that drive deregulated proliferation and high levels of replicative stress or from defects in ATM/p53 signaling. Thus, small molecule-mediated inhibition of ATR should enhance the effect of IR and DNA damaging chemotherapy on cancer cells.

Vertex Inc (Boston, MA, USA) developed a selective inhibitor of ATR protein (Vertex code VX-970). Merck KGaA acquired the rights for this compound and will continue the development. The Vertex study intervention, VX-970, will be referred to as berzosertib when used in this and future clinical studies.

Berzosertib is a potent, selective first-in class inhibitor of ATR. Inhibition of ATR enhances the cytotoxic effect of DNA damaging drugs and IR in several cancer cell line derived xenografts and primary patient-derived tumors xenografts. In contrast, normal cells seem to tolerate ATR inhibition since they can activate compensatory DDR signaling via the ATM/p53 pathway. In xenograft models, berzosertib markedly enhances the anticancer activity of numerous DNA damaging drugs and IR, often substantially delaying or completely halting tumor progression and promoting tumor regression.

Consistent with the compensatory role of the ATM/p53 pathway in response to ATR inhibition in normal cells, defects in this pathway result in increased cell sensitivity to ATR inhibition. In isogenic cell studies it has been shown that loss of ATM or of its principal substrate p53, can markedly increase cell sensitivity to ATR inhibition. Similarly, in a large panel of 119 genetically diverse cancer cell lines, TP53 mutational status was shown to correlate with response to ATR inhibition in combination with DNA damaging agents.

In nonclinical experiments, ATR inhibition by berzosertib has been shown to enhance the anticancer effects of DNA damaging agents, such as cisplatin and gemcitabine, and has been shown to exhibit activity as a single agent in a limited set of tumor lines.

Study VX13-970-002 was a Phase I clinical study initiated by Vertex studying berzosertib. For the initial dose escalation period (Parts A1, A2, B1, and B2), eligible participants had advanced stage solid tumors that have progressed through at least 1 line of therapy and had no approved treatment options. Early signs of clinical efficacy were observed in participants receiving berzosertib in the Vertex clinical study VX13-970-002. At the time of VX13-970-002 study completion, there was a participant from Part A1 still receiving treatment. This participant transferred to Study MS201923-0007 to continue receiving berzosertib.

Refer to the current berzosertib Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the Investigator.

These clinical studies were conducted in compliance with the clinical study protocol and International Council for Harmonisation (ICH) Good Clinical Practice (GCP; hereafter referred to as ICH GCP) and any additional applicable regulatory requirements.

3.1 Study Rationale

This study is designed to provide continuous access to treatment with berzosertib for eligible participants from Vertex clinical study VX13-970-002 (parent study), and to collect long-term safety data. Additional participants may be added via amendment(s) to this protocol in the future if new demand for participants transitioning into this rollover study emerges.

4 Study Objectives

4.1 Primary Objective

- To monitor safety of participants that are on long-term treatment with berzosertib.

4.2 Secondary Objectives

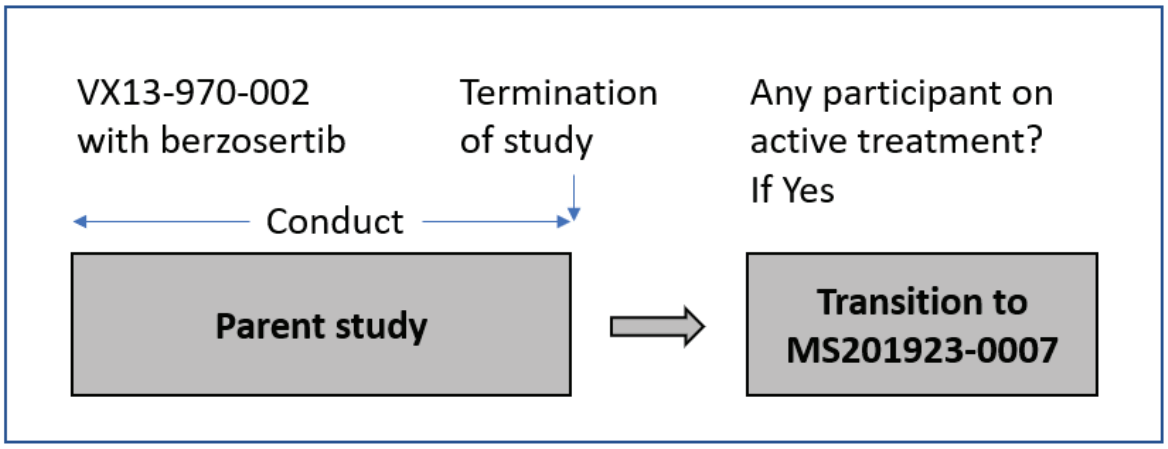
None.

5 Investigational Plan

5.1 Overall Study Design and Plan

Participants from the Vertex clinical study VX13-970-002 still on active berzosertib treatment at the time of termination/transition may be enrolled in the Merck KGaA-sponsored study and continue treatment with berzosertib as monotherapy or in combination with other drugs and be monitored for safety. A schematic of the study design is presented in Figure 1. A schedule of study procedures/assessments is provided in Table 1.

Figure 1 Study design diagram of ATR inhibitor Transition Rollover Study



Participants enrolled in the Merck KGaA-sponsored rollover study will continue treatment on the same dose and schedule as the original study, and will be monitored for safety as specified in Table 1. The participants will complete a Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib. Participants who transferred from combination treatment to berzosertib monotherapy before enrollment in this study should continue accordingly.

5.2 Discussion of Study Design

This will be a multicohort Safety Follow Up study. Participants will be transitioned from Vertex clinical study VX13-970-002. The participants will continue treatment on the same dose and schedule as the original study after being transitioned. The number and nature of the cohorts will be determined by the treatments in the studies from which participants are transitioning.

5.2.1 Scientific Rationale for the Study Design

To continue treatment and monitoring of safety of participants who are on treatment with berzosertib in a study at the time when that study is to be terminated.

5.2.2 Justification for Dose

Participants in this rollover study will continue to receive the dosage of berzosertib and any other study intervention(s) that are being used in the study from which they transitioned. In case of a dose/schedule modification in the previous study, participants will continue on the modified dose/schedule.

5.2.3 Rationale for Endpoints

This will be a study to monitor the safety of participants who are on long-term treatment receiving berzosertib either as monotherapy or combination treatment. Therefore, no other endpoints beyond safety monitoring are required.

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Study Population

Only participants that are ongoing with treatment in the Vertex study VX13-970-002 may be enrolled into this study. Participants will be transitioned from the VX13-970-002 study to enable them to continue treatment with berzosertib. Prior to performing any study assessments not part of the participant's routine medical care, the Investigator will ensure that the participant or the participant's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

- Ongoing treatment in Vertex clinical study VX13-970-002 (parent study)
- Participant must be able to understand and provide written informed consent
- Participant must be willing and able to comply with the scheduled visits, treatment plan, lifestyle, laboratory tests, contraceptive guidelines (as described in Appendix I), and other study procedures.

5.3.2 Exclusion Criteria

- Participants experiencing disease progression or unacceptable toxicity at the time of transition from the VX13-970-002 study into the Safety Follow Up study.

5.4 Criteria for Initiation of Study Treatment

Participants will continue the treatment with berzosertib as monotherapy or in combination with other study interventions as administered in the VX13-970-002 study.

5.5 Criteria for Participant Withdrawal

5.5.1 Withdrawal from Study Therapy

A participant must be withdrawn from study treatment if any of the following occur in this Safety Follow Up study:

- Participant withdraws consent
- Participant is reported to have disease progression or unacceptable toxicity
- Participation in another clinical study
- Any events that unacceptably endanger the safety of the participant
- Protocol noncompliance (to be discussed on a case-by-case basis with the Sponsor).

5.5.2 Withdrawal from the Study

Participants may withdraw from the study at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the study.

A participant must be withdrawn if any of the following occur during the study:

- Participant withdraws consent
- Participant is lost to follow up
- Participation in another clinical study.

5.6 Premature Termination of the Study

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for berzosertib. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons or because of discontinuation of clinical development of berzosertib. In case of termination of the study, the Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.7 Definition of End of Study

This rollover study will be ongoing while any participant is receiving berzosertib. The end of the study will be the day when the last participant has completed the Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib.

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

6 Study Intervention

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Description of Study Intervention

Study intervention dosing and schedule for participants in this rollover study will be identical to the dosing and schedule of the study intervention(s) received in the study from which the participant transitioned. This implies that participants receiving combinations of berzosertib with any other drugs in the study from which the participant is transitioned will continue to receive the same study interventions in this Safety Follow Up study.

The study intervention (berzosertib) administered in this study will be supplied and distributed by the Sponsor or designee. Combination drugs will be obtained from the local pharmacies.

Berzosertib will be supplied as CCI [redacted] to be diluted in CCI [redacted] before intravenous infusion.

6.2 Dosage and Administration

Dosage and schedule of berzosertib administration will depend on the details of treatment in the VX13-970-002 study from which the participant transitioned.

More general recommendations for study intervention administration and management (e.g., details of administration, dose modification for toxicity, missed doses etc.) are given in the

VX13-970-002 protocol from which the participants are transitioning. Details of dose preparation are provided in the Formulation Preparation Instructions (see Appendix III).

The dose of berzosertib will be infused intravenously over 60 minutes (± 10 minutes). If the total volume of the infusion exceeds 600 mL, the infusion time may be extended beyond 60 minutes, as tolerated, but no more than 90 minutes. Details of dose preparation for berzosertib will be provided in the Pharmacy Manual.

Intravenous administration of berzosertib is independent of food intake.

To minimize the possibility of phlebitis, berzosertib should be administered through a large bore catheter into a large caliber peripheral vein. If any participant develops phlebitis or signs or symptoms of inflammation that may progress to phlebitis or that the participant cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein).

6.3 Assignment to Treatment Groups

Participants on active treatment will continue receiving treatment at the same dosage and frequency as in the study the participant transitioned from.

6.4 Concomitant Medications and Therapies

All concomitant medications taken by the participant during the study, from the date of signature of informed consent are to be recorded in the appropriate section of the electronic Case Report Form (eCRF), noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.4.1 Permitted Medicines

Any medications that are considered necessary to protect participant welfare and will not interfere with the study intervention may be given at the Investigator's discretion.

Premedication with hydrocortisone and chlorphenamine and rescue medications may be administered to address anticipated adverse reactions or anticipated emergency situations (see Section 6.4.5).

Antiemetics and supportive therapies will be administered or dispensed to participants according to individual site Standard of Care.

6.4.2 Prohibited Medicines

In vitro drug metabolism studies suggest that berzosertib is a substrate of cytochrome P450 (CYP) 3A, and its systemic exposure may be affected by concomitant medications that are strong CYP3A inhibitors or inducers.

Prior and concomitant medication restrictions during treatment include:

- Grapefruit/grapefruit juice, Seville or blood oranges/marmalade
- Strong CYP3A inhibitors or inducers
- Ototoxic or Nephrotoxic medication for participants receiving carboplatin.

For a more complete list of study prohibited and cautioned medication/food/activity, see Appendix IV.

6.4.3 Other Interventions

Not applicable.

6.4.4 Special Precautions

6.4.4.1 Risk of Phototoxicity

All participants should be advised to avoid prolonged or intense sun exposure, sunlamps, and tanning beds. Use of sunscreen, clothing, and eyewear that decrease sun exposure is recommended.

6.4.4.2 Contraception

Women of childbearing potential and males must use a highly effective method of contraception (i.e., methods with a failure rate of less than 1% per year when used consistently and correctly) as detailed below throughout the study and for 6 months after the last dose of assigned treatment.

All participants must undergo appropriate contraceptive counselling. The Investigator or any skilled representative of the study site should counsel participants on the most effective method(s) for avoiding pregnancy during the study.

Men

Acceptable contraceptive methods must be used from Screening visit through 6 months after last dose of the study intervention, and include the following:

- True abstinence (abstinence of any sexual intercourse, when in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Condom with or without spermicide. In addition, the female partner must use a highly effective contraception method as outlined in Appendix I.
- Surgical sterilisation (vasectomy) with a negative sperm post-vasectomy semen analysis; If the absence of sperm has not been confirmed, men must use a condom and their female partner must use a highly effective contraception method as outlined in Appendix I.

  Men must not donate sperm from Screening visit through 6 months after last dose of the study intervention.

Women of Nonchildbearing Potential

Women in the following categories are not considered women of childbearing potential:

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone (FSH) > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, a follicle-stimulating hormone will be drawn at Screening.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment.

   All other female participants (including participants with tubal ligations and participants who do not have a documented hysterectomy) will be considered to be of childbearing potential.

Women of Childbearing Potential

A highly effective contraception as outlined in Appendix I must be used before start of first dose of study treatment, during the treatment period and for at least 6 months after the last dose of study treatment.

The following contraception methods are not considered to be highly effective birth control methods and must not be used:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods).

6.4.5 Management of Specific Adverse Events or Adverse Drug Reactions

Based on the observations made so far, participants experienced significant physical discomfort, defined variably by diaphoresis, flushing, dyspnea, nausea, diarrhea, change in mental status, and/or hypotension several minutes after administration of their second dose of berzosertib. Investigators may prophylactically premedicate all participants with 200 mg hydrocortisone approximately 60 minutes before infusion, and 10 mg of chlorphenamine approximately 30 minutes before infusion.

6.5 Packaging and Labeling of the Study Intervention

Berzosertib will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.6 Preparation, Handling, and Storage of the Study Intervention

Berzosertib single use vials must be carefully stored at CCI [redacted], in a location with restricted access, and separately from other drugs.

Following dilution of the test material, intravenous bags should be covered to protect from light and stored in the dark.

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor, and the medication should not be used until authorization has been received from the Sponsor. The study interventions must not be used for any purpose other than the study. The administration of the study intervention to participants who have not been enrolled into the study is not covered by the study insurance.

Disposal of the study interventions should be according to local regulations and institutional guidelines.

6.7 Study Intervention Accountability

The Investigator is responsible for ensuring berzosertib accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of study intervention, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Study intervention dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study site study intervention accountability records will include the following:
  - Confirmation of study intervention receipt, in good condition and in the defined temperature range

- The inventory of study intervention provided for the clinical study and prepared at the site
- The use of each dose by each participant
- The disposition of any unused study intervention
- Dates, quantities, batch numbers, vial/kit numbers (as applicable), expiry dates, formulation (for study intervention prepared at the site), and the individual participant study numbers.

The Investigator site should maintain records, which adequately document that participants were provided the doses specified in this protocol, and all study interventions provided were fully reconciled.

Unused study intervention must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed to a different participant.

A Study Monitor will periodically collect the study intervention accountability forms.

After completion of the study, any study intervention distributed to the site but not administered, dispensed to or taken by the participant(s) will be destroyed at the study site. Details will be agreed upon between the Sponsor and the Investigator. All unused medications will be carefully recorded and documented before destruction.

6.8 Assessment of Study Intervention Compliance

Berzosertib will be administered under the direct supervision of the Investigator or designee. For all doses of the study intervention, the number of units administered and missed doses will be recorded in the eCRF. All modifications in study intervention dose or interval between dosing, as well as the reason for modification, will be recorded in the eCRF.

6.9 Blinding

Not applicable.

6.10 Emergency Unblinding

Not applicable.

6.11 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical study protocol or planned for an individual participant enrolled in the study. Even if it does not meet other criteria for a serious adverse event (SAE), any overdose must be recorded in the study medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

For dose modification and toxicity, refer to the Dose Modification for Toxicity section from the VX13-970-002 protocol.

6.12 Medical Care of Participants after End of Study

After a participant has completed the study or has been withdrawn, further treatment will be administered, if required, in accordance with the study site's Standard of Care and generally accepted medical practice depending on the participant's individual medical needs.

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for participants with advanced tumors.

7 Study Procedures and Assessments

7.1 Schedule of Assessments

Prior to performing any study assessments that are not part of routine medical care for the participant, the Investigator will obtain written informed consent as described in Section 9.2.

A detailed Schedule of Assessments is provided in Table 1.

7.1.1 Enrollment

Participants still on active study intervention at the termination/transition of the VX13-970-002 will be enrolled in this Safety Follow Up study.

7.1.2 Treatment

The participant will continue treatment at the same dose and according to the same schedule as in the VX13-970-002 study.

7.1.3 Safety Follow Up

Safety Follow Up will include a Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib. Participants will be treated according to institutional standards of care, including monitoring of disease progression.

7.2 Demographic and Other Baseline Characteristics

At enrollment, the following demographic data will be documented in the eCRF: date of birth, sex (gender), race, and participant identifier from the parent study.

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of the nature, occurrence, and severity of treatment-emergent adverse events (TEAEs).

Physical examination, weight, vital signs, serum chemistry, hematology and urinalysis will be measured as per Standard of Care and institutional guidelines and as clinically indicated; only clinically significant values should be reported as AEs.

A clinically significant value is a result that a clinician would consider to be medically meaningful. Clinically significant values may be more severe than values expected for the participant's condition, age, and gender.

Comprehensive assessment of any apparent toxicity experienced by each participant will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) (Version 4.03), 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 of 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 following 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

According to Sponsor convention, 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 seriousness criteria described below.

If death occurs, the primary cause of death or event leading to death should 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 (for e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the study intervention using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of the study intervention, medical history, concomitant medication, course of the underlying disease, study procedures.

Unrelated: Not reasonably related to the study intervention. The AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. The AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an electrocardiogram [ECG] trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. ("Life-threatening" refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In this clinical study, any late spontaneous abortion, fetal death in utero, ectopic pregnancy, chronic fetal distress, stillbirth, neonatal death, or prematurity-related complication more than is typical for prematurity should be considered as an SAE (see Section 7.4.2).

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

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) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period (as defined in Section 7.4.1.3).

Adverse Events of Special Interest

No adverse events of special interest have been identified.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, whether reported by the participant or observed by the Investigator. Adverse events that are ongoing during transition from the VX13-970-002 study will be recorded at enrollment to ensure the outcome and end date of the AE are captured.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration, onset and resolution dates (and also onset and resolution times when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the participant is initially enrolled in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until 28 days after the last administration of berzosertib.

Any SAE assessed as related to berzosertib must be reported whenever it occurs, irrespective of the time elapsed since the last administration of berzosertib.

7.4.1.4 Procedure for Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system. Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow up information) may be reported by telephone; in these cases, an electronic SAE form must be completed immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial

reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow up will usually be made via the Study Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/ Suspected unexpected serious adverse reaction/ Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Participants with Adverse Events

Adverse events are recorded and assessed continuously throughout the study (see Section 7.4.1.3) and are assessed for final outcome at Safety Follow Up visit to be scheduled 28 (+7) days after the last administration of berzosertib. All SAEs ongoing at the Safety Follow Up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow up". Reasonable attempts to obtain this

information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female participants and to pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the course of the study, the participant must be discontinued from study medication immediately. The Sponsor/designee must be notified without delay and the participant must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected as per Standard of Care and institutional guidelines and as clinically indicated; only clinically significant values should be reported as AEs.

Laboratory assessments are summarized in Table 2.

Table 2 Laboratory Assessments

Hematology	White blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, neutrophils (absolute and percentage), lymphocytes (absolute and percentage), monocytes (absolute and percentage), eosinophils (absolute and percentage), basophils (absolute and percentage)
Biochemistry	Sodium, potassium, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatine kinase, gamma-glutamyl transferase, lactate dehydrogenase, albumin, calcium, phosphate, glucose, total bilirubin, total protein, cholesterol, triglycerides, uric acid, chloride
Urinalysis	Leukocytes, protein, bilirubin, urobilinogen, ketones, red blood cells, pH, nitrite, specific gravity, glucose, microscopy when indicated by abnormal dipstick results

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs will be measured as per Standard of Care and institutional guidelines and as clinically indicated.

7.4.4.2 Physical Examination

Physical examinations will be performed as per Standard of Care and institutional guidelines and as clinically indicated. Symptom directed physical examinations will be performed as clinically indicated at the Investigator's judgment.

7.5 Pharmacokinetics

Not applicable.

7.6 Biomarkers

Not applicable.

7.7 Other Assessments

Not applicable.

8 Statistics

CCI [redacted]

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

- Occurrence of AEs and treatment-related AEs in participants receiving berzosertib, graded according to NCI-CTCAE (Version 4.03).

8.3.2 Secondary Endpoints

Not applicable.

8.4 Analysis Sets

For the purposes of analysis, the following populations are defined:

Enrolled analysis set: All participants who sign informed consent for this study.

Safety analysis set: All participants who receive at least 1 dose of study intervention in this study. Participants will be analyzed according to the actual treatment they receive.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Continuous measurements will be summarized by means of descriptive statistics (i.e., number of observations (n, both available and missing), mean, standard deviation, minimum, median, maximum), and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

If not otherwise specified, "Baseline" refers to the last available measurement before administration of the first study intervention for each dose group from the VX13-970-002 study, as appropriate.

Depending on the number of participants enrolled, no summary statistics will be provided, and the data will be presented in listings only. Details will be provided in the Integrated Analysis Plan.

8.5.2 Analysis of Primary Endpoints

All safety data summaries will be based on the safety analysis set by dose group as from the VX13-970-002 study.

Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE

(Version 4.03) toxicity grades. Adverse events will be summarized by frequency and incidence using MedDRA.

Treatment-emergent adverse events (after transition) are defined as AEs that were reported or worsened after signing the Informed Consent Form of this rollover study up to the Safety Follow Up visit (28 [+7] days after the last administration of berzosertib).

Only TEAEs will be summarized in the tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study intervention. Some rules that will apply to the summarization of AEs are:

- A participant with multiple occurrences of the same AE or continuing AEs will only be counted once
- Only the maximum severity level will be presented in the severity summary
- Only the worst relationship level will be presented in the relationship summary.

Treatment-emergent AEs leading to study intervention modification or permanent discontinuation will be summarized.

Adverse events leading to death, SAEs, dose interruption of the study, or permanent discontinuation of the study intervention, and SAEs will be listed separately. Pretreatment AEs and TEAEs will be listed in individual participant data listings. Unresolved, ongoing AEs reported at the Safety Follow Up visit (28 [+7] days after the last administration of berzosertib) will be listed separately in an individual participant data listing.

Laboratory and vital signs measurements will be summarized by dose group and/or time point using descriptive statistics for observed values and change from baseline values (as appropriate).

Laboratory values outside the normal ranges will be identified in individual data listings. Shift from baseline according to normal range criteria may also be presented if deemed appropriate.

All clinical laboratory data will be stored in the database in the units in which they are reported and using the laboratory reference ranges as well as in the International System of Units. Participant listings and summary statistics at each assessment time will be presented using the International System of Units.

8.6 Interim and Additional Planned Analyses

Not applicable.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of

Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only participants who have given informed consent are enrolled in the study.

9.2 Participant Information and Informed Consent

An unconditional prerequisite for each participant prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Adequate information must therefore be given to the participant by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A participant information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the Investigator or a designate will inform the participant verbally of all pertinent aspects of the study, using language chosen so that the information can be fully and readily understood by laypersons. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the participant about the study and sign the Informed Consent Form (ICF), as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the participant and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the participant information sheet and any other written information to be provided to the participants and submit them to the IEC/IRB for review and opinion. Using the approved revised participant information sheet and other written information, The Investigator will explain the changes to the previous version to each study participant and obtain new written consent for continued participation in the study. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Participant Identification and Privacy

A unique number will be assigned to each participant, immediately after informed consent has been obtained. This number will serve as the participant's identifier in the study as well as in the clinical study database, and will be linked to the identifier assigned to the participant in the VX13-970-002 study. All participant data collected in the study will be stored under the appropriate participant number. Only the Investigator will be able to link study data to an individual participant via an identification list kept at the site. For each participant, original medical

data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but participant confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participants will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Participant Card

Participants will be provided with Emergency Medical Support cards supplied by the Sponsor for use during study participation in order to provide clinical study participants with a way of identifying themselves as participating in a clinical study and to 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 first point of contact for all emergencies will be the clinical study Investigator caring for the affected participant. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the study site 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.

9.5 Clinical Study Insurance and Compensation to Participants

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, this clinical study protocol will be submitted together with its associated documents (ICF, IB, Participant Information, and study specific material) to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at the Sponsor or contract research organization.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the study, the clinical study protocol version and the Participant Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical study protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.4). Relevant safety information will

be submitted to the IEC or IRB during the course of the study in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical study protocol and any applicable documentation (e.g., study intervention Dossier, Participant Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Study Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical study protocol in a complete, accurate, legible and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any participant names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Source Data and Participant Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every participant in the study. It must be possible to identify each participant by using this participant file. This file will contain the demographic and medical information for the participant listed below and should be as complete as possible.

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification, that is, the Sponsor study number for this clinical study, and participant number
- Dates for entry into the study (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical study protocol

- All AEs
- Date that the participant left the study including any reason for withdrawal from the study or study intervention (if applicable).

All documents containing source data must be filed, including, laboratory results. Such documents must bear the participant number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic participant files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site. Printing the files will not be necessary if the monitor is permitted to access and review electronic participant files or other electronic study records at Investigator sites, provided that they are given their own unique access and is "Read Only."

Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Participant Identification List and the signed participant ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original participant files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.3 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH GCP and any other applicable regulations. The site Monitor will perform visits to the study site at regular intervals.

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be participant to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all study intervention and study intervention accountability records, and the original medical records or files for each participant.

10.4 Changes to the Clinical Study Protocol

Changes to the clinical study protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the participant's agreement to participate in the study requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.5 Clinical Study Report and Publication Policy

10.5.1 Clinical Study Report

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.5.2 Publications

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting data on EUDRA-CT is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.

11 References Cited in the Text

Not applicable.

12 Appendices

Appendix I: Contraception

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., Müllerian 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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or 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 nonestrogen 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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 II: Signature Pages and Responsible Persons for the Study

Signature Page –Protocol Lead

Study Title:	A Rollover Study to Provide Continued Treatment With M6620
IND Number:	Not applicable
EudraCT Number:	2017-002354-37
Clinical Study Protocol Date/Version:	01 March 2021/Version 4.0

Protocol Lead:

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Senior Medical Director
Institution:	Global Clinical Development Center - Oncology
Address:	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	Not applicable
E-mail address:	PPD

Signature Page – Coordinating Investigator

Study Title	A Rollover Study to Provide Continued Treatment With M6620
IND Number	Not applicable
EudraCT Number	2017-002354-37
Clinical Study Protocol Date/Version	01 March 2021/Version 4.0

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, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Coordinating Investigator
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD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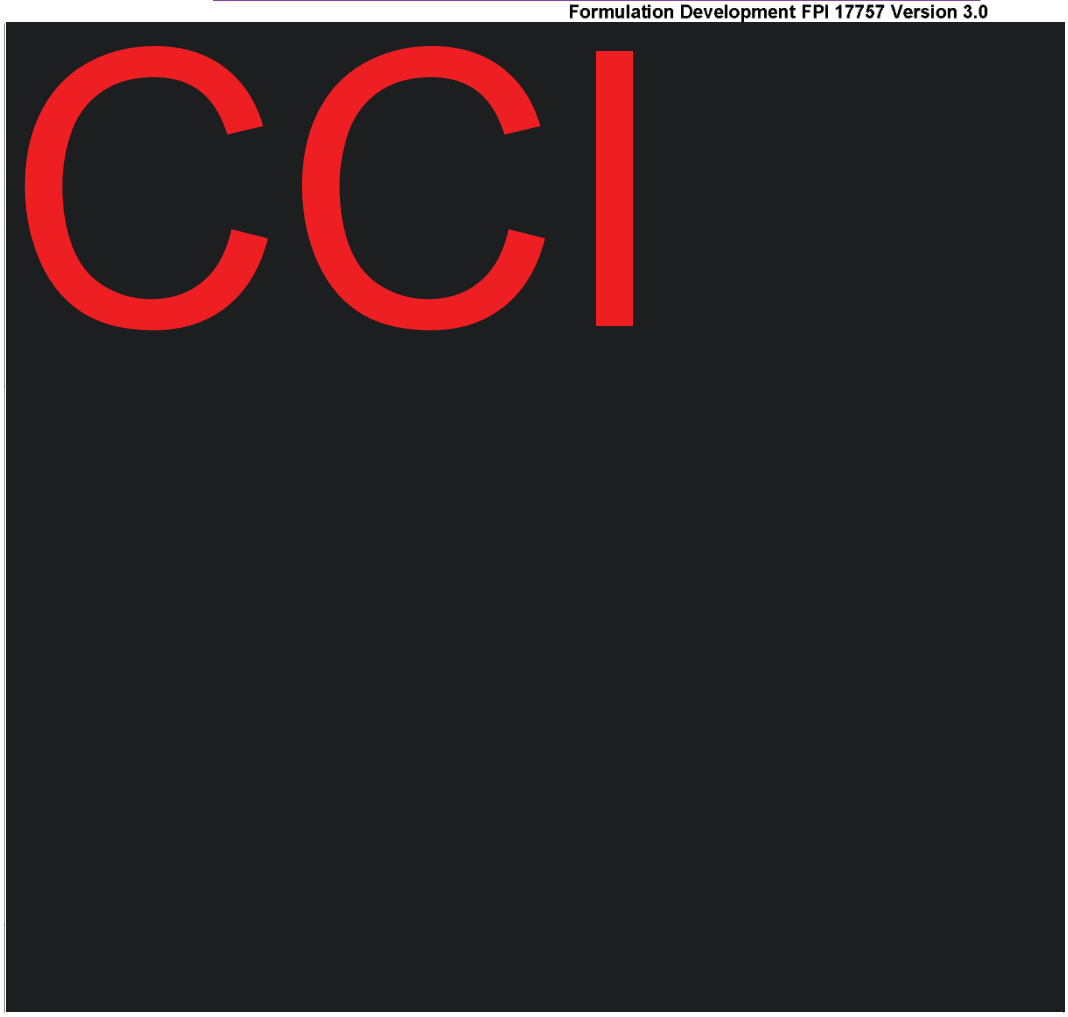
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Version	Author - Date	Revision History
1.0	PPD 09 September 2015	New Dose Preparation Instructions for VX-970 study XXXX based on Version X.X of Clinical Protocol
2.0	PPD 16 September 2015	Updated the FPI to revise the study number to VX12-970-001.
3.0	PPD 08 March 2016	Added Addendum specifying IV bag product number according to manufacturer and region

Appendix IV: Prohibited Medication, Food and Activities During the Study

Study prohibited Medication

Generic Name	Brand Name	Notes
Boceprevir	Victrelis	
Bosentan	Tracleer	Inducer
Carbamazepine	Tegretol, Biston, Calepsin, Carbatrol, Epitol, Equetro, Finlepsin, Sirtal, Stazepine, Telesmin, Teril, Timonil, Trimonil, Epimaz and others	Inducer
Chloramphenicol	Chloramycetin	
Ciclosporin	Neoral, Cicloral and others	
Clarithromycin	Biaxin, Klaricid, Klabax, Claripen, Claridar, Fromilid and others	
Conivaptan	Vaprisol	
Cyproterone	Androcur, Cyprostat, Cyproteron, Procur, Cyprone, Cyprohexal	
Delavirdine	Rescriptor	
Dexamethasone	Decadron, Dexasone, Hexadrol	Inducer
Dihydroergotamine	DHE 45	
Efavirenz	Sustiva, Stocrin	Inducer
Ergotamine	Ergormar, Cafergot	
Etravirine	Intelence	Inducer
Felbamate	Felbatol	
Gestodene		
Griseofulvin	Grisovin	Inducer
Indinavir	Crixivan	Inducer
Itraconazole	Sporanox	
Indinavir	Crixivan	
Ketoconazole	Nizoral	
Mibefradil	Posicor	
Mifepristone	Mifeprex	
Modafinil	Provigil, Alertec, Modavigil	
Nafcillin	Unipen, Nallpen	
Nefazodone	Serzone, Nefadar	
Nelfinavir	Viracept	
Nevirapine	Viramune	Inducer
Oxcarbazepine	Trileptal	
Phenobarbital	Solfoton, Luminal	Inducer
Phenytoin,	Phenytek, Dilantin and others	Inducer
Fosphenytoin	Cerebyx, Prodilantin and others	
Posaconazole	Noxafil	
Primidone	Mysoline	Inducer
Quinupristin/dalfopristin	Synercid	
Rifabutin	Mycobutin	Inducer
Rifampin	Rifidin, Rimactane	Inducer
Rifapentine	Priftin	Inducer
Ritonavir	Norvir	
Nitonavir/darunavir	Prezista	
Ritonavir/lopinavir	Kaletra	
Saquinavir	Invirase, Fortovase	
Telaprevir	Incivek	
Telithromycin	Ketek	
Tofisopam	Emandaxin, Grandaxin	

Troglitazone	Rezulin, Resulin, Romozin
Troleandomycin	TAO
Voriconazole	Vfend

Study Prohibited Food and Herbal Supplements

Name	**Notes/Description**
Grapefruit juice	Included sodas that contain concentrated grapefruit juice
Hyperforin	Inducer – constituent of St. Johns Wort
Pomelos	
Seville Oranges	
St Johns Wort	Inducer

Appendix V: Protocol Amendment History

The information for the current amendment is on the title page.

The following information provides a high-level summary of previous amendments with the most recent amendment listed first.

Amendment 2 (17 November 2020)

Section # and Name	Description of Change	Brief Rationale
Synopsis Table 1 Section 7.4.3 Clinical Laboratory Assessment Section 7.4.4.1 Vital signs Section 7.4.4.2 Physical Examination	Laboratory assessments (serum chemistry, hematology, and urinalysis), vital sign measurements, and physical examination will be only performed according to Standard of Care and institutional guidelines and as clinically indicated; only clinically significant changes will be recorded as adverse events (AEs).	To reduce the study assessments for the participant and clinical site, leveraging them according to the clinical site Standard of Care. The study requires any clinically significant values to be collected as AEs to ensure patient's safety throughout the study treatment.
Synopsis	Planned study period changed to" estimated 5 years"	For clarity.
Synopsis Section 8.3.1 Primary Endpoints	Primary endpoint updated to "Occurrence of adverse events (AEs) and treatment-related AEs in participants receiving berzosertib, graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) (Version 4.03)"	To align with current Merck KGaA endpoint library.
Table 2	Removed Table 2 (VX13-970-002 Part B2) SoA.	Since VX13-970-002 study was completed and no participants from Part B2 were transitioned to this study.
Section 3 Background Information Section 3.1 Study Rationale	Description of VX13-970-002 study was updated and description of VX12-970-001 study was deleted.	Since VX13-970-002 study was completed and no participants were transitioned to this study from Study VX12-970-001.
Figure 1	Updated and simplified Figure 1	For clarity.
Section 5.7 Definition of End of Study	Added the statement "The Sponsor may terminate the study at any time once access to berzosertib for participants still benefiting is provisioned via expanded access, marketed product or another mechanism of access as appropriate".	For flexibility and clarity.
Section 6.2 Dosage and Administration Section 6.4 Noninvestigational Medicinal Products to be Used(deleted) Section 6.4.1 Permitted Medicines	Text regarding infusion of berzosertib after chemotherapy (carboplatin and paclitaxel) removed	Since participant not receiving any chemotherapy agents (paclitaxel and carboplatin).

Section # and Name	Description of Change	Brief Rationale
Section 7.4 Assessment of Safety	Added the statement "Physical examination, weight, vital signs, serum chemistry, hematology and urinalysis will be measured as per Standard of Care and institutional guidelines and as clinically indicated; only clinically significant values should be reported as AEs. A clinically significant value is a result that a clinician would consider to be medically meaningful. Clinically significant values may be more severe than values expected for the participant's condition, age, and gender".	For clarity.
Section 7.4.1 Adverse Events	Section updated and text added to specify that "In this clinical study, any late spontaneous abortion, fetal death in utero, ectopic pregnancy, chronic fetal distress, stillbirth, neonatal death, or prematurity-related complication more than is typical for prematurity should be considered as an SAE."	To align with current Merck KGaA standard.
Section 7.4.1.4 Procedure for Reporting Serious Adverse Events	Specified that serious adverse events to be reported using Electronic Data Capture (EDC) and paper reports required only in case of EDC system failure.	This study will use electronic Case Report Forms.
Section 8.5.1 General Considerations	Specified that depending on the number of participants enrolled, no summary statistics will be provided and the data will be presented in listings only.	Only one participant was enrolled in this study to date. All other participants completed berzosertib study intervention within the initial study protocol.
Section 10.1 Case Report Form Handling	Removed text about paper Case Report Forms.	This study will use electronic Case Report Forms.
Section 10.2 Source Data and Participant Files	Added a clarification statement regarding when printing files is not necessary.	To add flexibility to study data management.
Appendix I Contraception	Contraception information updated.	To align with current Merck KGaA standard.
Appendix III Vertex VX13-970-002 Clinical Study Protocol	Removed previously appended Vertex protocol.	To align with Merck standard not to append a protocol with standalone documents.
Appendix IV Protocol Amendment History	The protocol amendment history information was moved to the front of the document.	To align with current Merck standards and style of reporting.
Throughout	Minor editorial and document formatting revisions	Minor; therefore, not summarized.

Amendment 1 (18 September 2017)

Section # and Name	Description of Change	Brief Rationale
Table 1 header and vital signs/footnote	Deleted 28 days in treatment cycle and added vital signs at Day 15.	For clarification and to update to company standards for vital sign measurements.

Section # and Name	Description of Change	Brief Rationale
Table 2 (VX13-970-002 Part B2) footnote	Vital sign measurements clarified in table footnote.	To update to company standards for vital sign measurements.
Table 2 (VX13-970-002 Part B2) footnote	The following footnote was added: "The participants who are not able to tolerate combination therapy due to toxicity associated with carboplatin and/or paclitaxel and continue on single agent M6620 should be assessed according to Schedule of Assessments for Participants Transitioned from Part A1: Single Agent Therapy once weekly (see Table 1)"	To provide for a plan in case of combination tolerability issues.
Section 5.1 Overall Study Design and Plan	Added sentence specifying that participants who transferred from combination treatment to M6620 monotherapy before enrollment in this rollover study should continue accordingly in this protocol.	For clarification.
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized