Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A single-dose, open-label, single arm study to investigate PK of xevinapant and its metabolite, D-1143-MET1 in healthy East Asian participants
Study Number:	MS202359_0004
Protocol Version:	10 Jun 2022/Version 1.0
Merck Compound:	Xevinapant
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	1
Brief Title:	Phase 1 PK Study in Healthy East Asian Participants
Principal Investigator:	PPD
Sponsor Name and Legal Registered Address:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 Darmstadt, 64293, Germany
Regulatory Agency Identifying Numbers:	EU trial number: 2022-002182-15
Keywords	• East Asian • Japanese • PK • Ethnic sensitivity

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1 Protocol Summary

1.1 Synopsis

Clinical Study Protocol Title: A single-dose, open-label, single arm study to investigate PK of xevinapant and its metabolite, D-1143-MET1, in healthy East Asian participants

Brief Title: Phase 1 PK Study in Healthy East Asian Participants

Rationale: This is an open-label, Phase 1 study investigating the pharmacokinetics (PK) of xevinapant and its metabolite D-1143-MET1 as well as safety in healthy East Asian participants following a single dose of 200 mg of xevinapant, which is the recommended Phase 3 dose (RP3D) in Study MS202359_0006 (formerly known as Debio 1143 SCCHN-301 and hereafter referred to as TrilynX), the ongoing global Phase 3 in combination with CRT in unresectable LA SCCHN.

Objectives and Endpoints:

Objectives	Endpoints	Ref. #
Primary		
To characterize the xevinapant PK after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	Xevinapant $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}	1
Secondary		
To evaluate the safety and tolerability of a single 200 mg dose of xevinapant in healthy East Asian participants and in healthy Japanese participants	Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead ECGs, and vital signs	2
To determine additional plasma PK parameters of xevinapant after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	Xevinapant $AUC_{0\text{-}24}$, t_{max}, $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution during terminal phase (Vz/F)	3
To characterize the PK of metabolite D-1143-MET1 after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	D-1143-MET1 $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, and $t_{1/2}$, D-1143-MET1/xevinapant molar ratio for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, C_{max}	4

Overall Design: This will be a single-dose, open-label study evaluating the PK and safety of xevinapant in healthy East Asian participants. At least 10 Japanese and 10 non-Japanese East Asian participants will be enrolled, with a planned total duration of the study for each participant of approximately 5 weeks, including an up to 4-week Screening Period, an In-house Period at the CRU (Day -1 to Day 4), and a Safety Follow-up on Day 8.

Brief Summary: All participants will be dosed on Day 1. Group 1 will enroll at least 10 Japanese participants and Group 2 will enroll at least 10 non-Japanese East Asian participants. East Asia includes Korea and Greater China, with preferably a similar

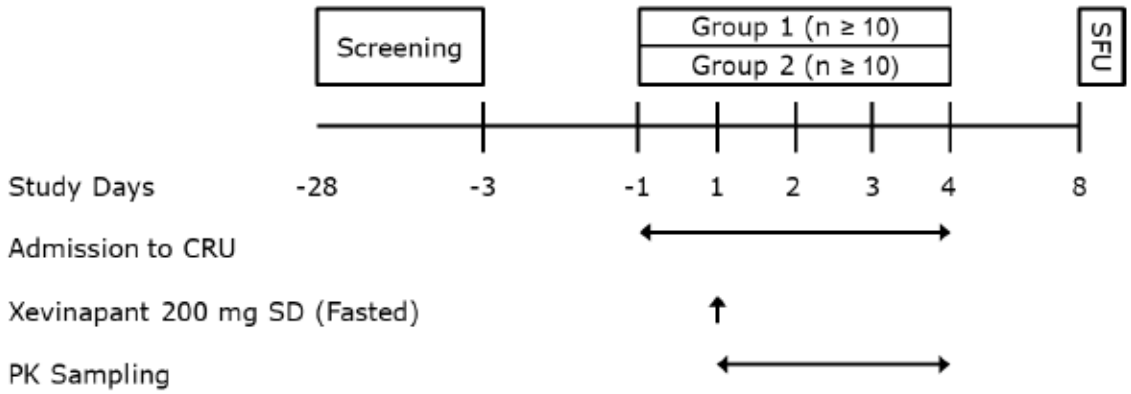
proportion of male and female participants enrolled across groups if feasible. Participants will be confined to the study site from Day -1 to Day 4 and will complete a Safety Follow-up televisit on Day 8. Adverse events will be followed from Screening through the Safety Follow-up televisit. Safety assessments will include physical examinations, vital signs, electrocardiograms, and clinical safety laboratory tests. PK and CCI [redacted] samples will be obtained.

Number of Participants: 24 participants (12 per group) will be initially assigned to study intervention such that approximately 10 evaluable participants per group complete the study.

Study Intervention Groups and Duration: Group 1 will enroll at least 10 Japanese participants. Group 2 will enroll at least 10 non-Japanese East Asian participants. East Asia includes Korea or Greater China. The planned total duration of the study for each participant will be approximately 5 weeks, including an up to 4-week Screening Period, an In-house Period at the CRU (Day -1 to Day 4), and a Safety Follow-up on Day 8.

Data and Safety Monitoring /Other Committee: No

1.2 Schema



Group 1: Japanese participants; Group 2: non-Japanese Asian participants
CRU = Clinical Research Unit, D = Day, PK = pharmacokinetics, SD = single dose, SFU = Safety Follow-up (SFU on D 8 is a televisit)

1.3 Schedule of Activities

Assessments & Procedures	Screening	Admission to CRU					SFU (Televisit)	Notes
Study Day	**-28 to -3**	**-1**	**1**	**2**	**3**	**4 (EoT)**	**8 (-1 / +2 days)**	
Written informed consent	X							Informed consent to be available before start of any study specific assessments.
Participants resident at CRU		X	X	X	X	X		Admission to CRU in the afternoon on Day -1 until discharge on Day 4 after completion of all study-related activities
Inclusion and exclusion criteria	X	X						Recheck clinical status before administration
Demography	X							Including age (year of birth), sex, race and ethnicity
Full physical examination	X	X				X		
Medical history	X							
Pregnancy test	X	X				X		Pregnancy test using serum (at Screening) and using urine (on Day -1 and End of Study), to confirm non-pregnant status (females only)
Follicle stimulating hormone	X							To confirm postmenopausal status (females only)
Serology	X							HIV, hepatitis B and C SARS-CoV-2
Drug and alcohol screen	X	X						
Clinical laboratory tests[a]	X	X	X	X		X		After at least 10 hours fasting, Day 1 sampling is predose
Safety 12-Lead ECG	X		X	X		X		Day 1: predose, 1 hour postdose, Day 2 (24 hours postdose), and Day 4 (72 hours postdose) (see Section 8.2.3 for further details)

Assessments & Procedures	Screening	Admission to CRU					SFU (Televisit)	Notes
Study Day	**-28 to -3**	**-1**	**1**	**2**	**3**	**4 (EoT)**	**8 (-1 / +2 days)**	
Vital signs	X	X	X	X	X	X		Height and Weight to be collected at Screening only. Day 1: predose, 1, 2, 4, 12 hours; Day 2: 24 hours, Day 3: 48 hours, Day 4: 72 hours
CCI								
Study intervention			X					
AE & SAE review	X	X	X	X	X	X	X	
Concomitant medications review	X	X	X	X	X	X	X	
PK blood sampling (plasma)			X	X	X	X		Day 1: predose, and 0.25, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours postdose; Day 2: 24 and 36 hours postdose; Day 3: 48 hours postdose, Day 4: 72 hours postdose. See Section 8.4 for collection windows and further details. The time and date of each collection to be recorded in eCRF.

[a]Urine samples will be collected at Screening and times of other clinical labs.

2 Introduction

Xevinapant is a novel, orally available antagonist of IAPs that promotes cancer cell death via apoptosis. Xevinapant fosters antitumor immunity and potentially sensitizes tumor cells for various cytotoxic therapies, including chemotherapy, radiotherapy and/or immunotherapy (Serova 2014, Matzinger 2015, Tao 2019).

Detailed information on the chemistry, pharmacology, efficacy, and safety of xevinapant is in the IB.

2.1 Study Rationale

This is an open-label, Phase 1 study investigating PK of xevinapant and its metabolite D-1143-MET1 as well as safety in healthy East Asian participants following a single dose of 200 mg of xevinapant, which is the recommended Phase 3 dose (RP3D) in Study MS202359_0006 (formerly known as Debio 1143-SCCHN-301 and hereafter referred to as TrilynX), the ongoing global Phase 3 in combination with CRT in unresectable LA SCCHN.

The proposed single dose of 200 mg of xevinapant is to be administered under fasted condition, thereby allowing:

- Evaluation of PK of xevinapant and its metabolite D-1143-MET1 in East Asian participants in the absence of any potential food effect
- Comparison of PK data between the healthy East Asian ethnic subgroups (including Japanese) included in this study
- Comparison of PK data between the healthy East Asian participants to be investigated in this study and healthy Caucasian participants evaluated in earlier studies (Debio 1143-107, Debio 1143-109)

This clinical study is part of the xevinapant global development program and aims to support the participation of East Asian subjects, including Japanese in global Phase 3 trials in the targeted patient populations and associated indications.

This clinical study will be conducted in compliance with the CSP, Good Clinical Practice (International Conference on Harmonization [ICH] Topic E6, GCP) and the applicable regulatory requirements.

2.2 Background

Head and neck carcinomas include a variety of epithelial tumors originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx. Head and neck cancers are the 7th most common cancer worldwide with an annual incidence of approximately 700,000 and a mortality rate estimated at 350,000 in 2018 (Bray 2018). In the US alone, 50,000 new cases and 10,000 deaths are reported annually, while in Europe, 140,000 new cases are reported annually

(Iglesias Docampo 2018). A vast majority of these cancers (90% to 95%) are SCCHN which are closely associated with alcohol and tobacco use. SCCHN of the oropharynx is also associated with HPV, essentially type 16 infection. Approximately two-third of patients are diagnosed as LA SCCHN (Denaro 2016).

Multidisciplinary treatments, including surgery, RT and chemotherapy alone or in combination represent the treatment options for SCCHN patients depending on the disease stage. Locally advanced disease is treated with curative intent and requires multimodal approaches including combined CRT either as adjuvant therapy after tumor resection or as definitive curatively intended treatment.

Due to the pivotal role of RT in many LA SCCHN settings, a lot of focus is being put on research into safe and powerful radiosensitizing agents. In addition, resistance of tumor cells to apoptosis is a major problem in current cancer treatment. Therefore, further development of new molecular anticancer therapies that specifically target resistance of cancer cells to apoptosis is warranted (Nicholson 2000).

IAPs are key endogenous inhibitors of apoptosis, and overexpression of these proteins was detected in numerous cancers, including SCCHN. IAPs have also been shown to interfere with the efficacy of RT (Tamm 2000).

Xevinapant is an antagonist of IAPs with chemosensitizing, radiosensitizing, and immunomodulatory activities. Nonclinical studies in several in vitro and in vivo SCCHN models demonstrated an efficient antiproliferative activity and a synergistic enhancement of intrinsic cellular radiation sensitivity when xevinapant was combined with RT. The synergistic effect of xevinapant combined with RT in vivo was able to cure tumors in 8 of 10 xenografted mice without any apparent toxicity whereas all mice died with RT alone (Matzinger 2015). These results indicate that xevinapant in combination with RT has a promising therapeutic potential in the treatment of SCCHN.

Based on current understanding of the mechanism of action, the value of adding xevinapant to platinum-based conventional CRT in the treatment of previously untreated patients with non-resected LA SCCHN has been investigated in a Phase 1-2 study (Debio 1143-201, refer to IB for further details). The Phase 2 part of Debio 1143-201 study (part B of the study) was a randomized, placebo-controlled, double-blind study. Efficacy results from the 24-month primary analysis have shown antitumor activity of xevinapant: patients treated with xevinapant were around 2.5 times more likely to have locoregional control 18 months after completing treatment, compared with patients having received a placebo. The ongoing global Phase 3 study TrilynX aims to confirm the value of xevinapant in the treatment of previously untreated LA SCCHN patients (including those from East Asia) with hypopharynx, larynx and/or HPV-16 negative OPC, who are suitable for definitive CRT and are more likely to relapse locally.

Xevinapant PK has been evaluated in clinical studies in patients with cancer, either as monotherapy or in combination with other cancer treatments, after once daily oral administration on Days 1 to 5, on Days 1 to 14 of 3-week cycles and on Days 1 to 10 and Day 15 to 24 of 4-week cycles (refer to IB). Xevinapant was well absorbed with t_{max} reached in about 1 to 2 hours. In the monotherapy treatment, PK of xevinapant was dose-proportional in the dose

range 100 to 900 mg. Half-life ($t_{1/2}$) is about 6 to 8 hours. In monotherapy, no accumulation after multiple dosing was observed. Apparent clearance was low, indicating a limited hepatic extraction. Renal clearance was low, with about 8% to 10% of xevinapant recovered unchanged in urine. In vitro binding of xevinapant to human plasma proteins was moderate (84% to 88%). D-1143-MET1, a metabolite with no significant antagonistic IAP activity in vitro, is a major circulating metabolite in human, with plasma exposure of the same order of magnitude as xevinapant. D-1143-MET1 formation from xevinapant is essentially extrahepatic. Xevinapant is a low permeability drug. In general, interindividual variability in PK disposition was large for xevinapant and its major metabolite D-1143-MET1 in cancer patients (e.g., 50 to 80 geoCV% for xevinapant AUCτ), but lower (35 geoCV% for AUC_{0-t}) in Caucasian healthy participants.

2.3 Benefit/Risk Assessment

Although a healthy participant population provides the optimal conditions to achieve the PK objectives of the study, risk to participants must be minimized since participants will derive no benefit from exposure to the study medication. The information obtained in this study will inform the prescribing information and will be used for the further multinational clinical development of xevinapant.

As of 31 July 2021, a total of 58 healthy adult participants have been exposed to xevinapant as a single agent in studies Debio 1143-107 and Debio 1143-109. Among the 58 healthy adult participants the most frequently reported events were headache (5/58; 8.6% participants), nausea (3/58; 5.2% participants), and abdominal pain upper, diarrhea and dizziness (each in 2/58; 3.4% participants). All other events were reported in a single participant. None of the TEAEs reported in healthy participants were serious or severe.

In xevinapant studies as of 31 July 2021, a total of 314 participants with a malignancy have received at least 1 dose of xevinapant (up to 900 mg). Sixty-four participants received xevinapant as single agent, 150 received xevinapant in combination with chemotherapy or CRT, and 100 in combination with immunotherapy. In addition, in an ongoing Phase 3 study TrilynX, 105 patients have received at least 1 blinded dose of xevinapant (200 mg/day, D1 to 14, every 3 weeks) / placebo in combination with CRT. Based on the safety data of the Phase 1 and Phase 2 studies, xevinapant doses of up to 200 mg/day were safely combined with either chemotherapy or CRT (refer to IB for further information).

The potential sensitivity of xevinapant to ethnic factors was assessed based on nonclinical and clinical data mainly derived from Caucasian participants following the guidance shown in Appendix D of ICH E5(R1), and these analyses suggested that the likelihood that race/ethnicity is a significant source of variability in PK is low.

More detailed information about the known and expected benefits and risks and reasonably anticipated potential adverse events of xevinapant may be found in the IB.

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

CCI [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	CCI	

2.3.2 Benefit Assessment

Healthy participants may expect no direct benefit beyond the thorough medical check-up that they will receive from participating in this clinical study.

However, the information obtained in this study will be used for the further global clinical development of xevinapant.

2.3.3 Overall Benefit: Risk Conclusion

Considering the former experience in healthy participants and the measures taken to minimize anticipated risk to participants in this study, the contemplated risks in association with the use of xevinapant are justified by the anticipated benefits for the global clinical development of xevinapant as a new treatment for participants with malignancies.

3 Objectives and Endpoints

Objectives	Endpoints	Ref. #
Primary		
To characterize the xevinapant PK after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	Xevinapant $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}	1
Secondary		
To evaluate the safety and tolerability of a single 200 mg dose of xevinapant in healthy East Asian participants and in healthy Japanese participants	Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead ECGs, and vital signs	2
To determine additional plasma PK parameters of xevinapant after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	Xevinapant $AUC_{0\text{-}24}$, t_{max}, $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution during terminal phase (Vz/F)	3
To characterize the PK of metabolite D-1143-MET1 after a single 200 mg dose in healthy East Asian participants and in healthy Japanese participants	D-1143-MET1 $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, and $t_{1/2}$, D-1143-MET1/xevinapant molar ratio for $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, C_{max}	4
CCI [redacted]		

4 Study Design

4.1 Overall Design

Study Design	Single-Dose PK Study
Control Method	Not applicable
Single or Multicenter	Single center
Control Group	Not applicable
Study Population Type	Healthy East Asian participants

Level and Method of Blinding	Open-label
Bias Minimalization Method(s)	Not applicable
Study Intervention Assignment Method	Not applicable, all participants will receive the same study intervention
Data and Safety Monitoring /Other Committee:	No
Study Intervention Groups and Duration of Study Intervention for Each Participant	1 day of dosing for all participants Target numbers of participants are set for each group. Group 1 will enroll at least 10 Japanese participants. Group 2 will enroll at least 10 non-Japanese East Asian participants. East Asia includes Korea or Greater China. Preferably a similar proportion of male and female participants will be enrolled across groups if feasible.
Total Duration of Study Participation per Participant	The planned total duration of the study for each participant will be approximately5 weeks, including an up to 4-week Screening Period, an In-house Period at the CRU (Day -1 to Day 4), and a Safety Follow-up on Day 8.
Parts of the Study	Not applicable
Method Used for Dose Escalation	Not applicable
Adaptive Aspects of Study Design	Not applicable

Screening, Treatment, and Follow-up Periods:	**Screening** Screening will be performed within Day -28 to Day -3. If there are no clinically significant findings at Screening and the participant meets all the protocol-defined inclusion and none of the exclusion criteria, the participant will be considered eligible for participation in the study. **Treatment period:** consists of 4-day in-house period. It will begin at the admission to CRU in the afternoon on Day -1. Participants will receive a 200 mg single dose of xevinapant as solution under overnight fasted condition on Day 1 and stay in the CRU until discharged on Day 4 approximately 72 hours after treatment and completion of all assessments. **Safety Follow-up Period:** occurs on Day 8.
Involvement of Special Committee(s):	No
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable

4.2 Scientific Rationale for Study Design

Clinical studies of xevinapant have been conducted mainly in Caucasians, thus the PK data in Asian ethnicities is not available. Though the possible ethnic sensitivity of PK of xevinapant and its significance on the clinical benefit/risk are considered to be low based on nonclinical and non-Asian clinical data considered in the context of ICH E5 principles, the investigation of xevinapant PK in East Asian healthy participants is considered informative for the assessment of data from the global Phase 3 studies involving East Asian populations. In this context, the present PK study is planned.

This is a single dose study of orally administered xevinapant solution in healthy East Asian participants (including Japanese) to evaluate the PK and safety. The overall safety and PK results of this study should support further global development of xevinapant, including further clinical studies and regulatory submission to Japan and other East Asian countries.

This study will be conducted in healthy male and female participants, preferably with a similar proportion across groups, if feasible. The inclusion and exclusion criteria are standard for a Phase 1 study in healthy participants (see Sections 5.1 and 5.2). Healthy participants ensure homogeneity of the study population, and available clinical data in healthy Caucasian participants demonstrated good tolerability after a single 200 mg dose. As SCCHN occurs in both men and women, this study will enroll participants of both sexes. Sex differences regarding safety, tolerability, and PK are not expected. Only women of nonchildbearing potential will be included.

The PK sampling time points in this study covering up to 72 hours postdose were chosen based on data from the HV studies in Caucasian participants (Debio 1143-107) to appropriately cover the expected time of exposure to xevinapant after a single-dose administration (see SoA, Section 1.3).

Clinical formulations and the dose (200 mg) that has been used in healthy participants in HV Study Debio 1143-109 is being used in the ongoing Phase 3 study (refer to IB Table 6-1 and 6-4).

The safety of xevinapant will be assessed throughout the study by evaluating AEs (including incidence, nature, and severity), clinical laboratory results, vital signs measurements, and real time, locally read safety ECGs. The safety monitoring proposed in this study is in accordance with the Benefit/Risk assessment (see Section 2.3).

The collection of plasma after a single dose of xevinapant will also allow further characterization of the exposure of the main circulating metabolite D-1143-MET1, as well as CCI analysis of other metabolites, if warranted.

Details on xevinapant development can be found in the Investigator's Brochure.

4.3 Justification for Dose

The proposed single dose of 200 mg administered under fasted conditions is identical to that used in studies Debio 1143-107 and Debio 1143-109 in healthy Caucasian participants with favorable tolerability. It is also the daily dose used in the ongoing Phase 3 study in combination with CRT in participants with LA SCCHN.

For more information on the selection of RP3D refer to AACR poster [Abstract No. 5424. Presented at the AACR Annual Meeting 2022, April 8-13, 2022; New Orleans, LA, and Virtual].

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant or the last scheduled procedure shown in Section 1.3.

A participant has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in Section 1.3.

5 Study Population

The purpose of this study is to assess the PK and safety of xevinapant in healthy East Asian participants, including healthy Japanese participants. Accordingly, Japanese participants and non-Japanese East Asian participants will be enrolled.

The criteria in Sections 5.1 and 5.2 are designed to enroll only individuals who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether an individual 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 individual's routine medical care, the Investigator will confirm that the individual 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
Ethnicity	1. Healthy participant of Japanese or other East Asian origin. a. Group 1: Japanese participants must be first generation (born in Japan) with both biological parents and all 4 biological grandparents being Japanese native born, lived for < 10 years outside of Japan, and have no significant change in lifestyle since leaving Japan. b. Group 2: Other non-Japanese East Asian participants must have both biological parents and 4 biological grandparents of East Asian descent, lived for < 10 years outside of their countries, and have no significant change in lifestyle since leaving from there. East Asia includes Korea or Greater China.
Age	2. Are 18 to 60 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	3. Are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring (blood pressure, heart rate, and 12-lead resting ECG).
Weight	4. Have a body weight within 50 and 110 kg and body mass index within the range 18.0 to 32.0 kg/m^2 (inclusive).

Sex and Contraception/ Barrier Requirements	5. 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. a. Male Participants: • Agree to the following during the study intervention period and for at least 90 days from the last dose, covering the time needed to eliminate study intervention and to complete a full cycle of spermatogenesis after the last dose of study intervention: o Refrain from donating sperm • Use a male condom: • When having sexual intercourse with a woman of childbearing potential, 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 Contraception and Barrier Requirements, since a condom may break or leak. b. Female Participants: • Are not breastfeeding • Are **not** pregnant, as confirmed by: • a negative serum (at Screening) and urine (Day -1) pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention. • Are **not** a woman of childbearing potential (see Appendix 3 Contraception and Barrier Requirements) defined as either: • At least 1 year postmenopausal (amenorrhea ≥ 12 months and FSH ≥ 40 mIU/mL) at Screening; OR • Surgically sterile (bilateral oophorectomy, hysterectomy or bilateral salpingectomy; tubal ligation

Category	Criterion
	alone is not sufficient) as documented by medical certificate • Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4. • The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy
Informed Consent	6. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the 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. History of clinically relevant disease of any organ system that may interfere with the objectives of the study or provide a risk to the health of the participant. 2. History of relevant drug hypersensitivity, ascertained or presumptive allergy/ hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other allergy reaction in general, which the Investigator considers may affect the safety of the participant and/or outcome of the study. 3. Ongoing or active clinically significant viral (including SARS-CoV-2), bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral antiinfectives ≤ 4 weeks prior to or during Screening Period, or completion of oral antiinfectives ≤ 2 weeks prior to Screening Visit. Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered to be sufficiently controlled will not be exclusionary. Note: An Investigator may use clinical judgment in testing for SARS-CoV-2 immediately prior to randomization depending on the participants' medical condition. However, within 3 to 5 days prior to randomization, all participants should be specifically questioned for COVID-19 symptoms or close contact with someone known to have SARS-CoV-2 infection to determine if SARS-CoV-2 testing (accepted according to local guidelines) should be performed. 4. History of splenectomy. 5. History of malignancy (hematologic or solid tumor) before the Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix. 6. History of or a positive Screening test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus type I and II.

Category	Criterion
Prior/Concomitant Therapy	7. Use of any prescribed medicine or over-the-counter drug (other than occasional use of ibuprofen or paracetamol < 1.5 g/day but including herbal remedies, vitamins, and minerals) within 2 weeks or 5 times the half-life of the respective drug, whichever is longer, before the first dose of study intervention. 8. Use of drugs and herbal remedies with enzyme inducing properties such as traditional Chinese medicine, St. John's Wort, within 3 weeks before the first dose of study intervention; grapefruit or grapefruit juice from 72 hours prior to first dosing 9. Vaccination with an attenuated virus during the last 3 months before the first administration of study intervention. 10. Known hypersensitivity to the study intervention or to one or more of the excipients used
Prior/Concurrent Clinical Study Experience	11. Use of any investigational drug in any clinical study within 5 half-lives from last administration

Category	Criterion
Diagnostic Assessments	12. Supine systolic blood pressure > 140 mmHg or < 90 mmHg or diastolic blood pressure > 90 mmHg or < 50 mmHg at Screening or Day 1 prior to dosing (any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion). 13. Pulse rate > 90 or < 50 beats per minute at Screening or Day 1 prior to dosing. 14. 12-Lead ECG recording with signs of clinically relevant pathology, in particular QTc according to Fridericia's formula > 450 ms, PR > 210 ms, or QRS duration > 120 ms. 15. ALT and AST, ULN at Screening. Any abnormal value of these parameters may be repeated and if the repeat result is within the laboratory reference range, it is not considered to have met the exclusion criterion. 16. Estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation < 80 mL/min/1.73m^2 at Screening. 17. Screening laboratory values other than AST, ALT for hematology, coagulation, biochemistry, or urinalysis outside the reference range. Minor deviations from normal are allowed if they are not clinically significant.

Category	Criterion
Other Exclusions	18. History of alcoholism or drug abuse within the past 2 years, or positive screen for alcohol or drugs of abuse at Screening or admission. 19. Consumption of an average weekly intake of > 14 drinks/week for men or > 7 drinks/week for women. One drink is equivalent to (12 g alcohol) = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 40% alcohol content by volume of distilled spirits. 20. Known excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee a day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to drug administration until 72 hours after administration. 21. Use of any tobacco products (cigarettes, pipes, cigars, e-cigarettes, or other nicotine delivery systems) within 90 days before the Screening Visit. Participants with positive urine cotinine levels during Screening or Day -1 will be excluded. 22. Donation or loss of more than 450 mL of blood in the 90 days prior to administration of xevinapant. 23. Inability to communicate or cooperate with the Investigator (e.g., language problem, illiterates, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions. 24. Other factors which in the opinion of the Investigator may interfere with study conduct.

5.3 Lifestyle Considerations

Lifestyle and dietary restrictions during participation in the study, including dietary restrictions are specified in the exclusion criteria 18 to 21 in Section 5.2 above.

5.3.1 Meals and Dietary Restrictions

Participants will abstain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 72 hours prior to first dosing until discharge.

Participants will abstain from taking resveratrol dietary supplements within 14 days before dose administration until after completion of the follow-up visit.

All xevinapant doses will be given after an at least 10-hour overnight fast. Fasting will be maintained for at least 2 hours after xevinapant administration. Water consumption is allowed ad libitum (as desired) except for 1 hour before until 1 hour after study intervention intake apart from the water taken with the dose.

During confinement, participants are only permitted to eat meals provided by the study site. On dosing days (see SoA in Section 1.3), participants will receive a standardized light meal after 4 hours, a snack approximately 7 hours and dinner approximately 10 hours after dosing.

Other meals will be provided at usual meal times of the study center.

Products containing poppy seeds (cake, rolls) may not be consumed within 48 hours before Screening and each admission until discharge.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During the dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until 72 hours after administration.
- During the in-house confinement period, participants will abstain from alcohol for 36 hours before the start of confinement period until discharge.

Use of cannabinoids and other drugs of abuse is not allowed during the whole study. Participants must have a negative test for drugs of abuse at Screening and at admission to each study period.

Use of tobacco products will not be allowed from 90 days before the Screening Visit until after the discharge (see exclusion criterion 21 in Section 5.2 above).

5.3.3 Activity

Participants will abstain from strenuous exercise for 7-days before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention

Not applicable.

6 Study Intervention(s) and Concomitant Therapies

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 Study Intervention(s) Administration

Study Intervention(s) Administered

Intervention Name	Xevinapant
Type	Drug
Dose Formulation	Bottle of CCI oral solution containing 200 mg xevinapant CCI [redacted]
Unit Dose Strength(s)	200 mg
Dose	200 mg
Dosage Regimen	Single dose
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Xevinapant will be provided in bottles. Each bottle will be packed and labeled per all applicable regulatory requirements and GMP Guidelines.
Former Name	Debio 1143

Study Arm(s)

Arm Name	• Group 1: Japanese participants • Group 2: non-Japanese East Asian participants
Arm Type	Experimental
Arm Description	Single 200 mg oral dose of xevinapant. Xevinapant will be administered with an oral syringe and a glass of 240 mL of water.

Associated Intervention Labels	Xevinapant

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

Xevinapant will be provided in glass bottles (for details, see Section 6.1).

The xevinapant oral solution should be stored under a controlled temperature at CCI [redacted]

Packaging and labeling of xevinapant solution will be in accordance with applicable regulatory requirements and applicable Good Manufacturing Practice guidelines. The information on the medication will be in accordance with approved submission documents.

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 applicable 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, bottle numbers, expiry dates, 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 redispensed 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 applicable manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

On Day 1, participants will be assigned a unique number (participant number) in ascending numerical order at the study site. There is only 1 treatment per group per ethnicity, thus, no randomization procedures will be applied.

6.3.2 Blinding

Blinding is not applicable as the study intervention administration is open label and none of the assessments is blinded.

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 CRF. A member of the study site staff other than the person administering the study intervention will confirm the study intervention dose and study participant identification at the time of dosing. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Dose Modification

No dose modifications are planned in this study.

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 because such care would not differ from what is normally expected for healthy participants.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than 200 mg 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 SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on an SAE and Overdose Report Form, following the procedure in Appendix 4.

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the signing of the ICF until completion of the study at the timepoints specified in the SoA, 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. For nondrug interventions, record the name, the indication, and dates administered.

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

6.8.1 Permitted Medicines

The only permitted medicines are the following:

1. Paracetamol (acetaminophen) up to 1,500 mg per day
2. Local treatment of an indwelling cannula induced thrombophlebitis is allowed, upon decision by the Principal Investigator.

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.

6.8.2 Prohibited Medicines

Any concomitant medication apart from paracetamol/acetaminophen is considered prohibited. Any medication, prescription or nonprescription (including vitamins and dietary, traditional Chinese medicine or herbal supplements), administered within 2 weeks or five half-lives before administration of study intervention, whichever is longer, is considered exclusionary for participation in the study, unless, in the opinion of the Investigator and Sponsor Medical Responsible, the medication will not interfere with the study.

If any prohibited medication is administered during the study it may warrant exclusion of further participation in the study, subject to Sponsor Medical Responsible review.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the entire study is specified in Appendix 2 Study Governance.

7.1 Discontinuation of Study Intervention

Not applicable as participants will receive a single dose of xevinapant of 200 mg.

7.2 Participant Discontinuation/Withdrawal from the Study

- The participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- If a participant has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- If a participant must be withdrawn from the study, the Sponsor Medical Responsible and Clinical Study Lead will be informed immediately.
- If there is a medical reason for the withdrawal, appropriate medical care will be provided.
- At the time of discontinuing from the study, 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 withdraws consent for future involvement in 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.

The Investigator will secure the safety of the study participants and make every attempt to collect the data.

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 will 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 will 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, were performed within the time frame defined in the SoA, and if reviewed and approved by the Sponsor.
- Approximately 116.5 ml of blood will be drawn throughout the study. A maximum of 470 mL of blood total may be taken throughout the study. These blood samples will be used for the following purposes: clinical laboratory tests, PK, and genetics and/or CCI [redacted]

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 CSR.

8.1 Efficacy Assessments and Procedures

Not applicable.

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

- 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

- Vital signs will be measured in supine position.
  - Blood pressure and participant's position during measurement; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Baseline 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.
  - Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals.
- Triplicate ECGs are required when abnormal ECG results are measured. If ECG parameters fall outside of clinical reference range, including QTcF > 450 ms, a repeat ECG is done. When triplicate ECGs are required, 3 individual ECG tracings will be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates will be completed in less than 4 minutes and will occur in a resting state without prior procedure such as blood draw. Triplicate measurements can be performed

based on Investigators discretion. When measured as triplicate, the average values will be considered. Additional ECGs during the course of the study will be at the discretion of the Investigator.

8.2.4 Clinical Safety Laboratory Tests

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 Clinical Laboratory Tests at the timepoints listed in the SoA. All samples will be clearly identified. The samples for scheduled laboratory tests will be collected in a fasted state. Participants will refrain from food and fluid with the exception of water for at least 10 hours prior to collection. Unscheduled tests may not require a fasted condition.
- 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 laboratories.
- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will 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.
- Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the Investigators or required by local regulation, to establish the absence of pregnancy at any time during the study. To confirm postmenopausal status, FSH will be assessed at Screening only.

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

- The definitions of an AE and SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Subinvestigators) 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, considered related to the study intervention or study procedures, 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-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 phone call at the timepoints 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 nonleading 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 toward 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, IRB/IEC, and Investigators.

- Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.
- 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 read it and confirm completion of this activity. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 6 months after the last administration of study intervention.
- 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 learning of the 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.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5 Adverse Events of Special Interest

An AESI is a noteworthy event of the particular study treatments that can be appropriate to monitor closely. CCI [redacted]

8.4 Pharmacokinetics

8.4.1 Blood Sampling and Bioanalysis

- Samples are collected only where allowed by local law/regulations.
- The actual date and time (24-hour clock time) of:
  - Each sample collection

- Study intervention administration prior to sample collection

will be recorded in the eCRF to determine the elapsed time of sampling in relation to the administration of study intervention.

- Whole blood samples of approximately 2 mL per PK sample collection time point will be collected for measurement of plasma concentrations of xevinapant and its metabolite D-1143-MET1. Collection times are specified in the SoA. 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.
- The quantification of xevinapant and D-1143-MET1 in plasma will be performed using a validated assay method.
- Concentrations will be used to evaluate the PK of xevinapant and its metabolite D-1143-MET1.
- Remaining samples collected for bioanalytical measurements may also be used for CCI t of metabolites of xevinapant or CCI biomarkers during or after the study. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Details on processes for collection and handling of these samples are in the Laboratory Manual.
- For details on PK sampling, refer to the SoA in Section 1.3.

8.4.2 PK Parameters

- PK parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® (version 6.4 or higher; Certara, L.P., Princeton, New Jersey, USA). SAS version 9.4 or higher will be used to calculate metabolic ratios.
- Concentration data may be used for integrated data analyses across studies and reported separately from the main CSR.
- The following PK parameters for xevinapant and its metabolite D-1143-MET1will be calculated from individual plasma concentration-time data for xevinapant and its metabolite(s), when appropriate:

Other PK parameters may be calculated if appropriate. Details will be in the IAP.

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_{024}	The AUC from time zero (= dosing time) to 24 hours

Symbol	Definition
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. AUC_{extra} = (extrapolated area/$AUC_{0-\infty}$) *100.
CL/F	The apparent total body clearance of study intervention following extravascular administration. CL/F= Dose $_{p.o.}$ /$AUC_{0-\infty}$.
C_{max}	Maximum observed concentration
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration. V_z/F = Dose/($AUC_{0-\infty}$*λ_z) following single dose.

The exact date/time of sample collection and study intervention (24-hour clock time) must be recorded in the eCRF and will be used in the calculation of PK parameters. The accepted time deviations from planned PK times that will not be considered a protocol violation are listed below:

Procedure	Time Point (Relative Time)	Window Allowance
Pharmacokinetics	Predose	- 90 min
	0.5 to 2 hours postdose	- / + 2 min
	> 2 to 12 hours postdose	- / + 5 min
	> 12 to 72 hours postdose	- / + 15 min

CCI

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

Healthcare resource utilization data are not collected in this study.

9 Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

9.2 Sample Size Determination

A maximum of 32 East Asian participants will be assigned to study intervention such that approximately 20 evaluable participants (at least 10 Japanese) complete the study.

Although no hypothesis tests will be performed, the sample size of the study should be sufficient to estimate the PK parameters in Japanese (Group 1) and non-Japanese East Asian (Group 2) participants with adequate precision.

PK data collected in studies in healthy Caucasian participants suggests that the total variability of $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} is moderate to high, with a geometric CV ranging from 30% to 40% (refer to IB Version 14). Based on these data a sample size of 10 participants per group is considered sufficient to estimate PK parameters of xevinapant in Japanese, non-Japanese East Asian and in all East Asian participants.

In addition, the ratio of PK parameters between the ethnic categories in Group 1 versus Group 2 may also be estimated. Assuming CV (%) of 35% for PK parameters of xevinapant, the precision for the estimated PK parameters ratio to be achieved with a given number of evaluable participants is summarized in Table 1 if 20 evaluable participants are included in this study (10 per group), and the observed ratio is 1.0, then the 90% CI for the ratio will, with 80% probability, be contained in 0.7435 to 1.3451. A further increase in sample size does not substantially improve the precision. On the other hand, even with a slightly smaller number of completed participants, the precision will not be markedly decreased.

Therefore, 24 participants (12 per group) will be initially assigned to study intervention such that approximately 10 evaluable participants per group complete the study, allowing for a 17% drop-out rate. If the number of completers is less than 10 in one group, then up to 4 additional participants may be included in each group (up to 32 participants in total).

Table 1 90% CI with 80% tolerance probability

N1	N2	CV = 30%	CV = 35%	CV = 40%
8	8	0.7450-1.3423	0.7112-1.4062	0.6796-1.4715
10	10	0.7741-1.2917	0.7435-1.3451	0.7147-1.3993
12	12	0.7951-1.2577	0.7668-1.3040	0.7402-1.3510

CI = confidence internal; CV = coefficient of variation.
Calculations performed in R version 4.0.1.

Assumption of N1 = N2 = 10 is based on total number of Japanese and non-Japanese East Asian participants per group targeted for this study.

9.3 Population for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	The PKAS will consist of all participants, who receive at least one dose of study intervention, and provide at least one measurable postdose concentration. A measurement BLQ is considered a valid measurement. Participants will be analyzed per the actual study intervention they received.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis set.

Endpoint	Statistical Analysis Methods
• Primary	• All primary safety endpoints measured to evaluate the safety of xevinapant will be summarized descriptively by ethnic group and overall. • The number and percentage of participants experiencing 1 or more AEs will be summarized by ethnic group and overall, relationship to study drug, severity, and seriousness. AEs will be coded using the Medical Dictionary of Regulatory Activities (most recent version) terminology. • Absolute values and change from baseline for laboratory parameters and vital signs will be summarized using descriptive statistics. • Absolute values and changes from Baseline in the quantitative parameters from safety ECG recording will be summarized descriptively by ethnic group and overall.
• Secondary	• No secondary safety endpoints.

9.4.3 Other Analyses

Details on the PK analyses will be in the Integrated Analysis Plan that will be finalized before database lock.

9.4.3.1 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Primary: Xevinapant $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}	PK parameters and calculation method are in Section 8.4. Summary statistics will be provided by ethnic group and overall for the PK analysis set.
Secondary: Xevinapant $AUC_{0\text{-}24}$, t_{max}, $t_{1/2}$, CL/F, Vz/F	PK parameters and calculation method are in Section 8.4. Summary statistics will be provided by ethnic group and overall for the PK analysis set.
Secondary: D-1143-MET1 $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$ and C_{max}, t_{max}, and $t_{1/2}$, xevinapant: D-1143-MET1 molar ratio $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}	PK parameters and calculation method are in Section 8.4. Summary statistics will be provided by ethnic group and overall for the PK analysis set.

In addition, the ratio of PK parameters between the ethnic categories from this study and from historical data from healthy participant studies in non-Asian participants may also be estimated. These integrated analyses across studies will be specified in a separate Integrated Analysis Plan and not included in the CSR.

9.4.4 Sequence of Analyses

All final, planned analyses identified in the clinical study protocol will be performed only after the last participant has completed the last visit, i.e., Follow-up/Discontinuation visit with all study data in-house, all data queries resolved, and the database locked.

There are no planned formal interim analyses.

10 References

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11 Appendices

Appendix 1 Abbreviations

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CRF	case report form
CRT	chemoradiotherapy
CRU	clinical research unit
CSR	clinical study report
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of study intervention
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IAP	Integrated Analysis Plan
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	non-investigational medicinal product
PK	pharmacokinetic
QTcF	corrected QT interval by Fridericia' formula
RT	radiotherapy
SAE	serious adverse event
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse experience
ULN	upper limit of normal

UK	United Kingdom

Appendix 2 Study Governance

Financial Disclosure

Investigators and Subinvestigators 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 representative will explain the nature of the studyincluding the risks and benefits, to the participant and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; privacy and data protection 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 reconsented to the most current, approved version.

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.

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 Operations or Study Reference Manual.

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 International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - For studies with Japanese sites, the Japanese ministerial ordinance on GCP
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator 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 1 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.

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator and any Steering Committee or other relevant study-appointed committees or groups.

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

- Summary of data will be provided to www.ClinicalTrials.gov as well as to the European Clinical Trial Database, if applicable. Healthy participants might be provided with the results of the medical examinations at request. After finalization of the study, healthy participants might be provided with the information published on ClinicalTrials.gov and/or the European Clinical Trial Database at request.
- After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Principal Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.
- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, European Medicines Agency, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs 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 CRF. Details for managing CRFs are in the Operations or Study Reference Manual.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- 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 will be predefined and documented in the Project Management Plan to help support the identification of systematic issues that could potentially impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the quality tolerance limits thresholds and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 CRF 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 CRFs.
- Data recorded on CRFs 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 and its origin is found in Source Data Identification Form.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

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.
- Sponsor discontinuation of the study due to an unacceptable risk, any relevant toxicity, or negative change in the risk/benefit assessment.

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

Women of Childbearing Potential:

A woman is of childbearing potential (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.

Postmenopause:

Postmenopause 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, confirmation with more than 1 FSH measurement is required.
- A female on HRT and whose menopausal status are 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.

Permanent Sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

For individuals 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.

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 • IUD • IUS • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a woman of childbearing potential, 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 and the preferred and usual lifestyle of the participant.

Effective Methods

These methods have a failure rate of ≥ 1% per year when used consistently and correctly; therefore, they do not meet the criterion of a highly effective method.

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

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

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, 1) barrier methods (male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide) in addition to hormonal contraception or 2) a non-hormonal intrauterine device must be used. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Acceptable methods are considered effective, but **not** highly effective (i.e., have a failure rate of ≥1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are **not** acceptable methods of contraception.

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 (e.g., 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 per the Investigator's medical and scientific judgment, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent preexisting 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 SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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).

An 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 preexisting 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 CRF.
- As needed, the Sponsor 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 the Sponsor.
- 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 CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Do not confuse an AE that is assessed as severe with an SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the NCI-CTCAE, version 5.0 (publication date: 27 November 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 an 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.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor 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.
- The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the Investigator/Subinvestigator signs off this data in the system and any relevant associated data (e.g., additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered 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 electronic CRF and as a back-up method for an 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 CRF may be required in addition (e.g., medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Recording and Reporting of DLTs

- Each event that meets the DLT criteria will be recorded in the CRF within 24 hours after awareness of the event.
- Serious DLTs will be reported in an expedited manner, using the SAE reporting process, as specified above.
- Notification of each DLT related event (nonserious and serious) will be reported to the Sponsor or its designee within 24 hours from the date of awareness.

Reporting of AESIs

- For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

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 Clinical Laboratory Tests

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

Laboratory Assessments	Parameters			
Hematology	Red blood cell count Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit		Mean corpuscular hemoglobin concentration (MCHC)	
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase	Bilirubin (total)[a]
	Creatinine	Sodium	Alanine aminotransferase	Protein
	Glucose	Calcium	Alkaline phosphatase	C reactive protein
	Uric acid	Chloride	Gamma Glutamyl Transferase	Lactate dehydrogenase
	Urea	Magnesium	Amylase	Creatine Kinase (CK)[b]
	Cholesterol	Inorganic phosphate	Lipase	
	Triglycerides			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, and leukocytes by dipstick[c] • Microscopic examination (if blood, protein, nitrite, or leukocytes is abnormal).			
Other Screening Tests	• Urine drug screen: • Cocaine, Amphetamine, Methamphetamine, Opiate, Barbiturates, Benzodiazepine, Methadone, Cannabinoids, Tricyclic antidepressants, Cotinine, 3,4-methylenedioxymethamphetamine (Ecstasy) • Ethanol breath test • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • HIV1/HIV2 antibodies • SARs-CoV-2 according to local requirement • Follicle Stimulating Hormone (to confirm postmenopausal status, female only) • Serum or highly sensitive urine human chorionic gonadotropin pregnancy test to confirm non-pregnant status (females only). • Thyrotropin • Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009)			

CK=creatine kinase; HIV=human immunodeficiency virus MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration MCV=mean corpuscular volume.

a In case of increased bilirubin (total), the direct bilirubin will be determined.

b In case of increased CK, myocardium/brain type (CK-MB) will be determined; if the ratio of CK/CK-MB is above 6, troponin will be determined as well.

c Only if blood, protein, nitrite, or leukocytes are positive on the dipstick.


CCI

Appendix 7 Sponsor Signature Page

Study Title: A single-dose, open-label, single arm study to investigate PK of xevinapant and its metabolite, D-1143-MET1 in healthy East Asian participants

Regulatory Agency Identifying Numbers: EU Trial Number 2022-002182-15

Clinical Study Protocol Version: 1.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

PPD

Name, Academic Degree: PPD

Function/Title: Medical Responsible

Institution: Merck Healthcare KGaA

Address: Frankfurter Strasse 250
Darmstadt, 64293, Germany

General Merck Phone Number: PPD

General Merck Fax Number: Not Applicable

Appendix 8 Principal Investigator Signature Page

Study Title:	A single-dose, open-label, single arm study to investigate PK of xevinapant and its metabolite, D-1143-MET1 in healthy East Asian participants
Regulatory Agency Identifying Numbers:	EU Trial Number 2022-002182-15
Clinical Study Protocol Version:	1.0
Site Number:	

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

PPD

Signature

PPD

PPD

Name, academic degree:	
Title:	
Institution:	
Address:	
Telephone number.	
Fax number:	Not Applicable
E-mail address:	PPD