Integrated Analysis Plan

Study Number:	MS202359_0004
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 Phase:	1
Merck Compound:	Xevinapant
Protocol Version:	10 June 2022/Version 1.0

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Integrated Analysis Plan Date and Version:	06 October 2022 / Version 1.0

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Approval Page

Integrated Analysis Plan: MS202359_0004

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

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

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

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the concentration-time curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIPD	Clinically Important Protocol Deviation
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
EDMS	Electronic Document Management System
GCP	Good Clinical Practice
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IPD	Important Protocol Deviation
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MW	Molecular Weight
NA	Not Applicable
NCA	Non-compartmental Analysis
PD	Protocol Deviation or Pharmacodynamics
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile

SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening Analysis Set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	Système International
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULOQ	Upper Limit of Quantification
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	06 October 2022	PPD	Initial version

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS202359_0004. Results of the analyses described in this IAP will be included in the CSR. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol and is prepared in compliance with ICH E9. It describes analyses planned in the protocol, with the exception of CCI analysis for the effect of CCI variants on the PK of xevinapant which will be described and reported separately.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the Clinical Study Report (CSR) template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

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

5 Objectives and Endpoints

Objectives	Endpoints	IAP section
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}	16.1
Secondary		

Objectives	Endpoints	IAP section
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	15
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_{0-24}, t_{max}, $t_{1/2}$, CL/F, and V_z/F	16.1
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 $AUC_{0-tlast}$, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$, D-1143-MET1/xevinapant molar ratio for $AUC_{0-tlast}$, $AUC_{0-\infty}$, C_{max}	16.1
CCI		

6 Overview of Planned Analyses

All final, planned analyses identified in the IAP 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.

Statistical analyses will be performed on the basis of CDISC SDTM data. These SDTM data contain as clean as possible eCRF data as well as external data including pharmacokinetic data.

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses in the clinical study protocol.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

The Screening Analysis Set includes all participants who provided signed informed consent, regardless of the participant's randomization and study intervention status in the study.

Safety Analysis Set (SAF)

The Safety Analysis Set will include all participants who were administered any dose of any study intervention. Analyses will consider participants as treated.

PK Analysis Set (PKAS)

The PK Analysis Set 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 according to the actual study intervention they received.

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

	Analysis Set	
Analyses	**SAF**	**PKAS**
Baseline Characteristics	✓	
Previous and Concomitant Therapies	✓	
Compliance and Exposure	✓	
Safety and Tolerability	✓	
PK		✓

8.2 Subgroup Definition and Parameterization

Not applicable.

9 General Specifications for Data Analyses

The results of this study will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by ethnic group (Japanese, non-Japanese East Asian and overall) and/or scheduled time point, as applicable.

Listings

In the individual participant data listing all individual data will be listed as measured. Repeated and unscheduled measurements will be included in the listings. All listings will be sorted by treatment, ethnic group, subject ID, and/or nominal time point, as appropriate. Data which are measured before administration of the study intervention will be sorted by participant number and nominal time point (if appropriate).

Tables and Descriptive Statistics

All data will be summarized by ethnic group (Japanese, non-Japanese East Asian and overall), day, and/or nominal time point, as appropriate. Repeated and unscheduled measurements included in the listings will not be used for summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), mean, standard deviation (SD), median, 25th percentile (Q1) and 75th percentile (Q3), minimum (Min), and maximum (Max).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Study day 1 for this study is defined as the date of study intervention.

All analyses will be performed using SAS® Software version 9.4 or higher.

9.1 Definition of Baseline and Change from Baseline

If not otherwise specified, 'baseline' refers to the last scheduled measurement before administration of the study intervention.

However, if a participant is missing the baseline collection, the previous non-missing evaluation could become the baseline value (e.g. from screening/admission). If no baseline or previous to baseline evaluations exist, then the baseline value will be treated as missing.

Change from baseline is calculated as post-baseline visit value - baseline value.

9.2 Study Day / Study Intervention Day

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

9.3 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g. AE duration (days) = date of AE – date of study intervention administration + 1) if not otherwise specified.

The time since an event (e.g. relative day since first study intervention administration) will be calculated as reference date minus date of event.

9.4 Conversion Factors

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

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

9.5 Imputation of Missing Data

In this Phase I PK study, missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A participant who withdraws prior to the

last planned observation in a study period will be included in the analyses up to the time of discontinuation.

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

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing).
- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

There will be no imputation for missing or incomplete dates for prior or concomitant therapies.

For the derivation of previous and concomitant therapies the following rules will be applied:

Previous therapy:
- Start date ≤ Start of study med OR
- Start date = Missing

Concomitant therapy:
- End date ≥ Start of study med. AND (Start date ≤ End of study med OR Start date=Missing) OR
- End date = Missing AND (Start date ≤ End of study med. OR Start date = Missing)

The derivation is based on the following principles
- Imputation leads to max. reasonable duration
- Worst case: If medication is administered the same day as start of study medication, medication is classified as concomitant and prior

There will be no imputation for missing or incomplete dates for date of study intervention.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

The following will be presented in a summary table:

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of screened participants who discontinued from the trial prior to study intervention overall and grouped by the main reason for discontinuation:

  Participant did not meet all eligibility criteria

  Withdrew consent

  Other
- Number of treated participants
- Number and percentage of treated participants who completed study
- Number and percentage of treated participants who discontinued the study, with the primary reason of discontinuation by treatment and overall:

  Adverse event

  Lost to follow-up

  Protocol non-compliance

  Death

  Withdrawal by subject

  Other

A listing of discontinued participants will be provided.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing.

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive an incorrect dose
- Participants that receive an excluded concomitant medication

- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Any important protocol deviation is documented in SDTM datasets whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside of this IAP document.

Clinically important protocol deviations (CIPDs) are a subset of important protocol deviations that could impact the key objectives of the study and that would lead to the exclusion of a participant from an analysis set (see Section 8.1 Definition of Analysis Sets).

CIPDs may be identified during the course of the study but will not require amendments to this IAP.

Important protocol deviations or important events that might have an effect on PK include, but may not be limited to the following:

- Adverse events, diarrhea etc. (these instances will be discussed on a case-by case basis)
- Vomiting after administration following oral dosing (these instances will be discussed in alignment with applicable regulatory guidelines on a case-by case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g. dose administration delayed, dose change or missed doses)
- Pre-dose sample collected after the actual start of dosing
- Incomplete meal consumption prior to dosing
- Concomitant medication violations

Should one or more of these events be available at the Data Review Meeting, its implication for PK evaluation will be discussed and agreed amongst relevant study team members (e.g. Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team representative). Appropriate action will be taken such as flagging individual values to be excluded from analysis.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

If participants are excluded from the PK Analysis Set, the reasons for exclusion will be listed.

A frequency table organized according to reason for exclusion from the PK Analysis Set, as well as a listing, will be provided.

11 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be presented for the Safety Analysis Set.

11.1 Demographics

Descriptive statistics will be presented for age, height, weight, and body mass index (BMI). Frequency counts and percentages will be presented for sex, race, and ethnicity. The summary will be performed by ethnic group and overall.

Specifications for computation:

$$\text{BMI } [\text{kg/m}^2] = \frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$$

11.2 Medical History

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

11.3 Other Baseline Characteristics

Other baseline measurements, such as serology, alcohol and drugs of abuse screen, pregnancy test and follicle-stimulating hormone assessment in women, will be listed.

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry will be part of Section 15 (Safety Evaluation).

12 Previous or Concomitant Therapies/Procedures

Medications will be presented for the Safety Analysis Set.

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

The World Health Organization Drug dictionary (WHO-DD), Version Global Mar2022 B3 or higher, will be used for coding of previous and concomitant medications and they will be described using Preferred Term (PT) as applicable.

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

13 Study Intervention: Compliance and Exposure

Exposure to study intervention will be recorded in the eCRF. The listing of exposure to the study intervention will include the treatment, ethnic group, dose, study intervention administered and date/time of administration.

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

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

All safety analyses will be performed for the Safety Analysis Set and will be presented by ethnic group. An additional column for all ethnic groups (overall) may be presented when specified.

15.1 Adverse Events

All AEs recorded during the course of the study will be coded with the MedDRA, Version 25.0 or higher, and assigned to a SOC and a PT.

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the administration of study intervention. Any AE occurring before the administration of study intervention on Day 1 and resolved before administration of study intervention or not worsening after administration of study intervention will be included in the AE listings but will not be included in the summary tables (unless otherwise stated). These will be referred to as "pre-treatment" AEs.

An AE of special interest (AESI) is a noteworthy event of the particular study treatments that can be appropriate to monitor closely. AESIs are noted in the CRF.

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

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

15.1.1 All Adverse Events

Treatment-emergent AEs and participants experiencing TEAEs will be summarized by ethnic group and overall in tables with:

- The number and percentage of participants with any TEAE, any related TEAE, any serious TEAE, any related serious TEAE, any Grade ≥3 TEAE, any related Grade ≥3 TEAE, any AESIs, any TEAE leading to death, any related TEAE leading to death, any TEAE leading to study discontinuation
- The number and percentage of participants with at least one TEAE by SOC and PT, and the number of events by SOC and PT
- The number and percentage of participants with at least one TEAE and the number of events by grade, SOC, and PT
- The number and percentage of participants with at least one related TEAE and the number of events by SOC and PT
- The number and percentage of participants with at least one related TEAE and the number of events by grade, SOC, and PT

Unless otherwise stated, AEs will be displayed with SOC terms and PTs within each SOC term sorted alphabetically.

For determining incidence counts, within each level of TEAE term, if a participant experiences more than one occurrence, the participant will only be counted once for that TEAE.

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

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

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

Not applicable.

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

15.2.1 Deaths

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

15.2.2 Serious Adverse Events

A listing of serious AEs (SAEs), if any, will be provided.

15.2.3 Other Significant Adverse Events

Not applicable.

15.3 Clinical Laboratory Evaluation

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

Continuous clinical laboratory data (hematology, and biochemistry) will be summarized by ethnic group (Japanese, non-Japanese East Asian and overall) and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation.

Box-and-whisker plots for the absolute change from baseline by ethnic group (Japanese, non-Japanese East Asian and overall) and time point will also be provided.

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

15.4 Vital Signs

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

15.5 Other Safety or Tolerability Evaluations

Safety ECG data will be summarized by ethnic group (Japanese, non-Japanese East Asian and overall) and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of safety ECG data will be provided.

A listing of meal details will be provided.

15.6 COVID-19 Impact

A listing of all participants affected by the COVID-19 related study disruption (e.g. AEs/SAEs, missed visit, missed dose, treatment/study discontinuation, protocol deviation including minor, screen failure, etc.) will be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

PK evaluation will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

All descriptive summaries of PK data will be performed on the PK Analysis Set. All PK data will be descriptively summarized by ethnic group and overall.

16.1.1 Descriptive Statistics of PK Concentration Data

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

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

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

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

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

16.1.2 Descriptive Statistics of PK Parameter Data

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

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

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures.

Descriptive statistics of PK parameter data will be calculated using full precision and rounded for reporting purposes only.

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

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

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

16.1.3 General Specifications for PK Concentration and PK Parameter Data

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

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g. AUC) and for graphical presentations. It is expected that samples with concentrations above the ULOQ will be diluted and retested.

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

Samples that are collected outside the specified time windows specified in the CSP will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean concentration plots.

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

If samples are collected outside of 10% of its nominal time point, these will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean/median concentration plots.

Any PK concentrations or PK parameters excluded from summary statistics will be included in subject listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or

a table of exclusions). Any flags should be included in the study specific SDTM and ADaM data sets.

PK concentrations and PK parameters excluded form summary statistics will not be included in combined individual and mean figures. Mean plots will only contain averages when n>2.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

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

16.1.4.1 Estimation of Pharmacokinetic Parameters in Plasma

PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 4 decimal places or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

The following PK parameters will be calculated where appropriate from xevinapant and its metabolite D-1143-MET1 plasma concentrations:

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. $AUC_{0\text{-}\infty}=AUC_{0\text{-}t}+C_{last\ pred}/\ \lambda_z$.
$AUC_{0\text{-}24}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 24 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\text{-}\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0\text{-}\infty}$)*100.

Symbol	Definition
CL/F	The apparent total body clearance of study intervention following extravascular administration, taking into account the fraction of dose absorbed. CL/F = Dose $_{p.o.}$ /$AUC_{0-\infty}$ (xevinapant only).
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_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification.
C_{last}	The observed concentration at the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification.
$t_{1/2}$	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, based on the fraction of dose absorbed. V_z/F = Dose/($AUC_{0-\infty}$*λ_z) following single dose (xevinapant only).
MR($AUC_{0-tlast}$)	Metabolic ratio of $AUC_{0-tlast}$. $AUC_{0-tlast}$ for D-1143-MET1 divided by the $AUC_{0-tlast}$ of xevinapant corrected for MW. MR($AUC_{0-tlast}$)=$AUC_{xevinapant}$*$MW_{xevinapant}$/$AUC_{D-1143-MET1}$*$MW_{D-1143-MET1}$ where $MW_{xevinapant}$ = 561.71 g/mol $MW_{D-1143-MET1}$ and = 476.61 g/mol
MR($AUC_{0-\infty}$)	Metabolic ratio of $AUC_{0-\infty}$. $AUC_{0-\infty}$ for D-1143-MET1 divided by the $AUC_{0-\infty}$ of xevinapant corrected for MW. MR($AUC_{0-\infty}$)=$AUC_{xevinapant}$*$MW_{xevinapant}$/$AUC_{D-1143-MET1}$*$MW_{D-1143-MET1}$ where $MW_{xevinapant}$ = 561.71 g/mol $MW_{D-1143-MET1}$ and = 476.61 g/mol
MR(C_{max})	Metabolic ratio of C_{max}. C_{max} for D-1143-MET1 divided by the C_{max} of xevinapant corrected for MW. MR(C_{max})= C_{max}xevinapant*MWxevinapant/C_{max}D-1143-MET1*$MW_{D-1143-MET1}$ where $MW_{xevinapant}$ = 561.71 g/mol $MW_{D-1143-MET1}$ and = 476.61 g/mol

Partial areas should be calculated using the nominal dosing interval. The actual dosing interval calculated from case report form (CRF) time data should not be used.

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

- First ($\lambda_{z\ low}$) and last ($\lambda_{z\ up}$) time point of the time interval of the log-linear regression to determine λ_z.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (adjusted Rsq) for calculation of λ_z.
- Span ratio.

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

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

In case profiles have a measurable pre-dose concentration less than or equal to 5% of its C_{max} value, the participant's data without any adjustments will be included in all PK measurements and calculations. If the pre-dose value is greater than 5% of the C_{max}, the participant will be dropped from all PK evaluations. However, this participant's data will be flagged and reported.

16.1.5 Statistical Analysis of PK Parameter Data

No formal statistical analysis of PK parameter data is planned.

16.1.6 Presentation of PK Concentration and PK Parameter Data

16.1.6.1 Listings and Tables

The following PK tables will be produced based on the PK Analysis Set:

- Descriptive statistics of concentrations by analyte and ethnic group (Japanese, non-Japanese East Asian and overall)
- Descriptive statistics of PK parameters by analyte and ethnic group (Japanese, non-Japanese East Asian and overall)

The following PK listings will be produced based on the Safety Analysis Set:

- Individual concentrations by analyte and ethnic group
- Individual PK parameters by analyte and ethnic group
- Individual diagnostic PK parameters by analyte and ethnic group
- PK Sampling date, actual time, nominal time, deviation from time and concentration by participant, analyte and ethnic group sorted in chronological order
- Phoenix WinNonlin NCA Core Output

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.

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

The following PK plots will be produced based on the PK Analysis Set:

- Overlaid individual concentration versus actual time postdose plots; linear and semi-log; by analyte and ethnic group
- Arithmetic mean concentration time plots; linear with standard deviation and semi-log without standard deviation; using scheduled (nominal) time points by analyte and ethnic group (Japanese, non-Japanese East Asian and overall); if any post-dose concentration is <LLOQ the line representing LLOQ will be added to the semi-log plots
- Boxplots for PK parameters ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}) by analyte and ethnic group

17 References

Not applicable.

18 Appendices

Not applicable.