Integrated Analysis Plan

Study Number:	MS200095_0053
Clinical Study Protocol Title:	Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy Participants
Study Phase:	Phase I
Merck Compound:	Tepotinib
Protocol Version:	15 Sep 2021/Version 1.0
Integrated Analysis Plan Author:	**Coordinating Author** Biostatistics, Merck PPD **Function** **Author(s) / Data Analyst(s)** Biostatistics, PPD PPD
Integrated Analysis Plan Date and Version:	18 Feb 2022 / Version Final 1.0
Integrated Analysis Plan Reviewers:	**Function** **Name** PPD

Approval Page

Integrated Analysis Plan: MS200095_0053

Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy 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
ANOVA	Analysis of VARIANCE
BLQ	Below Lower Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
eCRF	electronic Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
PT	Preferred Term
PK	Pharmacokinetics
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	18-Feb-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 MS200095_0053. 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 protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments.

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	Ref #
Primary		
To investigate the effect of multiple doses of itraconazole on tepotinib PK in healthy participants	Plasma tepotinib: $AUC_{0-\infty}$, $AUC_{0-tlast}$ and C_{max}	1
Secondary		
To assess the safety and tolerability of tepotinib when administered together with itraconazole in healthy participants	• Nature, occurrence, severity, and seriousness of TEAEs • Absolute values and changes in safety laboratory tests • Single 12-lead ECGs evaluated by Investigator • Vital signs assessed from time of first dose to end of study participation	2
To characterize the effect of multiple doses of itraconazole on additional tepotinib PK parameters in healthy participants	Plasma tepotinib: CL/F, V_Z/F, t_{max}, $t_{½}$	3
CCI		
[redacted]	[redacted]	[redacted]
[redacted]	CCI [redacted]	[redacted]

ECG=electrocardiogram, CCI [redacted], PK=pharmacokinetics, TEAE=treatment emergent adverse events.

6 Overview of Planned Analyses

The final, planned analyses identified in the CSP and in this IAP will be performed after the last participant has completed the last visit and after all data queries resolved as well as the database locked.

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

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

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's enrollment 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.
Pharmacokinetic (PK)	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance. With evaluable PK data, i.e., non-missing values for primary endpoints. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8.3 of the CSP, they will be excluded from the PK population. All PK analyses will be based on this analysis set.

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 study intervention 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 subject ID, study intervention, and nominal time point, as appropriate.

Tables and Descriptive Statistics

All data will be summarized by study intervention and nominal time point, as appropriate. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or 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), the number of participants with missing values, (nmiss), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values the number of participants with missing values should be indicated by a 0. Mean, Median, Q1, Q3, Min, Max will have the same precision

as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean.

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 that received the respective study intervention for AE and PK tables and for all other evaluations the analysis set of interest [N]. 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 start date of study intervention.

The following labels will be used for the study interventions in tables and listings, if not stated otherwise:

Tepotinib:	Tepotinib: 500 mg on Day 1
Itraconazole:	Itraconazole: 200 mg on Days 8-11
Itraconazole+Tepotinib:	Itraconazole: 200 mg on Days 12-18 plus Tepotinib: 500 mg on Day 12

All statistical 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 first 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.

Absolute changes from baseline are defined as

absolute change = visit value – baseline value

9.2 Study Day / Study Intervention Day

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

9.3 Definition of Duration and 'Time Since' Variables

The following definitions and calculations of duration, as applicable, will be applied:

- Duration of adverse event (AE) (in days hh:mm) = end date and time - start date and time of the AE, if missing time for either the beginning or end then = end date – start date + 1; in case of multiple records for the same AE, the duration will be calculated over all these records

- Days hh:mm from dosing (onset post administration) = start date and time of the event - date and time of last dose administration of tepotinib or itraconazole (calculated for each intervention, for TEAEs), if missing time for either the dosing or event then days hh:mm from dosing = event start date – date of dose administration + 1
- Relative (Rel.) Day in study of AE = start date of the event – date of first admin + 1 (for AEs on or after the day of dosing)
- Rel. Day in study of AE = start date of the event – date of first admin (for events before the day of dosing of the study only)

9.4 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.

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 first dosing overall and grouped by the main reason for discontinuation:
  - Participant did not meet all eligibility criteria
  - Withdrew consent
  - Other (COVID-19-related and COVID-19-non-related)
- Number of treated participants
- Number and percentage of treated participants who completed study
- Number and percentage of treated participants who discontinued the study or study intervention, with the primary reason of discontinuation:
  - Adverse event
  - Lost to follow-up
  - Protocol non-compliance
  - Death

- Withdrew consent
- Other (COVID-19-related and COVID-19-non-related)

The number and percentage of participants will be presented by group of study intervention and total, where applicable. Percentages will be presented with respect to the number of treated participants, where applicable.

A listing of discontinued participants will be provided.

A listing of participants affected by the COVID-19 related study disruption by unique participant identifier will also 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 first dosing in the study. A distinction will be made between important protocol deviations due to COVID-19 versus not due to COVID-19. The respective important protocol deviations will be flagged accordingly.

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

- Adverse events like 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 or trough sample collected after the actual dosing
- Non-compliance with food and drink requirements (e.g. non-fasted, incomplete meal consumption, caffeine intake)
- Concomitant medication, vitamins, dietary or herbal supplements

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.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing.

11 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be presented for the SAF.

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 overall.

BMI (kg/m^2) will be derived (i.e., not taken directly from the database) according to the following formula:

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

11.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), most current version at time of data base lock, and listed.

The medical history will be listed by participant including preferred term (PT) as event category and system organ class (SOC) body term as Body System category.

11.3 Other Baseline Characteristics

Other baseline measurements, such as virus screen, alcohol and drugs of abuse screen, pregnancy test in women, nicotine and alcohol consumption, will be listed.

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

12 Previous or Concomitant Therapies/Procedures

Medications will be presented for the SAF.

Previous medications are defined as any medication discontinued prior to the administration of first 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 first study intervention, or with a starting date prior to the administration of first study intervention and ongoing at the time of the first administration of study intervention.

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

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

13 Study Intervention: Compliance and Exposure

The dosing of each participant is monitored by the study nurse or investigator. A listing of date and time of each drug administration and each blood sampling, including time deviations as well as measured plasma concentrations, will be provided sorted by participant. Information on meal intake will be listed by participant, if provided.

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 study intervention and nominal timepoint, as appropriate.

Safety analyses will be done according to the as-treated principle.

15.1 Adverse Events

All AEs recorded during the course of the study will be coded with the MedDRA, latest version at time of data base lock, and assigned to a SOC and a PT.

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

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 Section 15.1 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Unless otherwise specified, TEAEs will be summarized, by number and percentage of participants with the TEAE in the category of interest, as well as the number of events, in total and by study intervention group, primary SOC and PT in alphabetical order for SOC and decreasing overall frequency for PT.

Each participant will be counted only once within each SOC or PT.

If an event was reported more than once due to change in intensity and change in relationship, the worst severity and the worst relationship to trial treatment will be tabulated.

15.1.1 All Adverse Events

Number of treatment-emergent AEs and participants experiencing TEAEs will be summarized for Tepotinib, Itraconazole, Itraconazole+Tepotinib and overall, each in tables with:

- The number and percentage of participants with any TEAE, any related TEAE, any tepotinib-related TEAE, any itraconazole-related TEAE, any serious TEAE, any related serious TEAE, any tepotinib-related serious TEAE, any itraconazole-related serious TEAE, any severe TEAE, any related severe TEAE, any tepotinib-related severe TEAE, any itraconazole-related severe TEAE, any AEs of special interest (AESI), any TEAE leading to death, any related TEAE leading to death, any tepotinib-related TEAE leading to death, any itraconazole -related TEAE leading to death, any TEAE leading to study discontinuation
- The number and percentage of participants with at least one TEAE and the number of events by SOC and PT.
- The number and percentage of participants with TEAEs excluding SAEs and number of events, with frequency of participants ≥ 5% in any study intervention arm by SOC and PT
- The number and percentage of participants with at least one TEAE and number of events by severity, SOC, and PT
- The number and percentage of participants with at least one related TEAE, tepotinib-related TEAE, itraconazole -related TEAE and number of events by SOC and PT
- The number and percentage of participants with at least one AESI recorded and number of events by SOC and PT.

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

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 yes.

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

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

A listing of TEAEs leading to discontinuation of study intervention, or discontinuation of study, if any, will be provided.

The frequency (number and percentage) of participants with TEAEs leading to permanent discontinuation of each study intervention by study intervention will also be provided in a table.

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.

Summary table of the number and percentage of participants with at least one SAE by SOC and PT will also be provided.

15.2.3 Other Significant Adverse Events

The following AESI were defined:

- AEs suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (noninfectious) are considered AESIs.

More information can be found in the CSP, section 8.3.7.

AESI will be identified in the AE listings. Summary table of the number and percentage of participants with at least one AESI by SOC and PT will also be provided.

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.

Safety laboratory parameters are separated into:

- Hematology (including coagulation)
- Biochemistry
- Urinalysis
- Other tests

Hematology and biochemistry will be summarized by study intervention and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation.

Summaries will include all assessments from screening on.

Listings of abnormal test results (low and high) will also be provided.

15.4 Vital Signs

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

Vital sign summaries will include all vital sign assessments from screening on. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

15.5 Other Safety or Tolerability Evaluations

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

ECG summaries will include all ECG assessments from screening on. All ECG assessments will be listed.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. The QT interval will be corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Investigator reported interpretation results will also be tabulated by study intervention and time point using the number and percentage of participants for each interpretation category (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS]).

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by PPD.

All statistical analyses and descriptive summaries of PK data will be performed on the PK Analysis Set.

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements of tepotinib and its metabolites CCI [redacted] in plasma will be descriptively summarized by day using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics will only be calculated for n>2 in which a measurement of below lower limit of quantification (BLQ) represents a valid measurement and will be taken as zero for summary statistics of PK concentration data.

Any mean or median value that is below the lower limit of quantification will be shown as BLQ.

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. In export datasets, as well as in the SDTM PC domain, PK concentrations will be provided with full precision and will not be rounded.

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

n	0 decimal place
Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data of tepotinib and CCI [redacted] CCI [redacted]) on Day 1 and 12 will be descriptively summarized by day using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For PK parameters related to time (e.g. tmax, tlag, tlast), only n, Min, Median, and Max may be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2.

PK parameters read directly from the measurements (i.e. Cmax) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

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

n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD:	4 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 Statistical Analysis of PK Parameter Data

Analysis of Primary Endpoints

The effect of co-administration of itraconazole on tepotinib exposure will be assessed. A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to the log-transformed PK parameters C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ based on the PK analysis set. Treatment differences on the log scale of tepotinib with itraconazole versus tepotinib alone (Day 12 versus Day 1) will be estimated for the C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ together with their 90% CIs. Point estimates and CIs will be back transformed to the original scale for presentation.

The analysis will be repeated with both SUBJECT and TREATMENT as fixed effects.

CCI [redacted]

[redacted]

The analysis will be repeated with both SUBJECT and TREATMENT as fixed effects.

CCI [redacted]

16.1.4 General Specifications for PK Concentration and PK Parameter Data

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration. Same applies to the pre-dose sample after multiple doses.

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

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

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

If samples are collected outside of 10% of the PK sampling time windows defined in the CSP in section 8.4, these will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean/median concentration plots.

PK concentrations which are erroneous due to a 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 will 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 important protocol deviations occurred likely to affect the PK profile of participants as specified in Section 10.2.1, the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

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

PK concentrations and PK parameters excluded from summary statistics will not be included in mean/median figures. Mean plots will only contain values where n>2.

CCI [redacted]

16.1.5 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4 or PPD will be used to derive PK parameters applying noncompartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, PPD will be used to generate additional PK parameters, produce tables, listings and figures.

16.1.5.1 Estimation of Pharmacokinetic Parameters in Plasma

PK parameters will be calculated using the actual elapsed time since dosing. In cases where the actual sampling time is missing, calculations may be performed using the scheduled time. Details (e.g. number of samples, participants affected) will be described in the CSR. In cases actual dosing time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rational should be included in the CSR. Otherwise, there will be no further imputation of missing data.

The following plasma PK parameters will be calculated where appropriate for tepotinib and C CCI CCI

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at tlast, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-tlast} + C_{last\ pred}/\lambda_z$
$AUC_{0-tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}), calculated using the mixed log-linear trapezoidal rule (linear up, log down).
AUC_{0-24}	The AUC from time zero (= dosing time) to timepoint 24 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-tlast}$/Dose (parent analyte only)	$AUC_{0-tlast}$ divided by actual dose.
AUC_{0-24}/Dose (parent analyte only)	AUC_{0-24} divided by actual dose.
C_{max}	Maximum observed concentration.
C_{max}/Dose (parent analyte only)	C_{max} divided by actual dose.
t_{lag}	The time prior to the first concentration at or above LLOQ.
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.
CL/F (parent drug only)	The apparent total body clearance of study intervention following extravascular administration. $CL/F = Dose_{po}/AUC_{0-\infty}$. Parent drug, only.
V_z/F (parent drug only)	The apparent volume of distribution during the terminal phase following extravascular administration $V_z/F = Dose/(AUC_{0-\infty} \times \lambda_z)$ following single dose. Parent drug, only.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)×100.
[redacted]	CCI [redacted]
[redacted]	[redacted]

The IMP dose administered is given for the monohydrate hydrochloride salt (ie, 500 mg IMP). A conversion factor for the freebase IMP was calculated and will be applied when 'dose' is used in deriving PK parameter formulas needing a dose value (CL/F, Vz/F).

Conversion factor = Molecular weight (MW) of base IMP divided by MW of salt form IMP = 492.574 g/mol / 547.05 g/mol = 0.900

Amount of dose * conversion factor = actual dose of IMP: 500 mg * 0.900 = 450 mg

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs. In such cases, the Sponsor will specify relevant units for reporting before the final PK evaluation.

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

In cases where the actual observation time is not equal to the scheduled observation time, partial AUC_{0-24h} until 24h will be calculated based on the estimated concentration at 24h and not the concentration at the actual observation time.

The following rules might be applied for calculation of partial AUC, after agreement with the Sponsor:

- In case suitable regression cannot be performed, partial areas may be calculated using the actual sampling time provided it is within 10% of the actual sampling time.
- In cases BLQ concentrations occur at the end of the collection interval, these concentrations might be set to missing for calculations of partial AUCs. This is an exemption to the general BLQ handling rule and should be applied in case its application would result in estimation of implausible partial AUC values. Implausibility is considered in cases partial AUCs were greater than $AUC_{0-\infty}$.

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

- First (λz low) and last (λz up) time point of the time interval of the log-linear regression to determine λz.
- Number of data points (Nλ) included in the log-linear regression analysis to determine λz.
- Goodness of fit statistic (adjusted Rsq) for calculation of λz.
- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. ($AUC_{extra\%}$)
- Span ratio of interval over which $t_{1/2}$ was estimates/$t_{1/2}$

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

If $AUC_{extra\%}$>20% and/or the coefficient of correlation (Rsq adj) of λz is <0.8 and/or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL etc.) will be listed, flagged and included in the parameter outputs. Should more than 10% of subjects be flagged for $AUC_{extra\%}$ and/or Rsq adj (for a particular analyte), a sensitivity analysis excluding flagged parameters may be performed after discussion with the Sponsor.

CCI [redacted]

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 (PK Analysis Set):

- Descriptive statistics of concentrations by analyte, matrix, day and study intervention
- Descriptive statistics of PK parameters by analyte, matrix, day and study intervention

The following PK Listings will be produced (Safety Analysis Set):

- Individual concentrations by analyte, matrix, day and study intervention
- Individual PK parameters by analyte, matrix, day and study intervention
- PK Sampling date, actual time, nominal time, deviation from time, percentage time deviation by participant, analyte, matrix and study intervention (day) sorted in chronological order

CCI [redacted]

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

The following graphical summaries and individual plots will be provided for tepotinib and [redacted] in plasma:

- Overlaid individual plasma concentration versus time plots on linear and semi-log scale, using actual times; by analyte and study intervention (day);
- Overlaid individual plasma concentration versus time plots by participant and analyte on linear and semi-log scale using actual times. If any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots.
- Arithmetic mean concentration time plots; linear (±SD for arithmetic mean) and semi-log; using scheduled (nominal) time points by analyte, matrix and study intervention (day); if any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots
- Boxplots for primary PK parameters $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} of tepotinib by study intervention (day) and analyte.
- Spaghetti plot of primary PK parameters $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} of tepotinib by study intervention (day) and analyte

17 References

Not applicable.

18 Appendices

Not applicable