Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200095-0032
Title	Phase I, Open-label, Single Sequence, Two-Period Study to Evaluate the Effect of Tepotinib on P-Glycoprotein by Investigating the Pharmacokinetics of the P-Glycoprotein Probe Substrate Dabigatran Etexilate in Healthy Subjects
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Signature Page

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1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve 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
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity
AUC_{extra}	The AUC from time t_{last} extrapolated to infinity
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$) x 100
AUC_{τ}	The area under the plasma concentration-time curve (AUC) over the dosing interval from T_1 = 0 h to T_2 = τ h
BMI	Body Mass Index
CI	Confidence Interval
CL/f	Apparent total body clearance considering the fraction of dose (f) absorbed
CL_{SS}/f	Apparent total body clearance of drug at steady state following oral administration, considering the fraction of dose (f) absorbed.
C_{max}	Maximum plasma concentration observed
$C_{max,SS}$	Maximum plasma concentration observed in steady state
$C_{min,SS}$	Minimum plasma concentration observed in steady state
CV%	Coefficient of Variation
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PT	Preferred Term
PK	Pharmacokinetics
SAE	Serious Adverse Event
Q1	25th Percentile
Q3	75th Percentile
QTcF	Corrected QT interval per Fridericia's formula
SEM	Standard Error of the Mean
SOC	System Organ Class
SD	Standard Deviation
SEM	Standard Error of the Mean
TEAE	Treatment Emergent Adverse Event
ULOQ	Upper Limit of Quantification

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	28-AUG-2018	PI	Original document

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 MS200095-0032. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will 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 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To investigate the effect of tepotinib on the primary pharmacokinetic (PK) endpoints of dabigatran following oral administration of the P-gp probe substrate dabigatran etexilate after multiple dose administration of tepotinib in healthy subjects.	PK profile of dabigatran in terms of area under the concentration-time curve (AUC) from time zero to the last sampling time (AUC_{0-t}), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}) of total dabigatran (unconjugated plus conjugated) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.	16.1.1
Secondary Objective	To investigate the PK effect of tepotinib on the secondary PK endpoints of dabigatran following oral administration of dabigatran etexilate	PK profile of total dabigatran (unconjugated plus conjugated) in terms of time of the maximum drug concentration (t_{max}), terminal half-life ($t_{1/2}$), percentage of $AUC_{0-\infty}$ obtained by extrapolation ($AUC_{extra\%}$), apparent total body clearance (CL/f), apparent volume of distribution during terminal phase ($V_{Z/f}$) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.	16.1.2
	To assess the safety and tolerability of tepotinib alone and upon co-administration of dabigatran etexilate.	Occurrence of treatment emergent adverse events (TEAEs, incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs in subjects receiving tepotinib alone and together with dabigatran etexilate assessed from Day -1 of Period 1 until the End of Trial Visit.	15
Exploratory Objective	To investigate the multiple dose PK of tepotinib and its metabolites (MSC2571109A and MSC2571107A)	PK profile of tepotinib and its metabolites MSC2571109A and MSC2571107A in terms of AUC over the dosing interval (AUC_{τ}), C_{max} at steady state ($C_{max,SS}$), minimum concentration at steady state ($C_{min,SS}$), t_{max} at steady state ($t_{max,SS}$), CL/f at steady state ($CL_{SS/f}$) (parent drug only), and $t_{1/2}$ if appropriate	16.1.3
	To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of dabigatran and/or tepotinib (if applicable; participation is optional).	Genetic variants and mutations in genes that potentially influence the PK of tepotinib and/or dabigatran.	16.2

6 Overview of Planned Analyses

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed only after the last subject has completed the last visit, i.e. end of trial visit/early termination visit with all trial data in-house, all data queries resolved, and the database locked.

An interim evaluation of the safety and tolerability as well as the PK data will be performed after the first 6 subjects have completed Period 2. The description of these analyses will not be part of this IAP.

The data presented will include:

- Treatment emergent adverse events
- Plasma concentrations of tepotinib
- PK parameters of tepotinib
- Vital signs
- ECG parameters
- Safety laboratory values

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

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted.

Scatter plots for the primary endpoint will show geometric means (GeoMean) instead of median, 25th Percentile and 75th Percentile (Q1 and Q3).

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

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

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Concomitant medication violations (see Section 6.5.1 of the protocol)
- Use of prohibited medicines (see Section 6.5.2. of the protocol)
- Subjects that receive incorrect treatment or dose
- Sample processing errors that may lead to inaccurate bioanalytical results
- Vomiting or diarrhea following oral dosing (these instances will be discussed on a case-by-case basis)

- Deviation from Good Clinical Practice
- Non-compliance to study procedures or deviations from study procedures likely to affect the primary endpoints (e.g. subject develops withdrawal criteria whilst on the study but is not withdrawn)
- Deviation from study medication compliance in terms of medical conditions and/or AEs that may have interfered with drug disposition or with respect to factors likely to affect the primary endpoints

All important protocol deviations will be documented in CDISC datasets whether identified through sites monitoring or medical review.

8.2 Definition of Analysis Sets and Subgroups

For purposes of analysis, the following populations are defined:

Population	Description
Screening	The screening analysis set will include all subjects who provided signed informed consent, regardless of treatment status in the trial. This set will be used for subject disposition.
Safety	The Safety Analysis Set will include all subjects who have received at least 1 dose of planned IMP. Subjects will be analyzed according to the actual treatment they receive.
Pharmacokinetic	The PK Analysis Set will include all subjects who have completed at least 1 period without any relevant protocol violations with respect to factors likely to affect the comparability of PK results, with adequate study medication compliance, and with evaluable dabigatran PK data. Assessment of data sufficiency will be done by the responsible pharmacokineticist before database lock, ie PK data will be available and included in the database before data base lock. Subjects may be excluded after vomiting or following diarrhea in a particular period as this could render the plasma concentration-time profile unreliable. The use of a concomitant medication that might interfere with the PK of any investigational drug could be a reason for excluding a subject.

9 General Specifications for Data Analyses

Statistical analyses will be performed using the computer program package SAS® System for Windows™ (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment and/or scheduled time point, as appropriate.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (ie, number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, 25th and 75th percentiles [Q1 and Q3], minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie, count and percentages), if not stated otherwise. 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. Unless otherwise stated the calculation of proportions will be based on the number of subjects at risk or with available measurements in the analysis set of interest for safety outputs. For subject disposition and demographic tables the denominator will be the number of subjects in the analysis set. Counts of missing observations will be included as a separate category.

If not otherwise specified, 'baseline' refers to the last scheduled measurement before administration of the first drug in each period. However, if a subject 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.

The following calculations and derivations, as applicable, will be used:

- Change from baseline: post-baseline visit value - baseline value
- Duration of 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
- Days hh:mm from dosing = start date and time of the event - date and time dose administration; (for treatment- emergent AEs), if missing time for either the beginning or end then = end date – start date + 1
- 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 AEs before the day of dosing)

Repeated laboratory assessments will be flagged as repeats in the subject data listings and not included in summary tables statistics (unless the scheduled measurement was considered unreliable, e.g. due to technical reasons, and needed to be replaced by an unscheduled repeat measurement).

In this phase 1 PK study missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A subject who withdraws prior

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

The following treatmentlabels will be used in listing and tables:

- dabigatran
- dabigatran + tepotinib

10 Trial Subjects

10.1 Disposition of Subjects and Discontinuations

This following will be presented in a summary table:

- Total number of subjects screened (ie, subjects who gave informed consent)
- Number of screened subjects who discontinued from the trial prior to treatment overall and grouped by the main reason for discontinuation:
    - Subject did not meet all eligibility criteria
    - Withdrew consent
    - Other
- Number of treated subjects
- Number and percentage of treated subjects who completed study
- Number and percentage of treated subjects who discontinued the study, with the primary reason of discontinuation:
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Withdrew consent
    - Other
- Number and percentage of subjects who completed period (for periods 1 and 2)

- Number and percentage of subjects who discontinued study in period and reason for discontinuation (for periods 1 and 2)

A listing of discontinued subjects will be provided.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

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

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a subject from an analysis set will be listed based on the safety set.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing based on the safety analysis set.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be given for both the safety and the pharmacokinetic set, if different.

Demographic characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit eCRF pages.

Demographic characteristics:

- Sex: male, female
- Race: Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, White, Other
- Ethnic origin: Hispanic or Latino, Not Hispanic or Latino, Japanese, Not Japanese
- Age (years): summary statistics
- Height (cm) at Baseline: summary statistics
- Weight (kg) at Baseline: summary statistics

- BMI (kg/m²) at Baseline: summary statistics

Age will be taken from the eCRF and cannot be derived from the data because only the year of birth is collected in the eCRF.

BMI will be re-derived (ie, not taken directly from the database) according to the following formula:

- BMI (kg/m²) = weight (kg) / (height (m) * height (m))

11.2 Medical History

The medical history will be listed by subject including the preferred term and MedDRA system organ class (SOC) body using MedDRA, current version.

11.3 Other Baseline Characteristics

Other baseline characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit eCRF pages.

Other baseline characteristics:

- Smoking status
- Alcohol consumption

12 Previous or Concomitant Medications/Procedures

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started and stopped before first administration of trial drug.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject).

In case the date values will not allow to unequivocally allocating a medication to previous or concomitant medication the medication will be considered as concomitant medication

Any previous and concomitant medication will be encoded with WHO-DD, latest version. Prior and concomitant medications will be listed by subject (all subjects).

The following information will be displayed in a listing: generic or trade name (as reported in eCRF), WHO drug name (including ATC-2nd level and preferred term), dose/unit, route, frequency, reason for use, start/end date and time.

Concomitant procedures will be presented in a data listing.

13 Treatment Compliance and Exposure

A listing of date and time of each drug administration and each blood sampling including time deviations will be provided sorted by subject.

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

Safety data analysis will be conducted on the Safety Analysis Set.

15.1 Adverse Events

The number and percentage of subjects experiencing at least one TEAE will be summarized by treatment as well as the number of events. A TEAE is an AE with onset after start of treatment. Tables by relationship to trial drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities terminology, latest version.

Incomplete TEAE-related dates will be handled 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 trial treatment then the onset date will be replaced by the minimum of start of trial treatment and TEAE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject'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.

15.1.1 All Adverse Events

All AEs recorded during the course of the trial (ie, assessed from signature of informed consent until the end of the Follow-up/End of Trial visit) will be coded according to MedDRA latest version and assigned to a SOC and PT.

TEAEs will be summarized by worst severity, using MedDRA latest version preferred term as event category and MedDRA primary system organ class (SOC) body term as Body System category. The severity of AEs will be graded using the "National Cancer Institute - Common Terminology Criteria for Adverse Events" (NCI-CTCAE) guideline, as detailed in the study protocol.

TEAEs related to trial treatment are those events with relationship missing, unknown or related.

The following will be summarized in an overview table with the number and percentage of subjects (and the number of events) by treatment and overall:

- Any TEAE
- Any trial treatment related TEAE
- Any TEAE related to dabigatran
- Any TEAE related to tepotinib
- Any serious TEAE
- Any trial treatment related serious TEAE
- Any dabigatran related serious TEAE
- Any tepotinib related serious TEAE
- Any severe TEAE (grade >=3)
- Any trial treatment related severe TEAE (grade >=3)
- Any dabigatran related severe TEAE (grade >=3)
- Any tepotinib related severe TEAE (grade >=3)
- Any TEAE leading to death
- Any trial treatment related TEAE leading to death
- Any dabigatran related severe TEAE leading to death
- Any tepotinib related severe TEAE leading to death

TEAEs will be summarized by treatment and overall in tables with:

- The number and percentage of subjects by treatment with at least one TEAE and the number of events overall and by SOC and PT.
- The number and percentage of subjects by treatment with at least one non-serious TEAE and the number of non-serious TEAE applying frequency threshold of 5%.

Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency (based on all treatment groups combined).

In addition the following tables will be provided:

- A table by severity of TEAEs with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.
- A table by relationship to trial treatment with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.

Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency (based on all treatment groups combined)

Pre-treatment AEs (AEs with onset after informed consent but before start of treatment) and TEAEs will be listed separately.

15.1.2 Adverse Events Leading to Treatment Discontinuation

TEAEs leading to permanent discontinuation of trial treatment will be summarized by treatment and overall including number of subjects, percentage and number of events.

A listing of TEAEs leading to permanent discontinuation of a trial treatment will additionally be provided.

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

15.2.1 Deaths

All deaths as well as reason for death will be based on information from the "Report of Subject Death" eCRFs.

Listing of deaths, if any, will be provided displaying date and cause of death (including TEAE leading to death and relatedness to trial treatment, when applicable), and date and time of treatment administration.

15.2.2 Serious Adverse Events

A summary table of SAEs, if any, by treatment and overall will be provided displaying the number and percentage of subjects by treatment with at least one SAE and the number of SAE overall and by system organ class and preferred term. Group/SOC terms and PTs within each group/SOC term will be sorted alphabetically.

Listing of SAEs, if any, will be provided in addition.

15.2.3 Other Significant Adverse Event

15.2.3.1 Adverse Events of Special Interest

Healthy subjects might experience asymptomatic elevations in serum lipase and amylase. Any elevation in serum lipase and amylase of Grade ≥ 3 will lead to the recording of an adverse event of special interest (AESI). The severity of these AEs should be defined based on clinical judgment of the Investigator and defined according to NCI-CTCAE Severity Scale.

Adverse events of special interest will be presented in a separate data listing.

15.3 Clinical Laboratory Evaluation

All laboratory data will be reported with SI units. Laboratory parameters will be listed by subject and time-point and summarized indicating the treatment at the respective time-point using descriptive statistics for absolute values and change from baseline over time. Data listings of abnormalities as per the NCI-CTCAE guideline will be provided. Shift tables for laboratory tests will be presented by treatment. Shift tables will be based on NCI-CTCAE grades, where possible, and on normal ranges otherwise. They will be produced for

- End of Trial versus Screening
- Discharge versus Pre-dose (Tepotinib admistration) within periods.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and NCI-CTCAE grade and will additionally be listed separately.

See section 7.4.3 of the clinical study protocol for a table of the safety laboratory evaluations.

Safety laboratory values are separated into:

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

Tables will be produced for the groups hematology (including coagulation), and biochemistry.

15.4 Vital Signs

Vital signs will be listed by subject and time-point and summarized for absolute values and changes-from-baseline by visit and treatment using descriptive statistics. Descriptive statistics tables will start at baseline.

15.5 ECG Evaluation

ECG data will be listed by subject and time-point and summarized for absolute values and changes-from-baseline by treatment group using descriptive statistics. Descriptive statistics tables will start at baseline. Clinically significant ECG findings for individual subjects will be listed and summarized.

The time intervals (PR, QRS, RR, QT and corrected QT intervals [based on Fridericia's formula, QTcF]) will be summarized descriptively by treatment.

The Fridericia's Correction (QTcF) is derived as follows:

Fridericia's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR-interval measured in seconds.

Observed QTcF values will be categorized according to their absolute values into the categories

- ≤ 430 ms,
- > 430 and ≤ 450 ms,
- > 450 and ≤ 480 ms,
- > 480 and ≤ 500 ms, and
- > 500 ms,

and categorized according to their absolute change from baseline into the categories

- ≤ 30 ms,
- > 30 and ≤ 60 ms, and
- > 60 ms.

The number and percentage of subjects by these categories at any post-dose assessment will be tabulated by treatment group.

All ECG measurements will be listed, with abnormalities indicated.

Investigator reported interpretation results will also be listed and tabulated treatment using the number and percentage of subjects for each interpretation category (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS].

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

General Specifications for Plasma Concentration Data

PK concentration data of total dabigatran and tepotinib and its metabolites in plasma will be presented in tables and descriptively summarized by treatment and nominal time point using n, arithmetic mean, SD, SEM, median, minimum, maximum, and CV%. Values below the LLOQ will be taken as zero for descriptive statistics of PK concentrations.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. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

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

For final evaluations values greater than the upper limit of quantification (ULOQ) are not accepted and should be replaced by valid numeric values from dilution measurement. 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.". Pre-dose 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 drug administration.

General Specifications for PK Parameter Data

PK parameter data of total dabigatran, tepotinib and its metabolites in plasma will be presented in tables and descriptively summarized by treatment using n, arithmetic mean, SD, standard error of the mean (SEM), median, minimum, maximum, CV%, GeoMean, the geometric coefficient of variation (GeoCV%), and the 95% CI for the GeoMean.

PK parameter C_{max} 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:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD, SEM:	4 significant digits
CV%, GeoCV%:	1 decimal place
Ratio of GeoMean and 95% CI	4 decimal places

To ensure a reliable estimate of the extent of exposure, AUC_{extra} should be less than or equal to 20%. If AUC_{extra} is greater than 20%, all parameters derived using λ_z (ie, λ_z, $t_{1/2}$, $AUC_{0-\infty}$ AUC_{extra}, Vz/f, CL/f) will be listed, but set to missing for the calculation of descriptive statistics.

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set. All available concentration/PK data will be listed. Data of subjects not in the PK analysis set or invalid data will be flagged accordingly.

16.1.1 Primary Endpoints

A general linear model with TREATMENT and SUBJECT as fixed effects will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of dabigatran (measured as total dabigatran) based on the PK analysis set. Treatment differences on the log scale of dabigatran with tepotinib vs dabigatran alone will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their 90% CIs. Point estimates and CIs will be back-transformed to the original scale.

The primary endpoints will be descriptively summarized. Scatter plots will be produced for the individual PK parameters by treatment group indicating the geometric means within each treatment group.

16.1.2 Secondary Endpoints

Summary statistics will be provided for all secondary PK parameters by treatment.

Individual estimates of relative bioavailability of dabigatran (dabigatran with tepotinib/dabigatran alone) will be calculated for each subject and listed and summarized.

For t_{max} of dabigatran the Hodges-Lehmann shift estimator (dabigatran with tepotinib - dabibatran alone) will be calculated together with the 90% confidence interval according to Tukey.

PK variables will be evaluated for all subjects of the PK population. PK variables will be listed for all subjects with available data in the safety set.

16.1.3 Exploratory Endpoints

Summary statistics will be provided for all exploratory PK parameters.

16.1.4 Plasma Concentration Data for Dabigatran, Tepotinib and Metabolites

Summary statistics will be provided by treatment and nominal timepoint.

The following tables will be produced separately for dabigatran, tepotinib and the metabolites:

- Summary of plasma concentrations by treatment and nominal time

The following figures will be produced for the dabigatran plasma concentrations:

- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear and semi-logarithmic scale
- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear scale including SD error bars
- Individual plasma concentration-time profiles overlaying subjects, for each treatment separately on linear and semi-logarithmic scale
- Individual plasma concentration-time profiles overlaying all treatments, separately for each subject on linear and semi-logarithmic scale

The following listing will be produced:

- Plasma concentrations will be listed by nominal time by treatment. Excluded plasma concentrations will be flagged.

16.1.5 Estimation of Individual Pharmacokinetic Parameters

The following non-compartmental PK parameters (see Table 1 and Table 2) will be calculated from the individual plasma total dabigatran (unconjugated plus conjugated), tepotinib and metabolites concentration-time data using commercial software such as Phoenix®/WinNonlin® (Version 6.2 or higher) at Nuvisan GmbH.

Table 1 Definition of PK Parameters for Dabigatran after Single Dose Administration

Symbol	Definition
AUC_{0-t}	Area under the plasma 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 (LLOQ), calculated per the mixed log linear trapezoidal rule (ie, linear up/log down)
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity, calculated as AUC_{0-t} + AUC_{extra}. AUC_{extra} represents the extrapolated part of $AUC_{0-\infty}$ calculated by $C_{lastpred}/\lambda_z$, where $C_{lastpred}$ is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for λ_z determination at which the measured plasma concentration is at or above LLOQ
C_{max}	Maximum plasma concentration observed
t_{last}	The last sampling time at which the plasma concentration is at or above the lower limit of quantification
t_{max}	Time to reach the maximum plasma concentration
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$
λ_z	Terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve
CL/f	Apparent total body clearance of drug from plasma following extravascular administration, calculated as dose/$AUC_{0-\infty}$
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$) x100.

Table 2 Definition of PK Parameters for Tepotinib and Metabolites MSC2571109A and MSC2571107A after Multiple Dose Administration

Symbol	Definition
AUC_{τ}	The area under the plasma concentration-time curve (AUC) at steady state over the dosing interval from $T_1 = 0$ h to $T_2 = \tau$ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down), $\tau = 24$ h
CL_{SS}/f	Apparent total body clearance of drug at steady state following extravascular administration, considering the fraction of dose absorbed. CL_{SS}/f = Dose p.o. / AUC_{τ} (parent drug only)
$C_{max,SS}$	Maximum observed plasma concentration during a complete dosing interval at steady state
$C_{min,SS}$	Minimum observed plasma concentration during a complete dosing interval at steady state
$t_{max,SS}$	The time to reach the maximum observed plasma concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$F_{rel,test/reference}$	Relative bioavailability, defined as $AUC_{0-\infty,test}/AUC_{0-\infty,reference}$, $F = \frac{AUC_{0-\infty,\,test}}{AUC_{0-\infty,\,reference}} * 100$

Individual PK parameters will be calculated using actual sampling times. The predose sample will be considered as if it had been taken simultaneously with the administration of study drug. PK variables will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Plasma concentrations below LLOQ before the last quantifiable data point will be taken as zero for calculating the AUC (ie, embedded BLQ values set to zero). Plasma concentrations below LLOQ after the last quantifiable data point will not be considered for the determination of λ_z.

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

- The time interval (h) of the log-linear regression ($\lambda_{z\,low}$, $\lambda_{z\,upp}$) to determine λ_z.
- Number of data points included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq) for calculation of λ_z.

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. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any <LLOQ concentrations that occur after the last quantifiable data point should not be used.

The coefficient of correlation (R^2) should be ≥0.8 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the corresponding values should be flagged in the listing displaying Individual Plasma Pharmacokinetic Diagnostic Parameters for Each Treatment. Any flags should be included in the study specific SDTM. Then the rate constants and all derived parameters (e.g. $AUC_{0-\infty}$, $\%AUC_{extra}$, CL/f, $t_{1/2}$, and V_Z/f) will be included in the parameter listings and will be discussed appropriately in alignment with the protocol lead and quantitative pharmacology representative.

Partial areas AUC_τ should be calculated using the scheduled dosing interval, as defined in the Clinical Trial Protocol. The actual dosing interval calculated from eCRF time data should not be used. The following rules apply when calculating the partial area AUC_τ within the observed time interval fromT_1 to T_2:

- If the start time of the interval (T_1) occurs before the first observation, the observation at T_1 will be estimated using the linear interpolant between the first datapoint and C_0. For single dose data C_0= 0 when the drug was administered via an extravascular route. For steady state models, C_0 is the minimum concentration value occurring within the time interval T_1 to T_2.

- If either T_1 or T_2 falls within the time range in which samples were taken, but does not coincide with an observed data point, then a linear or logarithmic interpolation is performed to estimate the corresponding concentration value. Whether a linear or logarithmic interpolation is used will depend on the method of AUC calculation e.g. linear up log down.

- If the end time of the interval (T_2) occurs after the last measurable concentration and the terminal regression (λ_z) is estimable, then λ_z is used to estimate the concentration at time T_2. The log trapezoidal rule will be used to calculate the area from the last observation time to the end time of the partial area (T_2). If λ_z cannot be estimated the partial area will not be calculated.

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).

Conversion factor = Molecular weight (MW) of base IMP divided by MW of salt form IMP = 492.574 g/mol / 547.05 g/mol = 0.9004

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

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

16.2 Pharmacogenetics

The results of the pharmacogenetic analysis, as applicable, will be described in a separate report.

17 References

None.

18 Appendices

None.