Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200095-0044
Title	Phase 1, Open-label, 3-Parts Study with Crossover Design in each part to Investigate the Bioequivalence of the Tablet Formulation of Tepotinib TF3 compared to TF2 (Part A), and to Investigate the Influence of Food on the Pharmacokinetics of each Tablet Formulation TF2 (Part B) and TF3 (Part C) of Tepotinib in Healthy Subjects
Trial Phase	1
Investigational Medicinal Product(s)	Tepotinib (MSC2156119J)
Clinical Trial Protocol Version	29 May 2018 / Version 1.0
Integrated Analysis Plan Author	**Coordinating Author** On behalf of PI , PI Merck **Function** — **Author(s) / Data Analyst(s)** PI , Nuvisan — PI PI , Nuvisan — PI
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1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of VARIANCE
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GMR	Geometric Mean Ratio
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
LCI	Lower Confidence Interval Bound
LLOQ	Lower Limit of Quantification
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
Max	Maximum
Min	Minimum
PT	Preferred Term
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
Q1	First Quartile
Q3	Third Quartile
QTcF	Corrected QT interval per Fridericia‟s formula
SAE	Serious Adverse Event
SEM	Standard Error of the Mean

SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TF2	Tablet Formulation 2
TF3	Tablet Formulation 3
UCI	Upper Confidence Interval Bound
ULOQ	Upper Limit of Quantification

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	14-NOV-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 MS200095-0044. 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 Objectives	• Part A: To demonstrate bioequivalence between the new tablet formulation (TF3, test treatment) and the tablet formulation used in clinical studies (TF2, reference treatment) after single dose administration in healthy subjects under fasting conditions	Primary Endpoints: Part A: • Area under the plasma concentration-time curve (AUC) from time zero (=dosing time) to the last sampling time at which the concentration is at or above the lower limit of quantification (AUC_{0-t}) • AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$) • maximum plasma concentration (C_{max}) of tepotinib observed from time zero to	16.1.1.1

		168 h postdose of each period	
	• Parts B and C: To investigate the food effect, ie the difference in PK between administration after a high-calorie, high-fat breakfast and administration under fasting conditions in healthy subjects, for both TF3 and TF2.	Parts B and C: • AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of tepotinib observed from time zero to 168 h postdose of each period.	16.1.1.2
Secondary Objectives	• To further investigate the PK of tepotinib	Secondary endpoints: • Time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance considering the fraction of dose absorbed (CL/f) and apparent volume of distribution during terminal phase (V_z/f) of tepotinib observed from time zero to 168 h post-dose of each period.	16.1.2
	• To assess the safety and tolerability of tepotinib (TF3 and TF2) under fasting and non-fasting conditions.	• 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.	15
	• Part A: To investigate the PK of metabolites after administration of both tablet formulations (TF3 and TF2) of tepotinib	Exploratory Endpoints: • PK profiles of tepotinib metabolites: • AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period	16.1.3
Exploratory Objectives	• Parts B and C: To investigate the effect of food on the PK of metabolites of tepotinib	• AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period	16.1.3
	• To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib (if applicable).	• Genetic variants and mutations in genes that potentially influence PK of tepotinib.	16.2

6 Overview of Planned Analyses

6.1 Interim Analysis

A two-stage design is used in Part A. Based on the measured variability, the corresponding power for the number of subjects in Stage 1 will be estimated. The final bioequivalence analysis for Part A will be performed after Stage 1 or Stage 2, depending on the result of the interim.

6.2 Final Analysis

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

A data review meeting will be held prior to database lock for both the interim and final analysis. 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.

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

Part A (Bioequivalence)

The PK Analysis Set for Part A will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have valid primary endpoints for both treatments.

All PK analyses for Part A will be based on this analysis set.

Parts B and C (Food Effect)

The PK Analysis Set for each Part B and C, will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have at least 3 post-dose concentration measurements.

All PK analyses for Parts B and C will be based on the respective PK analysis set.

All Parts (Safety)

The Safety Analysis Set will include all subjects who have received at least 1 dose of planned IMP in the respective Parts. Subjects will be analyzed according to the actual treatment they receive.

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.

For all Parts (A, B and C)

Subjects in a particular period may be excluded after vomiting or with diarrhea 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.

Relevant decisions will be made before database lock.

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.

This study has three separate parts (A, B and C). Outputs applicable to more than one part will be paged by part with the part indicated in a sub-heading.

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, the first and third quartile [Q1 and Q3], minimum [Min], and maximum [Max]) 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. 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 dosing or event then = event start date – date of dose administration + 1
- Rel. Day in period of AE = start date of the event – date of First Admin in period + 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 of the study only)

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 treatment labels will be used:

- Part A
  - TF2, fasted
  - TF3, fasted
- Part B
  - TF2, fasted
  - TF2, fed
- Part C
  - TF3, fasted
  - TF3, fed

10 Trial Subjects

The subjects will be enrolled into either Part A, B or C, and will be recruited separately for each of the study parts. Subject disposition will be presented separately for each part.

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
  - Adverse event
  - Lost to follow-up
  - Death
  - Other
- Number of treated subjects by treatment and overall
- Number and percentage of treated subjects who completed study by treatment and overall

- Number and percentage of treated subjects who discontinued the study, with the primary reason of discontinuation by treatment and overall:
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Withdrew consent
    - Other

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
- 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 CRF), 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 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, version 5.0 (publication date: 27 Nov 2017), 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 TEAEs

- Any trial treatment related TEAEs

- Any serious TEAEs

- Any trial treatment related serious TEAEs

- Any TEAE (grade >=3)

- Any trial treatment related TEAEs (grade >=3)

- Any TEAEs leading to death

- Any trial treatment related TEAEs 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. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency.

- 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.

In addition the following tables will be provided. 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):

- 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.

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” CRFs.

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 AE 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 and by post-dose CTCAE grade shift relative to baseline. Shift tables will be based on NCI-CTCAE grades, where possible, and on normal ranges otherwise.

Shift tables will be presented for:

- End of Trial versus Screening
- Discharge Day 4 versus Pre-dose (Tepotinib administration) 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. Any out-of-range values will additionally be listed separately including NCI-CTCAE grade.

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
- Biochemistry

- Urinalysis
- Other tests

Tables will be produced for the groups Hematology, 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 (period-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 by absolute values and changes-from-baseline (period-baseline) by treatment group using descriptive statistics. Baseline is the pre-dose assessment in each period. See section 9 for a description of how missing baseline values are handled. 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 period 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 and changes from period baseline will be listed, with abnormalities (as reported of the investigator on the ECG eCRF page) indicated.

Investigator reported interpretation results will also be tabulated by 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

Concentrations of tepotinib and its metabolites in plasma will be presented in tables and descriptively summarized by treatment and nominal time point using number of observations (n), Mean, SD, standard error of the mean (SEM), median, Min, Max, and CV%. 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

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data. 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 will be descriptively summarized: n, Mean, SEM, SD, CV%, Min, median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM).

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

16.1.1.1 Primary Endpoints in Part A

Statistical Hypotheses for Part A (Bioequivalence) - Two-stage Adaptive Design

The following null hypothesis for the ratio of the geometric means will be used to assess bioequivalence

H_0: $\mu_T/\mu_R \leq 0.8000$ or $1.2500 \leq \mu_T/\mu_R$ for at least one parameter (AUC_{0-t} or

$AUC_{0-\infty}$ or C_{max})

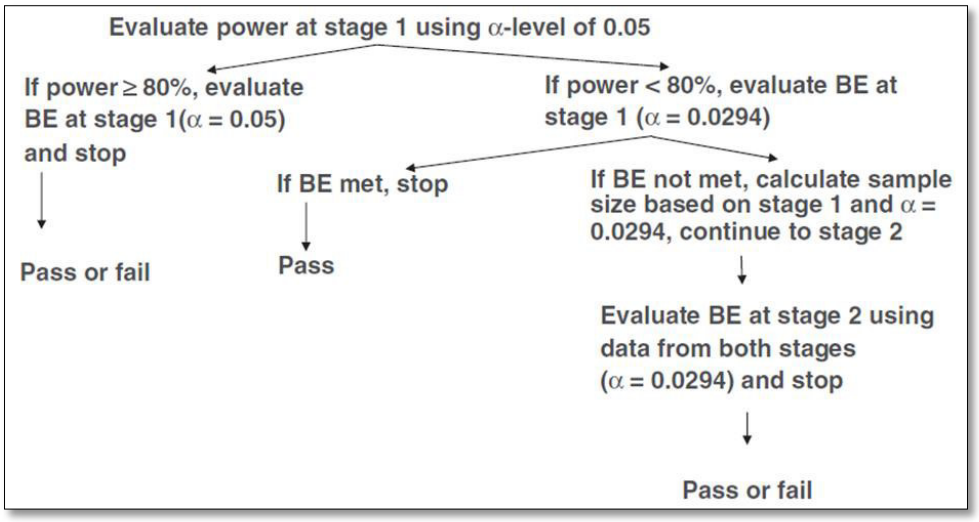
H_1: $0.8000 < \mu_T/\mu_R < 1.2500$ for all parameters (AUC_{0-t} and $AUC_{0-\infty}$ and C_{max})

where μ_T and μ_R are the geometric means for the test and reference treatment respectively.

The test treatment is the new tablet formulation (TF3) and reference is the tablet formulation used in clinical studies (TF2) both under fasting condition.

The null hypothesis will be tested using a two-stage adaptive design Figure 1 . The procedure will follow the method C described by Montague [1] and Potvin [2].

Figure 1 Diagram of Two-Stage Adaptive Design



Source: (Montague et al [1]) Figure 2; BE: Bioequivalence

The power at stage 1 will be estimated using a geometric mean ratio (GMR) of 0.95 and CV(%) as the maximum intra-individual CV(%) for the three PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The CV(%) for each parameter will be estimated by analysis of variance (ANOVA) on the log transformed parameter. The ANOVA will include TREATMENT, PERIOD, SEQUENCE and SUBJECT within SEQUENCE as fixed effects.

If the power is >= 80% then bioequivalence will be evaluated at an alpha level of 0.05. If the power is < 80% and the bioequivalence criteria not met at an alpha level of 0.0294, the study will proceed to the second stage with a re-estimated sample size. The re-estimated sample size will be the minimum even number of subjects required for the combined data from stages 1 and 2 to have at least 80% power (based on the newly estimated CV[%], an assumed GMR of 0.95 and an adjusted alpha of 0.0294.).

The significance level for the second stage analysis will be set to 0.0294.

The null hypothesis will be rejected if the CI corresponding to the α-level (either 90% or 94.12%) for the ratio of the geometric mean lies within the interval 0.8000 to 1.2500.

Analyses in Part A

Primary analysis

An analysis of variance (ANOVA) model with TREATMENT, PERIOD, SEQUENCE and SUBJECT(SEQUENCE) as fixed effects will be fitted for the log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ based on the PK analysis set. If a Stage 2 is required and the number

of subjects in stage 2 is sufficiently large, STAGE will be included as additional effect to the ANOVA model for the analysis of both stages. A linear model with STAGE, TREATMENT, PERIOD(STAGE), SEQUENCE and SUBJECT(STAGE*SEQUENCE) as fixed effects will be applied to the log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ based on the PK analysis set.

Treatment differences TF3-TF2 under fasting condition on the log scale will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their CIs (90% if the power >=80% or 94.12% if the power <80% according to the adaptive sample size sequential method in Figure 1). 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.

The PK variables also be listed for all subjects of the PK population.

Sensitivity analysis

In order to take into account that the study will be carried out in two or more cohorts (due to the logistical reasons, only a limited number of subjects are available at one time), the primary statistical model is modified to reflect the multigroup nature of the study. An analysis of variance (ANOVA) model with COHORT, TREATMENT, PERIOD(COHORT), SEQUENCE and SUBJECT(COHORT*SEQUENCE) as fixed effects will be fitted for the log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ based on the PK analysis set.

Treatment differences TF3-TF2 under fasting condition on the log scale will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their CIs (90% if the power >=80% or 94.12% if the power <80% according to the adaptive sample size sequential method in Figure 1). Point estimates and CIs will be back-transformed to the original scale.

The primary endpoints will be descriptively summarized.

16.1.1.2 Primary Endpoints in Parts B and C

No hypotheses were defined for Parts B or C.

A mixed model with TREATMENT, PERIOD, SEQUENCE as fixed effects and a random effect for SUBJECT(SEQUENCE) will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ based on the PK analysis set. Treatment differences Fed-Fasted on the log scale will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their 90% CIs for each of the tablet formulations TF2 (Part B) and TF3 (Part C) separately. Point estimates and CIs will be back-transformed to the original scale.

Part B: Tepotinib PK parameters after administration of the tablet formulation TF2 under fasting administration vs. tepotinib TF2 after a high fat, high calorie breakfast

Part C: Tepotinib PK parameters after administration of the tablet formulation TF3 under fasting administration vs. tepotinib TF3 after a high fat, high calorie breakfast

Individual estimates of relative bioavailability will be calculated for each subject and descriptively summarized.

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.

The PK variables will also be listed for all subjects of the PK population.

16.1.2 Secondary Endpoints

The secondary endpoints will be descriptively summarized.

For t_{max}, the Hodges-Lehmann shift estimates will be given for, TF2 fed - TF2 fasted, TF3 fed - TF3 fasted together with the 90% confidence intervals according to Tukey.

The PK variables will also be listed for all subjects of the PK population.

16.1.3 Exploratory Endpoints

Similar analyses will be performed for the parameters based on the metabolites of tepotinib (using 90% confidence intervals for all treatment comparisons);

- Part A: TF3 - TF2, both under fasting condition
- Part B: TF2, fed - TF2, fasted
- Part C: TF3, fed - TF3, fasted

The ANOVA model will have the same effects as the primary analysis applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in each of the study parts A, B and C:

- Part A: A linear model with TREATMENT, PERIOD, SEQUENCE and SUBJECT(SEQUENCE) as fixed effects
- Part B and C: A mixed model with TREATMENT, PERIOD, SEQUENCE as fixed effects and a random effect for SUBJECT(SEQUENCE)

The PK endpoints AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period for the tepotinib metabolites MSC2571109A and

MSC2571107A will be descriptively summarized by treatment and listed for all subjects in the PK population.

16.1.4 Plasma Concentration Data

The following figures will be produced for the tepotinib and metabolites 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**) will be calculated from the individual plasma total 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 Tepotinib and its Metabolites 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 using 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

Symbol	Definition
	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 observed 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
$AUC_{extra\%}$	AUC_{extra} / $AUC_{0-\infty}$ x 100.
$F_{rel,fed/fasted}$	Relative bioavailability (Fasted versus Fed), defined as F = ($AUC_{0-\infty,fed}/AUC_{0-\infty,fasted}$)*100, where $AUC_{0-\infty,fasted}$ is $AUC_{0-\infty}$ under fasting administration and $AUC_{0-\infty,fed}$ is $AUC_{0-\infty}$ after a high fat, high calorie breakfast, calculated in Part B and C.

Individual PK parameters will be calculated using actual sampling times. The pre-dose 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 below the limit of quantitation 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.

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

1. Montague TH, Potvin D, DiLiberti CE, et al. Additional results for „Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceut Statist. 2012;11(1):8-13.
2. Potvin D, DiLiberti CE, Hauck WW, et al. Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceut Statist. 2007.DOI: 10.1002/pst.294.

18 Appendices

None.