Appendix 16.1.9 Documentation of Statistical Methods

Appendix 16.1.9.1 Integrated Analysis Plan

- Integrated Analysis Plan, Version 1.0 – 31 July 2018

Appendix 16.1.9.2 Statistical Outputs

- Supporting Document for Table 15.4.3.1 – The Mixed Procedure
- Supporting Document for Table 15.4.3.2 – The Mixed Procedure
- Supporting Document for Table 15.4.3.3 – The Mixed Procedure
- Supporting Document for Table 15.4.3.4 – The Mixed Procedure
- Supporting Document for Table 15.4.3.5 – The Mixed Procedure

Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200095-0028
Title	Open-Label, Parallel-Group Phase 1 Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib
Study Phase	I
Investigational Medicinal Product(s)	Tepotinib
Clinical Study Protocol Version	24 April 2018 / Version 2.0
Integrated Analysis Plan Author	**Coordinating Author** PI , Merck PI **Function** **Author(s) / Data Analyst(s)** PI , IQVIA PI PI , IQVIA PI
Integrated Analysis Plan Date and Version	31 July 2018 / Version 1.0
Integrated Analysis Plan Reviewers	

Function	Name
PI , IQVIA	PI
PI , IQVIA	PI
PI , IQVIA	PI
PI , IQVIA	PI
Medical Responsible, Merck	PI
PI , Merck	PI
PI , Merck	PI
PI , Merck	PI
PI , Merck	PI
PI , Merck	PI
PI , Merck	PI
PI , Merck	PI

Signature Page

Integrated Analysis Plan: MS200095-0028

Open-Label, Parallel-Group Phase 1 Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib

Merck responsible	Date	Signature
PI , PI	Via ELDORADO approval process	
PI , PI	Via ELDORADO approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADAM	Analysis Data Model
AE	Adverse event
ALBI	Albumin-Bilirubin
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity
$AUC_{0-\infty,u}$	The AUC for unbound drug from time zero (dosing time) extrapolated to infinity
AUC_{0-t}	The 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
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$
BLQ	Below the lower limit of quantification
BMI	Body mass index
CI	Confidence interval
CL/f	The apparent total body clearance of drug following extravascular administration.
CL/f_u	The apparent total body clearance of unbound drug following extravascular administration.
C_{max}	Maximum observed plasma concentration
$C_{max,u}$	Maximum observed unbound plasma concentration
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CV%	Coefficient of variation
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
f_u	Average free fraction of analyte, ie unbound
GCP	Good Clinical Practice
GeoCV%	Geometric coefficient of variation

GeoMean	Geometric mean
IAP	Integrated analysis plan
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
$MRAUC_{0-\infty}$	Metabolite to parent drug ratio for $AUC_{0-\infty}$
MRC_{max}	Metabolite to parent drug ratio for C_{max}
MW	Molecular weight
N, n	Number of subjects or number of non-missing observations
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ODWG	Organ Dysfunction Working Group
PK	Pharmacokinetic/Pharmacokinetics
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
SAE	Serious adverse event
SD	Standard deviation
SDTM	Study Data Tabulation Model
SEM	Standard error of the mean
SI	Système International
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment-emergent adverse event
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	The time to reach the maximum observed concentration

ULN	Upper limit of normal
Vz/F	Apparent volume of distribution during the terminal phase following extravascular administration
WHO DDE	Enhanced World Health Organization Drug dictionary
λ_z	Terminal elimination rate constant

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	31Jul2018	PI PI PI	Original document

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS200095-0028. 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 the clinical study protocol (CSP) and is prepared in compliance with International Council for Harmonisation (ICH) E9. The first version (version 1.0) of this IAP focused on the detailed description of the statistical analyses for pharmacokinetics (PK) and safety variables. The Part 2 of the study is optional for which the analysis is not currently defined in this IAP.

5 Objectives and Endpoints

	Objective	Endpoint	IAP Section
Primary Objective	To assess the PK of tepotinib in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects)	Primary Endpoints • Tepotinib (plasma) area under the curve from time zero to the last quantifiable concentration sampling time (AUC_{0-t}), area under the curve from time zero to infinity ($AUC_{0-\infty}$), and maximum concentration observed (C_{max})	16.1
Secondary Objectives	To further investigate the PK of tepotinib and its metabolites MSC2571109 and MSC2571107 in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects)	Secondary Endpoints • Tepotinib (plasma) time to reach maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), apparent total body clearance (CL/f), apparent volume of distribution (Vz/f), the extrapolated part of $AUC_{0-\infty}$ ($AUC_{extra\%}$); The free fraction (ie, unbound) of tepotinib will be determined to estimate unbound parameters $AUC_{0-\infty,u}$, $C_{max,u}$, and $CL/f_{,u}$ • Tepotinib metabolites MSC2571109 and MSC2571107 (plasma), AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, $AUC_{extra\%}$, and metabolite to parent drug ratio for $AUC_{0-\infty}$ ($MRAUC_{0-\infty}$) and metabolite to parent drug ratio for C_{max} (MRC_{max})	16.1

	Objective	Endpoint	IAP Section
	To assess safety and tolerability of tepotinib in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects).	• Occurrence of treatment-emergent adverse events (TEAEs), changes from baseline in laboratory safety tests, 12-lead electrocardiograms (ECG) morphology and time intervals (PR, QRS, RR, QT, and QTcF), and vital signs	15

The analyses of the endpoints will be described in the respective sections for PK and safety, regardless of whether the endpoint is a primary endpoint or not.

6 Overview of Planned Analyses

6.1 Interim Analysis

There is no formal interim analysis planned.

6.2 Final Analysis

All final, planned analyses identified in the CSP and this IAP will be performed only after the last subject has completed the End of Study visit with all study data in-house, all data queries resolved, and the database locked.

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 Study Protocol

There are no changes to the planned analyses.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

Important protocol deviations or events are protocol deviations or events 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 important deviations or events will be identified and confirmed prior to or at the Data Review Meeting:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn
- Subjects that receive an incorrect dose

- Subjects that receive a prohibited concomitant medication
- Deviation from Good Clinical Practice (GCP)
- Other events/factors related to PK data include, but may not be limited to, the following:
    - Sample processing errors that may lead to incorrect bioanalytical results
    - Incomplete samples collected
    - Use of prohibited medication that could affect PK
    - Events that could affect PK (ie such as vomiting within 2 times the median t_{max}, after dosing), to be evaluated on a case-by-case basis.

Subset of these important protocol deviations are considered clinically important, if leading to the exclusion of a subject from an analysis set (see Section 8.2).

All protocol deviations are documented in Study Data Tabulation Model (SDTM) datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set

The Screening Analysis Set will include all subjects who provide signed informed consent, regardless of treatment status in the study. This analysis set will be used for subject disposition.

Safety Analysis Set

The Safety Analysis Set will include all subjects who receive the study treatment. All safety analyses will be based on this analysis set.

Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who receive the study treatment and have at least 1 postdose PK measurement without important protocol deviations/violations or events that may affect the PK. All PK analyses will be based on this analysis set.

The use of the analysis sets in the different analyses (no subgroup analyses are planned) is presented in the following table:

Analyses	Screening Analysis Set	Safety Analysis Set	PK Analysis Set
Subject Disposition	✓		
Baseline Assessments		✓	
Previous or Concomitant Medications / Procedures		✓	
Treatment Compliance and		✓	

Analyses	Screening Analysis Set	Safety Analysis Set	PK Analysis Set
Exposure			
PK Analysis			✓
Safety and Tolerability		✓	

9 General Specifications for Data Analyses

Listings

All listings will be sorted by hepatic function group (impairment and healthy control), subject, and/or scheduled timepoint, as appropriate. Data from assessments which are only performed before administration of the investigational medicinal product (IMP) will be sorted by subject and scheduled timepoint (if appropriate).

Tables

All data will be summarized by hepatic function group and/or scheduled timepoint, 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, eg, clotted samples.

Presentation of Continuous and Qualitative Variables for Safety

Continuous variables will be summarized using descriptive statistics, ie, number of subjects (N), number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), median, 25th Percentile - 75th Percentile (Q1 - Q3), minimum (Min) and maximum (Max).

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

When the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

Mean, Median, Q1, Q3, Min, and Max will have the same precision as the raw data included in the SDTM datasets for non-derived data. Standard deviation will be presented with one digit more than the mean. Derived data will be rounded to reasonable digits whereas maximal digits should be available in Analysis Data Model (ADaM) datasets then the similar precision definitions will be followed for descriptive statistics. Percentage will be reported using 1 decimal digit, if not otherwise specified.

Definition of Baseline

If not otherwise specified, "baseline" refers to the last non-missing scheduled measurement prior to dosing, as appropriate. It will in general correspond to Day 1 predose for laboratory parameters, vital signs, and ECG data. However, if a subject is missing the baseline collection, the previous non-missing evaluation (as applicable) will become the baseline value. If no baseline or previous to baseline evaluations exist then the baseline value will be treated as missing.

Common Calculations

For quantitative measurements:

- Change from baseline: Value at Visit X – Baseline Value

Definition of Duration

Duration will be calculated by the difference of start and stop/end date + 1 if not otherwise specified.

Conversion Factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of Missing Data

Unless otherwise specified, missing data will not be replaced. Handling of missing data for PK parameter calculations are discussed under Section 16.1.

Software

Pharmacokinetic parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 6.4 or higher (Certara, L.P., Princeton, New Jersey, USA), and/or SAS® Windows Version 9.4 or higher (Statistical Analysis System, SAS-Institute, Cary, North Carolina, USA). Pharmacokinetic figures will be developed using SAS®. All statistical analyses will be performed using SAS®.

10 Study Subjects

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

10.1 Disposition of Subjects and Discontinuations

A summary table describing the number and percentage of subjects (as applicable) in each of the following disposition categories will be produced by hepatic function group and overall:

- Total number of subjects screened (ie, subjects who gave informed consent)
- Number of subjects treated (used as denominator for percentage calculation for the categories below)
- Number of subjects who completed the study
- Number of subjects who discontinued the study/treatment, with the reason of discontinuation.

Corresponding individual listings for study termination status and study entry (including screening failures) will be presented. Subjects discontinued the study/treatment will be listed with the corresponding reasons.

Summary of the number and percentage (as applicable) of subjects included in each analysis set (as described in Section 8.2) will be presented.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The listing of important protocol deviations will be provided.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

For subjects and/or individual concentration or parameter data excluded from the PK Analysis Set, the reasons for exclusion will be listed.

11 Demographics and Other Baseline Characteristics

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

11.1 Demographics

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

Subjects with hepatic impairment will be assigned to a group of mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment at Screening by use of the Child-Pugh system. A listing of points scored for observed findings based on Child-Pugh criteria will be presented.

11.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), current version, and listed. Prior surgery, if any, will also be listed.

11.3 Other Baseline Characteristics

Other baseline characteristics and assessments, including nicotine and alcohol consumption, virus screen, alcohol breathalyzer test, cotinine test, drugs of abuse screen, pregnancy test in women, and follicle-stimulating hormone (FSH) in postmenopausal women, will be listed.

12 Previous or Concomitant Medications/Procedures

Medications will be presented for the Safety Analysis Set.

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

The Enhanced World Health Organization Drug dictionary (WHO DDE), current version, will be used for coding of prior and concomitant medications.

Previous and concomitant medications, as well as concomitant procedures, if any, will be listed.

13 Treatment Compliance and Exposure

The IMP will be administered by the study center staff within the confines of the study center. The administration of IMP, meal consumption and fasting details will be listed for the Safety Analysis Set.

14 Efficacy Analyses

There are no efficacy endpoints and analyses defined for this CSP.

15 Safety Analyses

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

All analyses will be performed for the Safety Analysis Set.

15.1 Adverse Events

All AEs recorded during the course of the study will be coded according to the MedDRA, current version, and each AE will be assigned to a System Organ Class (SOC) and a Preferred Term (PT).

Treatment-emergent AEs are those events with onset dates occurring after the IMP administration on Day 1. Any AE occurring before the IMP administration on Day 1 and resolved before the administration 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”.

In case of (partly) incomplete AE-related dates, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent.

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

15.1.1 All Adverse Events

Treatment-emergent adverse events will be summarized by hepatic function group and overall in tables with:

- The number and percentage of subjects with any TEAE, any IMP related TEAE, any serious TEAE, any IMP related serious TEAE, any grade >=3 TEAE, any IMP related grade >=3 TEAE, any TEAE leading to death, any IMP related TEAE leading to death, any TEAE leading to study discontinuation
- The number and percentage of subjects with at least one TEAE by SOC and PT
- The number and percentage of subjects with at least one TEAE by SOC, PT, and worst grade according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), current version
- The number and percentage of subjects with at least one IMP related TEAE by SOC and PT
- The number and percentage of subjects with at least one TEAE by PT only, sorted in decreasing incidence overall
- The number and percentage of subjects with at least one non-serious TEAE by SOC and PT.

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

For determining incidence counts, if a subject experiences more than one occurrence of the same TEAE, the subject will only be counted once for that TEAE.

If an AE is reported for a given subject more than once during treatment, the worst grade and the worst relationship to study treatment will be tabulated.

Adverse events related to IMP are those events with relationship missing or ‘related’.

In case a subject had events with missing and non-missing grade, the maximum of the non-missing grade will be displayed.

15.1.2 Adverse Events Leading to Study Discontinuation

A listing of TEAEs leading to study discontinuation, if any, will 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" case report forms (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 listing of serious TEAEs, if any, will be provided.

15.3 Clinical Laboratory Evaluation

All clinical laboratory data will be stored in the database in the units in which they were reported with the laboratory reference ranges. Listings and summary statistics at each assessment time will be presented using the Système International (SI) units. Laboratory data not reported in SI units will be converted to SI units before processing.

Continuous clinical laboratory data (hematology and biochemistry) will be summarized by hepatic function group and timepoint using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation.

When applicable, laboratory results will be graded using the NCI-CTCAE, current version, and summarized by worst post-baseline toxicity grade and shift from baseline to highest grade.

Based upon laboratory normal ranges, these laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range), and high (above the upper limit). Listings of all clinical laboratory data for each subject will be provided with values outside the normal ranges indicated. Listings of abnormal test results (low and high) will be provided.

15.4 Vital Signs

Vital signs data (including oral temperature, systolic and diastolic blood pressure, and pulse rate) will be summarized by hepatic function group and timepoint using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of vital signs data will be provided.

15.5 Other Safety or Tolerability Evaluations

Safety 12-lead ECG data will be summarized by hepatic function group 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. Listings of ECG data will be provided. Overall

ECG assessments (normal, abnormal/not clinically significant, abnormal/clinically significant) will also be listed.

Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summary or listing of the physical examination will not be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

All statistical analyses and descriptive summaries of PK data will be performed on the PK Analysis Set. Pharmacokinetic parameters will not be summarized if more than 50% of the dataset are missing for a respective parameter.

16.1.1 Primary Endpoints

As the primary analysis, an analysis of variance (ANOVA) model including hepatic function group as a fixed effect will be applied to log-transformed tepotinib PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} of the subjects with Mild Impairment (Child-Pugh class A), Moderate Impairment (Child-Pugh class B) and the healthy subjects of the matched control group. Least-squares means and corresponding 95% CIs by group, differences and corresponding 90% CIs between the hepatic impairment groups and control will be estimated on the log scale. Point estimates and CIs will be back-transformed to the original scale for presentation.

Additionally, a generalized linear model including hepatic function group and sex (gender) as fixed effects, age and weight as covariates, will be applied to the same primary PK parameters.

Boxplots will be prepared for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} of tepotinib by hepatic function group.

Primary endpoints will be descriptively summarized as described below for secondary endpoints.

In a further analysis, the subjects with liver impairment will be evaluated according to the Albumin-Bilirubin (ALBI) score and the Organ Dysfunction Working Group (ODWG) classification (1, 2).

To categorize subjects based on the ALBI score (1), the following equation will be used: linear predictor = (log10(bilirubin) × 0.66) + (albumin × −0.085), where bilirubin is in µmol/L and albumin in g/L. Calculating the subject-level linear prediction (xb) and applying the cut points assigned each subject to one of three prognostic groups, named the ALBI grade, 1 to 3. The cut points are as follows: xb ≤ −2.60 (ALBI grade 1), more than −2.60 to ≤ −1.39 (ALBI grade 2), and xb more than −1.39 (ALBI grade 3). The linear prediction values will be derived for healthy subjects as well.

To categorize subjects based on the ODWG classification (2), the following will be followed: subjects will be assigned to four groups based on hepatic function, defined according to bilirubin and aspartate aminotransferase (AST) levels relative to the upper limit of normal (ULN) using the classification developed for organ dysfunction studies by the National Cancer Institute (NCI)

ODWG. Normal function is defined as bilirubin and AST ≤ULN. Subjects with mild hepatic impairment have bilirubin ≤ULN and AST >ULN, or bilirubin >1.0–1.5 x ULN (with any AST). Moderate and severe hepatic impairments are defined as bilirubin >1.5–3 x ULN and >3 x ULN, respectively, with any AST.

The classifications for both ALBI and ODWG will be derived using the laboratory data obtained at Screening, while the same will be performed for laboratory data at Day 1 predose, for comparison purpose. These additional classifications will be presented in a listing.

Using the ALBI or ODWG classification, the generalized linear model including hepatic function group and sex (gender) as fixed effects, age and weight as covariates, will be applied to the same primary PK parameters. In addition, a similar model using the ALBI linear prediction values as a continuous variable, will also be performed.

16.1.2 Secondary Endpoints

Secondary endpoints are: Tepotinib (plasma) t_{max}, $t_{1/2}$, CL/f, Vz/f, $AUC_{extra\%}$; unbound tepotinib parameters $AUC_{0-\infty,u}$, $C_{max,u}$, and $CL/f_{,u}$

Tepotinib metabolites MSC2571109 and MSC2571107 (plasma), AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, $AUC_{extra\%}$, $MRAUC_{0-\infty}$, and MRC_{max}.

All pharmacokinetic parameters data will be descriptively summarized using (refer to Section 9): n, Mean, SD, standard error of the mean (SEM), coefficient of variation (CV%), Min, Median, Max, Q1 and Q3 as appropriate, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM).

Non-derived data will have the same precision as SDTM data (number of digits) for the following descriptive statistics: mean, median, Q1, Q3, Min, and Max. Statistics on derived data (i.e., SD) is to be presented with one digit more than the mean.

PK parameter C_{max} will be reported with the same precision as the source data and mean t_{max} (h) will be reported to two decimal places. All other PK parameters will be reported to 3 significant figures. 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 individual values and descriptive statistics of PK parameter data:

Listings:	3 significant digits
Mean, Min, Median, Max, GeoMean, 95% CI, Q1 and Q3:	3 significant digits
SD, SEM:	4 significant digits
CV%, GeoCV%:	1 decimal place

For the secondary PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the tepotinib metabolites, the primary ANOVA model including hepatic function group as a fixed effect as defined for the primary endpoints will be applied. Boxplots will also be provided as described for primary PK parameters included in the statistical analysis.

16.1.3 Concentration Data

A listing of PK blood sample collection times by individual, as well as derived sampling time and time deviations, will be provided. Actual elapsed sample collection times will be rounded to two decimal places with units of hours. All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory regardless of how many significant figures or decimal places the data carry. Pharmacokinetic parameters and actual elapsed sample collection times will be rounded for reporting purposes in by-subject listings.

Plasma concentrations of tepotinib, its metabolites (MSC2571109 and MSC2571107) and the free-fraction of tepotinib in plasma will be listed and presented in summary tables by hepatic function group and/or nominal timepoint, as appropriate, showing: number of non-missing observations (n), Mean, SD, CV%, Min, median, and Max. Values below the lower limit of quantitation (LLOQ) will be identified as (BLQ), will be taken as zero for descriptive statistics. All data will be evaluated as observed; no imputation method for missing values will be used.

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 individual values and descriptive statistics of PK concentration data:

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

Pharmacokinetic plasma concentrations which are erroneous due to a protocol deviation (as defined in the protocol), documented handling error or analytical error (as documented in the bioanalytical report) may be qualified as invalid if agreed with the Sponsor prior to performing a statistical analysis. In this case the rationale must be provided in the CSR. Invalid concentrations will be flagged within the listings. Any other PK concentrations that appear implausible to the Pharmacokineticist/PK Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

Arithmetic mean plasma tepotinib (including free fraction tepotinib) and its metabolites (MSC2571109 and MSC2571107) concentration versus scheduled (nominal) time plots for all hepatic function groups will be provided using a linear and semi-logarithmic scale. Mean plots

will include SD bars (±SD) when plotted on a linear scale. The mean plasma concentration-time profiles will be plotted for subjects included in the PK Analysis Set.

Individual plasma tepotinib and its metabolites (MSC2571109 and MSC2571107) concentration versus actual time plots will be provided using a linear and semi-logarithmic scale. Plots of individual profiles of plasma tepotinib and its metabolites (MSC2571109 and MSC2571107) concentration versus actual time for all subjects within each hepatic function group, presented on a single plot (ie, spaghetti plots), will be provided by hepatic function group, separately, using a linear and semi-logarithmic scale.

16.1.4 Estimation of Pharmacokinetic Parameters

For PK parameters, the standard rounding procedure will be as follows: in export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision, and will not be rounded.

For the PK analysis, predose and postdose sample concentrations that are BLQ will be assigned a numerical value of zero for the calculation of PK parameters.

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

Pharmacokinetic parameters will be calculated using standard non-compartmental methods. Pharmacokinetic parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data. At least 3 quantifiable, postdose concentration points will be required in the PK profile to obtain any PK parameter estimate.

Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data other than for a missing predose concentration as stated above.

For each subject in the PK Analysis Set, the following PK parameters will be calculated for tepotinib and tepotinib metabolites MSC2571109 and MSC2571107, where appropriate:

Symbol	Definition
AUC_{0-t}	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the LLOQ. Calculated using the mixed log linear trapezoidal rule (linear up, log down). Units: ng x h/mL.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0-\infty\_pred}=AUC_{0-t}+C_{lastpred}/\lambda_{z.}$

Symbol	Definition
	Units: ng x h/mL.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\rightarrow\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0\rightarrow\infty}$) *100. The predicted $AUC_{0\rightarrow\infty}$ should be used. Units: %.
CL/f	The apparent total body clearance of drug following extravascular administration. (tepotinib only) $CL/f = Dose_{p.o.}/AUC_{0-\infty\_pred}$. Units: L/h.
C_{max}	Maximum observed concentration, taken directly from the observed concentration-time profile. Units: ng/mL.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, the first occurrence in case of multiple/identical C_{max} values will be used). Units: h.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$. Units: h.
Vz/f	The apparent volume of distribution during the terminal phase following extravascular administration Vz/F = Dose/ ($AUC_{0-\infty\_pred}$ x λ_z) following single dose. (tepotinib only). Units: L.
λ_z	Terminal elimination rate constant (lambda_z). Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve. Units: h^{-1}.
$MRAUC_{0-\infty}$	Metabolite (MSC2571109 or MSC2571107) $AUC_{0-\infty\_pred}$ to tepotinib $AUC_{0-\infty\_pred}$ ratio.
MRC_{max}	Metabolite (MSC2571109 or MSC2571107) C_{max} to tepotinib C_{max} ratio.

Symbol	Definition
f_u	Fraction of analyte unbound. Free fraction will be calculated as the ratio of free concentration divided by total concentration at a given sampling point. Both unbound (ie, plasma ultrafiltrate) concentrations and unbound fractions will be listed for each scheduled sample collection. The average f_u will represent the average of all available fractions (assuming concentration independent protein binding). If only a single unbound concentration is available, the derived fraction of the single timepoint for the respective analyte will be used for all calculations. If the unbound concentration is below the LLOQ at a given timepoint, that timepoint will be omitted from the calculation of the average and only the available timepoints will be used. If the unbound concentration falls below LLOQ in all 4 samples, f_u and unbound PK parameters will not be presented. (tepotinib only)
$C_{max,u}$	Maximum unbound plasma drug concentration, calculated as $C_{max}*f_u$ (tepotinib only)
$AUC_{0-\infty,u}$	Area under the concentration-time curve for unbound drug from time zero to infinity, calculated as $AUC_{0-\infty\_pred}*f_u$ (or AUC0-t*f_u if $AUC_{0-\infty\_pred}$ is not adequately estimable (tepotinib only);
$CL/f,_u$	Unbound apparent oral clearance, calculated as $CL/f,_u = Dose_{p.o.}/AUC_{0-\infty\_pred}/f_u$ (tepotinib only). Units: L/h
Note: Predicted estimates for $AUC_{0-\infty}$, and all parameters derived (ie, $AUC_{extrap\%}$, $AUC_{0-\infty,u}$ CL/f, $CL/f,_u$, and Vz/F) will be presented	

If f_u appears to be concentration dependent or time dependent, an alternate approach for calculation of unbound PK parameters may be employed and will be discussed in the CSR.

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 ($\lambda_{z\ lower}$, $\lambda_{z\ upper}$) to determine λ_z
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z
- Goodness-of-fit statistic (Rsq) for calculation of λ_z
- The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. Units: %.

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

The Rsq should be ≥ 0.800, or $AUC_{extra\%} \leq 20.0\%$. If these criteria are not met, then the rate constants and all derived parameters (eg, $AUC_{0-\infty}$, $AUC_{extra\%}$, CL/f, λ_z, $MRAUC_{0-\infty}$, MRC_{max}, $t_{1/2}$, V_z/f) will be included in the parameter output Listings and flagged as invalid for descriptive statistics. These exclusions are to be discussed appropriately. Any flags should be included in the study specific SDTM.

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 = conversion factor

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

No MW conversion factor for the parent-to-metabolite ratios will be applied.

A Phoenix WinNonlin NCA Core Output will be provided in a separate listing. Individual PK parameters will be calculated using actual sampling times.

Missing concentrations (eg, no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and displayed generally as "N.R.".

16.2 Pharmacodynamics

There are no pharmacodynamic assessments planned

17 References

1. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol*. 2015; 33(6) 550-558.

2. LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: Phase 1 NCI Organ Dysfunction Working Group study NCI-6432. *Clin Cancer Res*. 2012; 18(10), doi:10.1158/1078-0432.CCR-11-2873.

18 Appendices

There are no appendices.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PI	Business Approval	02-Aug-2018 12:37 GMT+02
PI	Technical Approval	06-Aug-2018 10:23 GMT+02

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1497

Fit Statistics	
-2 Res Log Likelihood	19.5
AIC (Smaller is Better)	21.5
AICC (Smaller is Better)	21.8
BIC (Smaller is Better)	22.2

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		10.0665	0.1580	15	63.73	<.0001	0.05	9.7298	10.4032
GRP	1	0.1370	0.2234	15	0.61	0.5489	0.05	-0.3391	0.6132
GRP	2	0.08370	0.2234	15	0.37	0.7131	0.05	-0.3924	0.5599
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	0.19	0.8280

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.05331	0.2234	15	-0.24	0.8146	0.1	-0.4449	0.3383
Moderate vs Healthy	-0.1370	0.2234	15	-0.61	0.5489	0.1	-0.5286	0.2546

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.2035	0.1580	15	64.59	<.0001	0.05	9.8668	10.5402
GRP	2	10.1502	0.1580	15	64.26	<.0001	0.05	9.8135	10.4869
GRP	3	10.0665	0.1580	15	63.73	<.0001	0.05	9.7298	10.4032

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1434

Fit Statistics	
-2 Res Log Likelihood	18.8
AIC (Smaller is Better)	20.8
AICC (Smaller is Better)	21.1
BIC (Smaller is Better)	21.5

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		10.0921	0.1546	15	65.29	<.0001	0.05	9.7626	10.4216
GRP	1	0.1287	0.2186	15	0.59	0.5647	0.05	-0.3372	0.5947
GRP	2	0.07732	0.2186	15	0.35	0.7285	0.05	-0.3886	0.5433
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	0.18	0.8406

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.05141	0.2186	15	-0.24	0.8173	0.1	-0.4347	0.3318
Moderate vs Healthy	-0.1287	0.2186	15	-0.59	0.5647	0.1	-0.5120	0.2545

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.2208	0.1546	15	66.12	<.0001	0.05	9.8913	10.5503
GRP	2	10.1694	0.1546	15	65.79	<.0001	0.05	9.8399	10.4989
GRP	3	10.0921	0.1546	15	65.29	<.0001	0.05	9.7626	10.4216

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=1 ANALYTE=Tepotinib PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.05441

Fit Statistics	
-2 Res Log Likelihood	4.3
AIC (Smaller is Better)	6.3
AICC (Smaller is Better)	6.6
BIC (Smaller is Better)	7.0

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		5.6642	0.09523	15	59.48	<.0001	0.05	5.4612	5.8671
GRP	1	0.3423	0.1347	15	2.54	0.0226	0.05	0.05523	0.6293
GRP	2	0.3664	0.1347	15	2.72	0.0158	0.05	0.07940	0.6535
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	4.63	0.0271

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	0.02417	0.1347	15	0.18	0.8599	0.1	-0.2119	0.2603
Moderate vs Healthy	-0.3423	0.1347	15	-2.54	0.0226	0.1	-0.5784	-0.1062

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	6.0064	0.09523	15	63.08	<.0001	0.05	5.8035	6.2094
GRP	2	6.0306	0.09523	15	63.33	<.0001	0.05	5.8276	6.2336
GRP	3	5.6642	0.09523	15	59.48	<.0001	0.05	5.4612	5.8671

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=2 ANALYTE=Metabolite 2571107A PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.3645

Fit Statistics	
-2 Res Log Likelihood	32.8
AIC (Smaller is Better)	34.8
AICC (Smaller is Better)	35.1
BIC (Smaller is Better)	35.5

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		6.9608	0.2465	15	28.24	<.0001	0.05	6.4354	7.4861
GRP	1	0.05676	0.3486	15	0.16	0.8728	0.05	-0.6862	0.7997
GRP	2	0.06146	0.3486	15	0.18	0.8624	0.05	-0.6815	0.8044
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	0.02	0.9809

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	0.004702	0.3486	15	0.01	0.9894	0.1	-0.6063	0.6158
Moderate vs Healthy	-0.05676	0.3486	15	-0.16	0.8728	0.1	-0.6678	0.5543

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	7.0175	0.2465	15	28.47	<.0001	0.05	6.4922	7.5429
GRP	2	7.0222	0.2465	15	28.49	<.0001	0.05	6.4969	7.5476
GRP	3	6.9608	0.2465	15	28.24	<.0001	0.05	6.4354	7.4861

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=2 ANALYTE=Metabolite 2571107A PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.3549

Fit Statistics	
-2 Res Log Likelihood	32.4
AIC (Smaller is Better)	34.4
AICC (Smaller is Better)	34.7
BIC (Smaller is Better)	35.1

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		6.9878	0.2432	15	28.73	<.0001	0.05	6.4694	7.5062
GRP	1	0.03890	0.3440	15	0.11	0.9115	0.05	-0.6942	0.7720
GRP	2	0.04692	0.3440	15	0.14	0.8933	0.05	-0.6862	0.7801
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	0.01	0.9894

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	0.008022	0.3440	15	0.02	0.9817	0.1	-0.5950	0.6110
Moderate vs Healthy	-0.03890	0.3440	15	-0.11	0.9115	0.1	-0.6419	0.5641

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	7.0267	0.2432	15	28.89	<.0001	0.05	6.5083	7.5452
GRP	2	7.0348	0.2432	15	28.92	<.0001	0.05	6.5164	7.5532
GRP	3	6.9878	0.2432	15	28.73	<.0001	0.05	6.4694	7.5062

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=2 ANALYTE=Metabolite 2571107A PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1691

Fit Statistics	
-2 Res Log Likelihood	21.3
AIC (Smaller is Better)	23.3
AICC (Smaller is Better)	23.6
BIC (Smaller is Better)	24.0

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		2.3136	0.1679	15	13.78	<.0001	0.05	1.9557	2.6715
GRP	1	0.3205	0.2374	15	1.35	0.1970	0.05	-0.1856	0.8266
GRP	2	0.3836	0.2374	15	1.62	0.1270	0.05	-0.1225	0.8897
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	1.50	0.2545

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	0.06307	0.2374	15	0.27	0.7942	0.1	-0.3532	0.4793
Moderate vs Healthy	-0.3205	0.2374	15	-1.35	0.1970	0.1	-0.7368	0.09571

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	2.6341	0.1679	15	15.69	<.0001	0.05	2.2763	2.9920
GRP	2	2.6972	0.1679	15	16.07	<.0001	0.05	2.3393	3.0551
GRP	3	2.3136	0.1679	15	13.78	<.0001	0.05	1.9557	2.6715

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=3 ANALYTE=Metabolite 2571109A PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.3431

Fit Statistics	
-2 Res Log Likelihood	31.9
AIC (Smaller is Better)	33.9
AICC (Smaller is Better)	34.2
BIC (Smaller is Better)	34.6

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		9.8062	0.2391	15	41.01	<.0001	0.05	9.2965	10.3159
GRP	1	-0.3118	0.3382	15	-0.92	0.3711	0.05	-1.0327	0.4090
GRP	2	-0.5028	0.3382	15	-1.49	0.1578	0.05	-1.2236	0.2181
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	1.13	0.3501

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.1909	0.3382	15	-0.56	0.5807	0.1	-0.7838	0.4019
Moderate vs Healthy	0.3118	0.3382	15	0.92	0.3711	0.1	-0.2810	0.9047

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	9.4944	0.2391	15	39.70	<.0001	0.05	8.9847	10.0041
GRP	2	9.3034	0.2391	15	38.91	<.0001	0.05	8.7937	9.8131
GRP	3	9.8062	0.2391	15	41.01	<.0001	0.05	9.2965	10.3159

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=3 ANALYTE=Metabolite 2571109A PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.3420

Fit Statistics	
-2 Res Log Likelihood	31.8
AIC (Smaller is Better)	33.8
AICC (Smaller is Better)	34.2
BIC (Smaller is Better)	34.6

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		9.8232	0.2387	15	41.15	<.0001	0.05	9.3143	10.3320
GRP	1	-0.3185	0.3376	15	-0.94	0.3604	0.05	-1.0382	0.4011
GRP	2	-0.5127	0.3376	15	-1.52	0.1497	0.05	-1.2323	0.2069
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	1.18	0.3355

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.1942	0.3376	15	-0.58	0.5738	0.1	-0.7860	0.3977
Moderate vs Healthy	0.3185	0.3376	15	0.94	0.3604	0.1	-0.2733	0.9104

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	9.5046	0.2387	15	39.81	<.0001	0.05	8.9958	10.0135
GRP	2	9.3105	0.2387	15	39.00	<.0001	0.05	8.8016	9.8193
GRP	3	9.8232	0.2387	15	41.15	<.0001	0.05	9.3143	10.3320

Supporting Document for Tables 15.4.3.1.1/2, 15.4.3.6.1/2, and 15.4.3.7.1/2

The Mixed Procedure

ANAL=Primary Model ANALYTEN=3 ANALYTE=Metabolite 2571109A PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3

Dimensions	
Covariance Parameters	1
Columns in X	4
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1481

Fit Statistics	
-2 Res Log Likelihood	19.3
AIC (Smaller is Better)	21.3
AICC (Smaller is Better)	21.6
BIC (Smaller is Better)	22.0

Solution for Fixed Effects									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		5.1042	0.1571	15	32.49	<.0001	0.05	4.7693	5.4391
GRP	1	-0.1380	0.2222	15	-0.62	0.5438	0.05	-0.6116	0.3356
GRP	2	-0.2181	0.2222	15	-0.98	0.3418	0.05	-0.6918	0.2555
GRP	3	0							

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	15	0.49	0.6202

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.08011	0.2222	15	-0.36	0.7235	0.1	-0.4696	0.3094
Moderate vs Healthy	0.1380	0.2222	15	0.62	0.5438	0.1	-0.2515	0.5276

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	4.9662	0.1571	15	31.61	<.0001	0.05	4.6313	5.3011
GRP	2	4.8861	0.1571	15	31.10	<.0001	0.05	4.5512	5.2210
GRP	3	5.1042	0.1571	15	32.49	<.0001	0.05	4.7693	5.4391

Supporting Document for Tables 15.4.3.2.1/2

The Mixed Procedure

ANAL=Additional Model 1 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	8
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1353

Fit Statistics	
-2 Res Log Likelihood	31.2
AIC (Smaller is Better)	33.2
AICC (Smaller is Better)	33.6
BIC (Smaller is Better)	33.7

Solution for Fixed Effects										
Effect	Sex	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			8.6908	0.8762	12	9.92	<.0001	0.05	6.7816	10.6000
GRP		1	0.1863	0.2154	12	0.87	0.4039	0.05	-0.2829	0.6556
GRP		2	0.001881	0.2223	12	0.01	0.9934	0.05	-0.4824	0.4862
GRP		3	0							
SEX	F		0.2845	0.2210	12	1.29	0.2224	0.05	-0.1971	0.7660
SEX	M		0							
AGE			0.02540	0.01327	12	1.91	0.0797	0.05	-0.00351	0.05431
BLWEIGHT			-0.00224	0.007054	12	-0.32	0.7567	0.05	-0.01761	0.01313

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	12	0.46	0.6442
SEX	1	12	1.66	0.2224
AGE	1	12	3.67	0.0797
BLWEIGHT	1	12	0.10	0.7567

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.1845	0.2333	12	-0.79	0.4445	0.1	-0.6003	0.2314
Moderate vs Healthy	-0.1863	0.2154	12	-0.87	0.4039	0.1	-0.5702	0.1975

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.3427	0.1718	12	60.21	<.0001	0.05	9.9684	10.7169
GRP	2	10.1582	0.1634	12	62.17	<.0001	0.05	9.8022	10.5142
GRP	3	10.1563	0.1666	12	60.98	<.0001	0.05	9.7934	10.5192

Supporting Document for Tables 15.4.3.2.1/2

The Mixed Procedure

ANAL=Additional Model 1 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	8
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1290

Fit Statistics	
-2 Res Log Likelihood	30.6
AIC (Smaller is Better)	32.6
AICC (Smaller is Better)	33.0
BIC (Smaller is Better)	33.1

Solution for Fixed Effects										
Effect	Sex	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			8.7302	0.8555	12	10.21	<.0001	0.05	6.8663	10.5941
GRP		1	0.1766	0.2103	12	0.84	0.4173	0.05	-0.2815	0.6348
GRP		2	-0.00247	0.2170	12	-0.01	0.9911	0.05	-0.4753	0.4704
GRP		3	0							
SEX	F		0.2832	0.2158	12	1.31	0.2140	0.05	-0.1870	0.7533
SEX	M		0							
AGE			0.02489	0.01295	12	1.92	0.0787	0.05	-0.00333	0.05312
BLWEIGHT			-0.00205	0.006887	12	-0.30	0.7714	0.05	-0.01705	0.01296

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	12	0.44	0.6547
SEX	1	12	1.72	0.2140
AGE	1	12	3.69	0.0787
BLWEIGHT	1	12	0.09	0.7714

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.1791	0.2278	12	-0.79	0.4470	0.1	-0.5851	0.2269
Moderate vs Healthy	-0.1766	0.2103	12	-0.84	0.4173	0.1	-0.5514	0.1981

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.3580	0.1677	12	61.77	<.0001	0.05	9.9926	10.7234
GRP	2	10.1789	0.1595	12	63.81	<.0001	0.05	9.8313	10.5265
GRP	3	10.1814	0.1626	12	62.61	<.0001	0.05	9.8271	10.5357

Supporting Document for Tables 15.4.3.2.1/2

The Mixed Procedure

ANAL=Additional Model 1 ANALYTEN=1 ANALYTE=Tepotinib PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	3	1 2 3
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	8
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.05446

Fit Statistics	
-2 Res Log Likelihood	20.3
AIC (Smaller is Better)	22.3
AICC (Smaller is Better)	22.7
BIC (Smaller is Better)	22.7

Solution for Fixed Effects										
Effect	Sex	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			4.9944	0.5558	12	8.99	<.0001	0.05	3.7833	6.2055
GRP		1	0.3604	0.1366	12	2.64	0.0217	0.05	0.06269	0.6581
GRP		2	0.3267	0.1410	12	2.32	0.0390	0.05	0.01950	0.6339
GRP		3	0							
SEX	F		0.1918	0.1402	12	1.37	0.1964	0.05	-0.1137	0.4973
SEX	M		0							
AGE			0.01072	0.008416	12	1.27	0.2270	0.05	-0.00762	0.02905
BLWEIGHT			-0.00008	0.004475	12	-0.02	0.9863	0.05	-0.00983	0.009671

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	2	12	4.33	0.0384
SEX	1	12	1.87	0.1964
AGE	1	12	1.62	0.2270
BLWEIGHT	1	12	0.00	0.9863

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Healthy	-0.03366	0.1480	12	-0.23	0.8239	0.1	-0.2974	0.2301
Moderate vs Healthy	-0.3604	0.1366	12	-2.64	0.0217	0.1	-0.6039	-0.1169

Least Squares Means									
Effect	Actual Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	6.0850	0.1090	12	55.85	<.0001	0.05	5.8476	6.3224
GRP	2	6.0514	0.1036	12	58.38	<.0001	0.05	5.8255	6.2772
GRP	3	5.7246	0.1057	12	54.18	<.0001	0.05	5.4944	5.9548

Supporting Document for Tables 15.4.3.3.1/2

The Mixed Procedure

ANAL=Additional Model 2 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	2	1 2
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	7
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1329

Fit Statistics	
-2 Res Log Likelihood	30.7
AIC (Smaller is Better)	32.7
AICC (Smaller is Better)	33.1
BIC (Smaller is Better)	33.3

Solution for Fixed Effects										
Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			8.7925	0.8576	13	10.25	<.0001	0.05	6.9398	10.6452
GRP		1	0.07693	0.1980	13	0.39	0.7040	0.05	-0.3509	0.5048
GRP		2	0							
SEX	F		0.2610	0.2177	13	1.20	0.2519	0.05	-0.2093	0.7313
SEX	M		0							
AGE			0.02202	0.01279	13	1.72	0.1087	0.05	-0.00561	0.04965
BLWEIGHT			-0.00095	0.006651	13	-0.14	0.8883	0.05	-0.01532	0.01342

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
GRP	1	13	0.15	0.7040
SEX	1	13	1.44	0.2519
AGE	1	13	2.97	0.1087
BLWEIGHT	1	13	0.02	0.8883

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Grade 2 vs Grade 1	-0.07693	0.1980	13	-0.39	0.7040	0.1	-0.4276	0.2738

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.2339	0.1155	13	88.57	<.0001	0.05	9.9843	10.4836
GRP	2	10.1570	0.1826	13	55.61	<.0001	0.05	9.7624	10.5516

Supporting Document for Tables 15.4.3.3.1/2

The Mixed Procedure

ANAL=Additional Model 2 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	2	1 2
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	7
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1264

Fit Statistics	
-2 Res Log Likelihood	30.1
AIC (Smaller is Better)	32.1
AICC (Smaller is Better)	32.4
BIC (Smaller is Better)	32.6

Solution for Fixed Effects										
Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			8.8252	0.8362	13	10.55	<.0001	0.05	7.0186	10.6318
GRP		1	0.07404	0.1931	13	0.38	0.7076	0.05	-0.3432	0.4912
GRP		2	0							
SEX	F		0.2601	0.2123	13	1.23	0.2422	0.05	-0.1985	0.7187
SEX	M		0							
AGE			0.02162	0.01247	13	1.73	0.1066	0.05	-0.00532	0.04856
BLWEIGHT			-0.00079	0.006486	13	-0.12	0.9051	0.05	-0.01480	0.01322

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
GRP	1	13	0.15	0.7076
SEX	1	13	1.50	0.2422
AGE	1	13	3.01	0.1066
BLWEIGHT	1	13	0.01	0.9051

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Grade 2 vs Grade 1	-0.07404	0.1931	13	-0.38	0.7076	0.1	-0.4160	0.2680

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.2536	0.1127	13	91.01	<.0001	0.05	10.0102	10.4970
GRP	2	10.1796	0.1781	13	57.16	<.0001	0.05	9.7948	10.5643

Supporting Document for Tables 15.4.3.3.1/2

The Mixed Procedure

ANAL=Additional Model 2 ANALYTEN=1 ANALYTE=Tepotinib PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	2	1 2
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	7
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.05782

Fit Statistics	
-2 Res Log Likelihood	19.9
AIC (Smaller is Better)	21.9
AICC (Smaller is Better)	22.3
BIC (Smaller is Better)	22.5

Solution for Fixed Effects

Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			5.3831	0.5657	13	9.52	<.0001	0.05	4.1610	6.6052
GRP		1	0.3320	0.1306	13	2.54	0.0246	0.05	0.04981	0.6143
GRP		2	0							
SEX	F		0.1793	0.1436	13	1.25	0.2338	0.05	-0.1309	0.4896
SEX	M		0							
AGE			0.007516	0.008436	13	0.89	0.3892	0.05	-0.01071	0.02574
BLWEIGHT			-0.00241	0.004387	13	-0.55	0.5916	0.05	-0.01189	0.007065

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
GRP	1	13	6.46	0.0246
SEX	1	13	1.56	0.2338
AGE	1	13	0.79	0.3892
BLWEIGHT	1	13	0.30	0.5916

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Grade 2 vs Grade 1	-0.3320	0.1306	13	-2.54	0.0246	0.1	-0.5634	-0.1007

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	6.0424	0.07622	13	79.28	<.0001	0.05	5.8778	6.2071
GRP	2	5.7104	0.1205	13	47.40	<.0001	0.05	5.4501	5.9707

Supporting Document for Tables 15.4.3.4.1/2

The Mixed Procedure

ANAL=Additional Model 3 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	4	1 2 3 4
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	9
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.08508

Fit Statistics	
-2 Res Log Likelihood	24.2
AIC (Smaller is Better)	26.2
AICC (Smaller is Better)	26.7
BIC (Smaller is Better)	26.6

Solution for Fixed Effects										
Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			9.3885	0.7424	11	12.65	<.0001	0.05	7.7545	11.0224
GRP		1	-0.1884	0.3126	11	-0.60	0.5588	0.05	-0.8764	0.4995
GRP		2	-0.6956	0.3290	11	-2.11	0.0581	0.05	-1.4197	0.02848
GRP		3	-0.2941	0.3782	11	-0.78	0.4533	0.05	-1.1266	0.5384
GRP		4	0							
SEX	F		0.2710	0.1777	11	1.52	0.1556	0.05	-0.1202	0.6622
SEX	M		0							
AGE			0.01568	0.01134	11	1.38	0.1942	0.05	-0.00928	0.04064
BLWEIGHT			0.000633	0.005388	11	0.12	0.9086	0.05	-0.01123	0.01249

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	3	11	3.18	0.0671
SEX	1	11	2.32	0.1556
AGE	1	11	1.91	0.1942
BLWEIGHT	1	11	0.01	0.9086

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Normal	-0.5072	0.1779	11	-2.85	0.0158	0.1	-0.8266	-0.1877
Moderate vs Normal	-0.1057	0.2401	11	-0.44	0.6684	0.1	-0.5369	0.3256
Severe vs Normal	0.1884	0.3126	11	0.60	0.5588	0.1	-0.3729	0.7498

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.3293	0.09690	11	106.59	<.0001	0.05	10.1160	10.5426
GRP	2	9.8222	0.1600	11	61.39	<.0001	0.05	9.4700	10.1743
GRP	3	10.2237	0.2364	11	43.24	<.0001	0.05	9.7032	10.7441
GRP	4	10.5177	0.3078	11	34.17	<.0001	0.05	9.8402	11.1953

Supporting Document for Tables 15.4.3.4.1/2

The Mixed Procedure

ANAL=Additional Model 3 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	4	1 2 3 4
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	9
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.08325

Fit Statistics	
-2 Res Log Likelihood	24.0
AIC (Smaller is Better)	26.0
AICC (Smaller is Better)	26.4
BIC (Smaller is Better)	26.4

Solution for Fixed Effects										
Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			9.3997	0.7343	11	12.80	<.0001	0.05	7.7835	11.0159
GRP		1	-0.1909	0.3092	11	-0.62	0.5495	0.05	-0.8713	0.4896
GRP		2	-0.6743	0.3254	11	-2.07	0.0625	0.05	-1.3905	0.04188
GRP		3	-0.2966	0.3741	11	-0.79	0.4447	0.05	-1.1201	0.5269
GRP		4	0							
SEX	F		0.2699	0.1758	11	1.54	0.1530	0.05	-0.1170	0.6569
SEX	M		0							
AGE			0.01571	0.01122	11	1.40	0.1890	0.05	-0.00898	0.04040
BLWEIGHT			0.000689	0.005330	11	0.13	0.8994	0.05	-0.01104	0.01242

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	3	11	2.99	0.0777
SEX	1	11	2.36	0.1530
AGE	1	11	1.96	0.1890
BLWEIGHT	1	11	0.02	0.8994

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Normal	-0.4834	0.1759	11	-2.75	0.0190	0.1	-0.7994	-0.1675
Moderate vs Normal	-0.1057	0.2375	11	-0.45	0.6648	0.1	-0.5323	0.3208
Severe vs Normal	0.1909	0.3092	11	0.62	0.5495	0.1	-0.3643	0.7461

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	10.3443	0.09585	11	107.92	<.0001	0.05	10.1334	10.5553
GRP	2	9.8609	0.1583	11	62.31	<.0001	0.05	9.5125	10.2092
GRP	3	10.2386	0.2339	11	43.78	<.0001	0.05	9.7238	10.7534
GRP	4	10.5352	0.3045	11	34.60	<.0001	0.05	9.8650	11.2054

Supporting Document for Tables 15.4.3.4.1/2

The Mixed Procedure

ANAL=Additional Model 3 ANALYTEN=1 ANALYTE=Tepotinib PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
GRP	4	1 2 3 4
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	9
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18

Number of Observations	
Number of Observations Used	18
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.02465

Fit Statistics	
-2 Res Log Likelihood	10.6
AIC (Smaller is Better)	12.6
AICC (Smaller is Better)	13.1
BIC (Smaller is Better)	13.0

Solution for Fixed Effects										
Effect	Sex	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			5.3757	0.3995	11	13.45	<.0001	0.05	4.4963	6.2551
GRP		1	0.4928	0.1682	11	2.93	0.0137	0.05	0.1225	0.8631
GRP		2	-0.03700	0.1771	11	-0.21	0.8383	0.05	-0.4267	0.3527
GRP		3	0.3271	0.2036	11	1.61	0.1364	0.05	-0.1209	0.7752
GRP		4	0							
SEX	F		0.1597	0.09566	11	1.67	0.1233	0.05	-0.05088	0.3702
SEX	M		0							
AGE			0.000470	0.006104	11	0.08	0.9400	0.05	-0.01297	0.01391
BLWEIGHT			0.001500	0.002900	11	0.52	0.6152	0.05	-0.00488	0.007883

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
GRP	3	11	11.55	0.0010
SEX	1	11	2.79	0.1233
AGE	1	11	0.01	0.9400
BLWEIGHT	1	11	0.27	0.6152

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Mild vs Normal	-0.5298	0.09573	11	-5.53	0.0002	0.1	-0.7017	-0.3579
Moderate vs Normal	-0.1657	0.1292	11	-1.28	0.2262	0.1	-0.3977	0.06642
Severe vs Normal	-0.4928	0.1682	11	-2.93	0.0137	0.1	-0.7949	-0.1907

Least Squares Means									
Effect	GRP	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
GRP	1	6.1083	0.05215	11	117.12	<.0001	0.05	5.9935	6.2231
GRP	2	5.5785	0.08611	11	64.78	<.0001	0.05	5.3889	5.7680
GRP	3	5.9426	0.1273	11	46.70	<.0001	0.05	5.6625	6.2227
GRP	4	5.6155	0.1657	11	33.89	<.0001	0.05	5.2508	5.9801

Supporting Document for Tables 15.4.3.5.1

The Mixed Procedure

ANAL=Additional Model 4 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-t (ng*h/mL) PARAMCD=AUCLST

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	6
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1263

Fit Statistics	
-2 Res Log Likelihood	30.7
AIC (Smaller is Better)	32.7
AICC (Smaller is Better)	33.1
BIC (Smaller is Better)	33.3

Solution for Fixed Effects									
Effect	Sex	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		8.4293	0.9121	13	9.24	<.0001	0.05	6.4587	10.3998
XB		-0.1272	0.1391	13	-0.91	0.3771	0.05	-0.4279	0.1734
SEX	F	0.2363	0.2142	13	1.10	0.2901	0.05	-0.2265	0.6991
SEX	M	0							
AGE		0.02223	0.01238	13	1.80	0.0958	0.05	-0.00451	0.04897
BLWEIGHT		-0.00026	0.006382	13	-0.04	0.9680	0.05	-0.01405	0.01353

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
XB	1	13	0.84	0.3771

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEX	1	13	1.22	0.2901
AGE	1	13	3.23	0.0958
BLWEIGHT	1	13	0.00	0.9680

Supporting Document for Tables 15.4.3.5.1

The Mixed Procedure

ANAL=Additional Model 4 ANALYTEN=1 ANALYTE=Tepotinib PARM=AUC0-inf (ng*h/mL) PARAMCD=AUCIFP

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	6
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.1201

Fit Statistics	
-2 Res Log Likelihood	30.1
AIC (Smaller is Better)	32.1
AICC (Smaller is Better)	32.4
BIC (Smaller is Better)	32.6

Solution for Fixed Effects									
Effect	Sex	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		8.4720	0.8894	13	9.53	<.0001	0.05	6.5505	10.3934
XB		-0.1238	0.1357	13	-0.91	0.3780	0.05	-0.4170	0.1693
SEX	F	0.2359	0.2089	13	1.13	0.2791	0.05	-0.2154	0.6872
SEX	M	0							
AGE		0.02181	0.01207	13	1.81	0.0939	0.05	-0.00426	0.04788
BLWEIGHT		-0.00012	0.006224	13	-0.02	0.9849	0.05	-0.01357	0.01333

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
XB	1	13	0.83	0.3780

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEX	1	13	1.28	0.2791
AGE	1	13	3.27	0.0939
BLWEIGHT	1	13	0.00	0.9849

Supporting Document for Tables 15.4.3.5.1

The Mixed Procedure

ANAL=Additional Model 4 ANALYTEN=1 ANALYTE=Tepotinib PARM=Cmax (ng/mL) PARAMCD=CMAX

Model Information	
Data Set	WORK.PK
Dependent Variable	LNEST
Covariance Structure	Diagonal
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information		
Class	Levels	Values
SEX	2	F M

Dimensions	
Covariance Parameters	1
Columns in X	6
Columns in Z	0
Subjects	1
Max Obs per Subject	18

Number of Observations	
Number of Observations Read	18
Number of Observations Used	18

Number of Observations	
Number of Observations Not Used	0

Covariance Parameter Estimates	
Cov Parm	Estimate
Residual	0.05756

Fit Statistics	
-2 Res Log Likelihood	20.5
AIC (Smaller is Better)	22.5
AICC (Smaller is Better)	22.9
BIC (Smaller is Better)	23.1

Solution for Fixed Effects									
Effect	Sex	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		4.6364	0.6158	13	7.53	<.0001	0.05	3.3061	5.9667
XB		-0.2404	0.09394	13	-2.56	0.0238	0.05	-0.4433	-0.03746
SEX	F	0.1546	0.1446	13	1.07	0.3044	0.05	-0.1578	0.4671
SEX	M	0							
AGE		0.009421	0.008355	13	1.13	0.2799	0.05	-0.00863	0.02747
BLWEIGHT		0.000026	0.004309	13	0.01	0.9952	0.05	-0.00928	0.009334

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
XB	1	13	6.55	0.0238

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEX	1	13	1.14	0.3044
AGE	1	13	1.27	0.2799
BLWEIGHT	1	13	0.00	0.9952