Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200527_0059
Title	Phase I Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)
Study Phase	Phase I
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Approval Page

Integrated Analysis Plan: MS200527_0059

Phase I Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)

1 Table of Contents

Tables

2 List of Abbreviations and Definition of Terms

$\%AUC_{extrap}$	Percentage of AUC Due to Extrapolation from the Last Quantifiable Concentration to Infinity
λ_z	Apparent Terminal Elimination Rate Constant
AE	Adverse Event
ANOVA	Analysis of VARIANCE
$AUC_{0-\infty}$	Area Under the Concentration-time curve from Time 0 Extrapolated to Infinity
$AUC_{0-\infty,u}$	Unbound $AUC_{0-\infty}$
AUC_{0-12}	Area Under the Concentration-time curve from Time 0 to 12 Hours Postdose
AUC_{0-24}	Area Under the Concentration-time curve from Time 0 to 24 Hours Postdose
$AUC_{0-tlast}$	Area Under the Concentration-time Curve from Time 0 to the Time of the Last Sampling Time at Which the Concentration is at or Above the Lower Limit of Quantification
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/f	Apparent Total Clearance
CL_u/f	Unbound Apparent Total Clearance
C_{max}	Maximum Observed Concentration
$C_{max,u}$	Unbound C_{max}
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
ECG	Electrocardiogram
EOT	End of Treatment
FSH	Follicle-stimulating Hormone
f_u	Free or Unbound Fraction of Evobrutinib

GCP	Good Clinical Practice
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IPD	Important Protocol Deviation
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
n	The number of participants with non-missing values
NA	Not Applicable
NC	Not Calculated
PK	Pharmacokinetic analysis population/Pharmacokinetics
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
R^2	Coefficient for Determination of Exponential Fit
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SCR	Screening Analysis Population
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
$t_{1/2}$	Apparent Terminal Elimination Half-life
TEAE	Treatment-Emergent Adverse Event
t_{last}	Time of the Last Quantifiable Concentration
t_{max}	Time of the Maximum Observed Concentration
TSH	Thyroid Stimulating Hormone
UNK	Unknown
V_z/f	Apparent Volume of Distribution During the Terminal Phase
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Woman of Childbearing Potential

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	02 February 2021	PPD	Initial version

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS200527_0059. 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 may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9 of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments.

All final, planned analyses identified in the clinical study protocol will be performed only after the last participant has completed the last visit, i.e. Follow-up/Discontinuation visit, with all study data in-house, all data queries resolved, and the database locked.

5 Objectives and Endpoints

Objectives	Endpoints	IAP section
Primary		
To investigate the PK of evobrutinib after a single dose to participants with hepatic impairment compared to participants with normal hepatic function	$AUC_{0-\infty}$, and C_{max}	16.1
Secondary		
To assess the safety and tolerability of evobrutinib when administered as a single dose to participants with normal hepatic function and with impaired hepatic function	Occurrence of treatment-emergent adverse events (TEAEs), changes from Baseline in laboratory safety tests, 12-lead ECG morphology and time intervals (PR, QRS, RR, QT, and QTcF), and vital signs from time of first dose to the End of Study	15
To characterize the effect of hepatic function on the PK of evobrutinib through secondary PK endpoints	t_{max}, $t_{½}$, AUC_{0-12} and AUC_{0-24}, $AUC_{0-tlast}$, CL/f, V_Z/f, unbound fraction in plasma (f_u), AUC for unbound drug from time zero to infinity ($AUC_{0-\infty,u}$), unbound C_{max} ($C_{max,u}$), and unbound apparent oral clearance ($CL_{,u}$/f)	16.1
Tertiary/Exploratory		
Not applicable		

6 Overview of Planned Analyses

The following analysis is planned for this trial:

- Primary analysis of trial to be performed only after the last participant has completed the last visit, i.e. Follow-up/Discontinuation visit, with all study data in-house, all data queries resolved, and the database locked.

Statistical analyses will be performed on the basis of Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) data. These SDTM data contain as clean as possible eCRF data as well as external data including pharmacokinetic data.

There are no planned formal interim analyses.

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the analyses planned per protocol.

8 Analysis Sets and subgroups

8.1 Definition of Analysis Sets

Screening Analysis Population (SCR)

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

Safety Analysis Population (SAF)

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

Participants will be analyzed according to the actual treatment they received.

All safety analyses will be based on the SAF analysis population.

Pharmacokinetic Analysis Population (PK)

The PK analysis population is a subset of the SAF analysis population and will consist of all participants who receive at least one dose of active IMP and provide at least one measurable postdose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement.

Participants will be analyzed according to the actual treatment they received.

All PK analyses will be based on the PK analysis population.

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

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

8.2 Subgroup definition and parameterization

Not applicable.

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

Study treatment group is defined and labelled as 30 mg evobrutinib. Study intervention is administered 30 minutes after a standard breakfast.

Hepatic function groups are defined and labelled as Normal, Mild (Child-Pugh Class A) and Moderate (Child-Pugh Class B). Unless otherwise indicated, all tables will be split by hepatic function groups. For demographics and baseline data, a total column is also presented.

The “start date” for this study is the start date of the study intervention.

Unless otherwise specified, comparisons will be presented for Child-Pugh class A versus Normal Hepatic Function and Child-Pugh class B versus Normal Hepatic Function.

All original and derived parameters will be listed. Repeated and unscheduled measurements will also be included in the listings.

All listings will be sorted by hepatic function group, participant identification number and scheduled time point and will include at least the treatment group, hepatic function group and time point, in chronological order. Data which are only measured before administration of study intervention will be sorted by participation number and time point.

Continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. Descriptive statistics will only be presented if $n \geq 3$. Missing observations will be shown as missing.

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

Descriptive statistics by nominal visit or time point, e.g. for laboratory measurements, will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

Repeated and unscheduled measurements will not be used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, or the repeated measurement occurred prior to study intervention administration and is defined as the baseline:

- Should the repeated measurement occur prior to study intervention administration, the last obtained reliable value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline
- If the repeated measurement occurs after study intervention administration, then the first (non-missing) value of any repeated measurements will be used in descriptive statistics and in the calculation of changes from baseline

Derived parameters are calculated using non-rounded data.

The following conventions are applied for reporting descriptive statistics of all continuous data, except for PK concentration data and PK parameter data (n refers to the number of decimal places reported for the original data):

- Mean: n + 1 decimal digits
- SD: n + 2 decimal digits
- Min: n decimal digits
- Median, Q1, Q3: n + 1 decimal digits
- Max: n decimal digits
- GeoMean: n + 1 decimal digits
- GeoCV, CV%: 1 decimal digit
- Point Estimate: n + 1 decimal digits

Statistical analysis will be performed using the computer program package SAS® System for Windows™ (release 9.4 or later version; SAS Institute, Cary NC, USA).

9.1 Definition of baseline and change from baseline

If not otherwise specified, ‘baseline’ refers to the last scheduled measurement before administration of the study intervention. If no baseline exists, then the baseline value will be treated as missing.

If an assessment that is planned to be performed before study intervention per protocol is performed on the same day as the start of study intervention, but the assessment time is not available, it will be assumed that it was performed prior to the start of study intervention and will be considered for derivation of baseline.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.2 Study day / study treatment day

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

9.3 Definition of duration and 'time since' variables

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

9.4 Conversion factors

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

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

9.5 Imputation of missing data

Unless otherwise specified all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented and imputed information will be flagged.

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

For the classification as treatment-emergent and calculation of duration, incomplete AE-related dates will be handled as described below. The incomplete dates without imputation will be presented in listings.

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

Adverse events	For the classification as treatment-emergent and calculation of duration, incomplete AE-related dates will be imputed as follows: • If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment. • If only the day part of the AE onset date is missing, but the month and year are equal to the start of study intervention, then the AE onset date will be replaced by the start of study intervention. For example, if the AE onset date is --/JAN/2015, and study intervention start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before start of study intervention, this date will be used for imputation instead of start of study intervention date. • If both the day and month of the AE onset date are missing but the onset year is equal to the start of study intervention, then the onset date will be replaced by the start of study intervention. For example, if AE onset date is --/---/2014, and study intervention start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014. • In all other cases the missing onset day or missing onset month will be replaced by 1. • Incomplete stop date 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 participant's death. In the latter case the date of death will be used to impute the incomplete stop date. • In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off this date will be kept.
Previous and concomitant medication	For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 2 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 1 Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	**Month**	**Year**	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	≥ Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	≥ Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
≥ Treatment start (complete date)			After treatment start

UNK = Unknown

Table 2 Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	≤ Treatment start (year)	Before treatment start	Previous
UNK	UNK	≤ Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and ≤ Treatment end [+ 30] days (year)	After treatment start	Concomitant
UNK	≤Treatment start (month and year)		Before treatment start	Previous
UNK	≤ Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and ≤ Treatment end [+ 30] days (month and year)		After treatment start	Concomitant
≤ Treatment start (date)			Before treatment start	Previous
≤ Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and ≤ Treatment end [+ 30] days (date)			After treatment start	Concomitant

UNK = Unknown

Dates of study intervention	No imputation will be done.

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented by hepatic function group and total, where applicable. Percentages will be presented with respect to the number of treated participants.

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of participants who discontinued from the study prior to treatment overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdrawal of consent, Other (COVID-19-related and COVID-19-non-related))
- Number and percentage of treated participants
- Number and percentage of treated participants who completed study treatment

Individual listings for study termination and analysis populations will be presented.

The number and percentage of participants in each analysis population will be presented by hepatic function group and total. Percentages will be presented with respect to the number of treated participants.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

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

Important protocol deviations include:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study treatment or an incorrect dose
- Participants that receive an excluded concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)

- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

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

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming.

Important protocol deviations will be summarized for:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

All important protocol deviations will be listed by participant. Minor protocol deviations related to COVID-19 will also be listed by participant.

Participants may be excluded from the PK analysis population if they have an AE of vomiting that occurs at or before 2 times median t_{max} of the group.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

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

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the safety analysis population by hepatic function group and total.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening Visit eCRF pages.

- The following demographic characteristics will be included:
  - Sex: male, female
  - Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other, not collected at this site, unknown
  - Ethnic origin: Hispanic or Latino/Not Hispanic or Latino, Japanese/Not Japanese
  - Age (years)
  - Weight (kg) at Screening

- Height (cm) at Screening
- BMI (kg/m^2) at Screening

Specifications for computation:

- Age [years]
  - (date of given informed consent - date of birth + 1) / 365.25 Note: Alternatively, Day 1, i.e. day of start of study treatment, may be used instead of the day of given informed consent.
  - In case of missing day for at least one date, but month and year available for both dates:

    For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing month for at least one date, but year available for both dates:

    For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

    The integer part of the calculated age will be used for reporting purposes.
- BMI [kg/m²] = $\frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$

11.2 Medical History

The medical history will be coded using the most recent MedDRA version at time of database lock.

Medical history will be listed by participant and will include the following: description of disease/procedure, MedDRA system organ class (SOC), MedDRA preferred term (PT), start date, end date (or ongoing, if applicable) and severity (if ongoing).

11.3 Other Baseline Characteristics

The albumin-bilirubin score is calculated as:

albumin-bilirubin score = [$\log_{10}$ Total Bilirubin (µmol/L) × 0.66] + [Albumin (g/L) × -0.085]

The baseline albumin-bilirubin score is defined as the arithmetic mean of the screening and baseline (Day -1) values. The albumin-bilirubin score will be summarized descriptively at screening, Day -1 and baseline.

The De Ritis ratio is calculated as:

De Ritis ratio = AST / ALT

The baseline De Ritis ratio is defined as the arithmetic mean of the screening and baseline (Day -1) values. The De Ritis ratio will be summarized descriptively at screening, Day -1 and baseline.

Nicotine usage, alcohol consumption and caffeine consumption data will be listed.

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

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the safety analysis population by hepatic function group.

Concomitant treatments are medications, other than study intervention, which are taken by participants from the time the participant signs the informed consent until completion of the study.

Previous medications are medications, other than study intervention, which started before first administration of study intervention.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Previous medications and concomitant treatments will be coded using the most recent WHO-DD version at time of database lock.

Previous medications and concomitant treatments will be listed by participant and include the following information: Medication name (trade name), generic name, WHO drug name (including ATC coding and PT), dose (and dose units), frequency, route of administration, start and end date/time, indication and origin (medical history, AE, disease related condition, prophylaxis or other). Duration will be calculated and included in the listing.

All **concurrent procedures**, which were undertaken during the on-treatment period will be listed according to the CRF page “Concomitant Procedures”. Concurrent procedures will be classified by medical review.

13 Study treatment: Compliance and Exposure

The following analyses will be performed based on the safety analysis population by hepatic function group.

No imputation of missing start dates of study treatments will be done.

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

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

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

Safety analyses will be done on the safety analysis population and according to the as-treated principle.

15.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are those events that begin or that worsen in severity after at least one dose of the study intervention has been administered.

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

AEs will be coded using the most recent MedDRA version at time of database lock.

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

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, by hepatic function group, primary SOC and PT in decreasing frequency.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

Adverse event counts and participants with AEs will be summarized for each hepatic function group by SOC and preferred term. In addition, AEs will be tabulated and listed per participant and analyzed by severity and relationship to study intervention.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in Section 9.5.

15.1.2 Adverse Events Leading to Discontinuation of Study Treatment

Since evobrutinib is administered only once in the study, discontinuation of study intervention is not applicable.

Adverse events leading to withdrawal/discontinuation from the study intervention will be listed for each participant and summarized for each treatment group by SOC and PT. Only TEAEs will be included in the tabulation.

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

15.2.1 Deaths

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome. A listing of all deaths occurring during the study will be presented.

15.2.2 Serious Adverse Events

A listing of all SAEs occurring during the study will be presented.

15.2.3 Other Significant Adverse Events

A listing of other significant AEs occurring during the study will be presented.

15.3 Clinical Laboratory Evaluation

The following parameters will be measured:

- **Hematology:** platelets, reticulocytes, hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH).
- **Clinical chemistry:** blood urea nitrogen, creatinine, glucose, uric acid, C-reactive protein, albumin, urea, potassium, sodium, calcium, chloride, inorganic phosphate, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-Glutamyl-transferase, lactate dehydrogenase, creatinine phosphokinase, bilirubin, total protein, cholesterol, triglycerides, amylase, lipase, coagulation (INR and prothrombin time [PT]) and Thyroid stimulating hormone (TSH).
- **Urinalysis:** specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte estrease and microscopic examination (if blood or protein is abnormal).
- **Drugs of Abuse and Alcohol Abuse** (Screening and Day -1 only): alcohol breath test and urine drug screen (to include at minimum: amphetamines, methamphetamines, barbiturates, ecstasy, cocaine, opiates, cannabinoids, benzodiazepines, methadone, phencyclidine, oxycodone, and tricyclic antidepressant).
- **Serum Pregnancy Test** (Screening, Day -1 and Follow-up/Discontinuation only).
- **Other:** FSH and estradiol (as needed if not a WOCBP only).
- **Other:** serum human chorionic gonadotropin (hCG) pregnancy test (as needed for a WOCBP).

- **Other:** urine microscopy, only if blood, protein, nitrite, or leukocyte esterase are positive on the dipstick
- **Serology**: HIV I and II antibodies, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and Quantiferon® Test.

Safety laboratory parameters will be listed for each participant including changes from baseline and flags for measurements outside the reference ranges, where applicable. Laboratory parameters (hematology, coagulation and clinical chemistry) will be summarized by time point including both absolute values and changes from baseline. Urinalysis parameters will be listed.

Values below the detection limit will be imputed by half of the detection limit.

In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g "> 7.2 mmol" will be analyzed as 7.3.

15.4 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include tympanic temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. One pulse and three blood pressure measurements will be taken. The average of the three blood pressure readings will be recorded in the CRF.

Vital signs parameters will be listed for each participant including changes from baseline and flags for measurements outside the reference ranges, where applicable. Vital signs parameters will be summarized by hepatic function group and time point including both absolute values and changes from baseline.

15.5 Other Safety or Tolerability Evaluations

Single 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG assessments will be done after 5 minutes rest in supine position.

12-lead ECG parameters will be listed for each participant including changes from baseline and flags for measurements outside the reference ranges, where applicable. 12-lead ECG parameters will be summarized by hepatic function group and time point including both absolute values and changes from baseline. Clinically noteworthy ECG findings for individual participants will be listed as appropriate.

15.6 COVID-19 Impact

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

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), 25th percentile (Q1) and 75th percentile (Q3), and maximum (Max).

Descriptive statistics will only be calculated for n>2 in which a measurement of <LLOQ represents a valid measurement.

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 are applied for reporting descriptive statistics of PK concentration data:

- Mean: 3 significant digits
- SD: 4 significant digits
- Min: 3 significant digits
- Median, Q1, Q3: 3 significant digits
- Max: 3 significant digits
- CV%: 1 decimal digit

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), minimum (Min), median (Median), 25th percentile (Q1) and 75th percentile (Q3), maximum (Max), geometric mean (GeoMean), and the geometric coefficient of variation (GeoCV%). For time to reach maximum observed concentration (t_{max}) and time of the last quantifiable concentration (t_{last}), only n, Min, Median, and Max will be reported.

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

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. 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 are applied for reporting descriptive statistics of PK parameter data:

- Mean: 3 significant digits
- SD: 4 significant digits
- Min: 3 significant digits
- Median, Q1, Q3: 3 significant digits
- Max: 3 significant digits
- GeoMean: 3 significant digits
- GeoCV, CV%: 1 decimal digit
- 95% CI: 3 significant digits

16.1.3 General Specifications for PK Concentration and PK Parameter Data

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.

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

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

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

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

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

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

If the actual time of sample collection deviates from the protocol defined time interval the concentration will be flagged and excluded from the summary statistics.

16.1.4 Estimation of Pharmacokinetic Parameters

The following PK parameters will be determined where possible from the plasma concentrations of evobrutinib using noncompartmental methods and the validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher).

The following pk parameters will be calculated where appropriate:

Parameter	Units[a]	Definition
$AUC_{0\text{-}tlast}$	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification[b.]
$AUC_{0\text{-}\infty}$	h*ng/mL	area under the concentration-time curve from time 0 extrapolated to infinity[c]
$AUC_{0\text{-}12}$	h*ng/mL	The area under the concentration-time curve (AUC) from time 0 to 12 hours postdose.
$AUC_{0\text{-}24}$	h*ng/mL	The area under the concentration-time curve (AUC) from time 0 to 24 hours postdose
$\%AUC_{extra}$	%	percentage of AUC due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time of the maximum observed concentration
t_{last}	h	time of the last quantifiable concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/f	mL/min	apparent total clearance
V_z/f	L	apparent volume of distribution during the terminal phase
f_u	%	free or unbound fraction of evobrutinib
$AUC_{0\text{-}\infty,u}$	h*ng/mL	unbound $AUC_{0\text{-}\infty}$[d]
$C_{max,u}$	ng/mL	unbound C_{max}[d]
CL_u/f	mL/min	unbound apparent total clearance[d]

a Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
b Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
c Based on the last predicted quantifiable concentration
d Calculated as the product of the bound parameter and the mean free fraction for that participant

Additional PK parameters may be determined where appropriate.

PK 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.

Free (unbound) fraction will be calculated as free concentration/total concentration. For each participant, 3 samples will be analysed to determine a percent of free fraction (unbound) evobrutinib. The values from these samples, if measurable, will be used to calculate a mean free fraction, presented as percentage. The percentage free will be divided by 100% to calculate unbound PK parameters.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

Partial areas should be calculated using the nominal dosing interval. The actual dosing interval calculated from the CRF should not be used. However, actual times for partial AUC intervals may be used if the sample was taken within +/-10% of the protocol defined time, and the partial area would not be calculable using scheduled time.

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

If $\%AUC_{extra}$>20% and/or the coefficient of correlation (Rsq adj) of λ_z is <0.8 and/or the observation period over which the regression line is estimated is less than twofold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, $CL_{/f}$ etc.) will be will be listed, flagged and included in the parameter outputs and may be excluded from the descriptive statistics. Any flags will be included in the study specific SDTM/ADaM and the exclusion of parameters agreed with the sponsor.

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

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

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
$\lambda_{z\ up}$	h	first time point of the time interval of the log-linear regression to determine λ_z.
$\lambda_{z\ low}$	h	last time point of the time interval of the log-linear regression to determine λ_z.
N_λ	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
Adjusted Rsq	NA	goodness of fit statistic (adjusted Rsq) for calculation of λ_z.

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the $t_{1/2}$ values will be flagged and the robustness of the estimates discussed in the CSR.

16.1.5 Presentation of PK Concentration and PK Parameter Data

Pharmacokinetic summaries will be done on the PK analysis population and according to the as-treated principle.

16.1.5.1 Listings and Tables

Concentrations of evobrutinib will be listed by participant and time point for each hepatic function group. The listing will include participant identifier, hepatic function group and actual sampling times. Concentrations below the lower limit of quantification (LLOQ) will be presented as the BLQ value in the listings.

Concentration data of evobrutinib will be summarized by hepatic function group and scheduled time point.

All pharmacokinetic parameters will be listed by participant and summarized for each hepatic function group.

16.1.5.2 Graphical Summaries and Individual plots (PK Analysis Set)

Individual plasma and arithmetic mean concentration time plots will be provided for each hepatic function group using linear (± SD) and semi-logarithmic scales.

Boxplots of pharmacokinetic parameters will be provided for each hepatic function group.

16.1.5.3 Primary Endpoint Analyses

Pharmacokinetic analyses will be done on the PK analysis population and according to the as-treated principle.

An analysis of variance (ANOVA) model including hepatic function group as a fixed effect will be applied to log-transformed PK parameters $AUC_{0-\infty}$, and C_{max} of evobrutinib of the hepatic impairment groups (Child-Pugh class A and Child-Pugh class B) and control group (Normal Hepatic Function). Separate models will be fitted for the comparison between the hepatic impairment groups (Child-Pugh class A and Child-Pugh class B) and the control group (Normal Hepatic Function). For each parameter, differences between the hepatic impairment groups and the control group will be estimated on the log scale (group mean ratio) together with corresponding 90% confidence intervals (CIs). The geometric least square means together with corresponding 95% CIs by hepatic function group will also be estimated. Point estimates and CIs will be back-transformed to the original scale.

The relationship between $AUC_{0-\infty}$ and C_{max} of evobrutinib and the hepatic function parameters (e.g., albumin-bilirubin score and De Ritis ratio as continuous variable) at baseline (arithmetic mean of screening and Day -1 values) will additionally be explored with a linear regression.

For secondary PK endpoints such as CL/f, $AUC_{0-\infty,u}$, $C_{max,u}$, and CL_u/f, the same ANOVA and linear regression analyses like for the primary endpoints will be performed.

17 References

Not applicable.

18 Appendices

18.1 SAS® codes

ANOVA

```
proc mixed data = <datain>
    (where = (hgroup in (‘Child-Pugh class A’ ‘Normal Hepatic Function’)));
  by param;
  class hgroup;
  model log_pk = hgroup;
  lsmean hgroup / cl alpha = 0.05;
  estimate 'Child-Pugh class A vs Normal Hepatic Function' hgroup 1 -1 / cl alpha = 0.1;
  ods output LSmeans = <out1>;
  ods output Estimates = <out2>;
run;
```

Linear regression

```
proc reg data = <datain> outset = <dataout>;
  by param;
  model log_pk = alb_bil;
run;
```

ELECTRONIC SIGNATURES

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Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	04-Feb-2021 08:40
PPD	Task Completed (Approval eSign): Approved	Business Approval	05-Feb-2021 09:00