Integrated Analysis Plan

Study Number:	MS200527_0070
Clinical Study Protocol Title:	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants
Study Phase:	Phase I
Merck Compound:	Evobrutinib (M2951)
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Integrated Analysis Plan Author:	

Coordinating Author	
Biostatistics, On behalf of Merck	PPD
Function	**Author(s) / Data Analyst(s)**
Biostatistics, Nuvisan GmbH	PPD
Integrated Drug Development, Certara Inc.	PPD PPD

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Integrated Analysis Plan Reviewers:

Function	**Name**
Clinical Pharmacology Lead, Merck	PPD
Clinical Pharmacologist, Merck	
Clinical PK/PD Scientist, Merck	
Global Patient Safety Lead, Merck	
Global Clinical Data Sciences, Merck	
Statistical Programmer Lead, Merck	
Pharmacometrics Lead, Merck	
Medical Writing Lead, Merck	

Approval Page

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A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANOVA	Analysis of VARIANCE
BLQ	Below Lower Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
eCRF	electronic Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
GBS	Global Biostatistics
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
LCI	Lower Limit of Confidence Interval
LLOQ	Lower Limit of Quantification
LOESS	Locally estimated scatterplot smoothing
ML	Maximum Likelihood
NCA	Noncompartemental Analysis
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
PK	Pharmacokinetics
QTc	Corrected QT interval
QTcB	Corrected QT interval by Bazett's formula
QTcF	Corrected QT interval by Fridericia' formula
QTcI	Individual-corrected QT interval
REML	Restricted Maximum Likelihood
SDTM	Study Data Tabulation Model
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
UCI	Upper Limit of Confidence Interval
VPC	Visual Predictive Check

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	06-FEB-2023	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_0070. Results of the analyses described in this IAP will be included in the CSR. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

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

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the CSR template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term ‘participant’ will be used instead of ‘subject’ or ‘patient’. However, in tables and listings the term ‘subject’ will be used to match CDISC requirements, except for in-text tables where ‘participant’ will be used to match the CSR and protocol templates. Similarly, the term ‘study intervention’ will be used in this document instead of ‘treatment’ to match protocol and CSR templates, however, tables and listings will use ‘treatment’ for brevity reasons. Exceptions from this rule are commonly used terms like "on-treatment", "treatment-emergent", "treatment policy", "subject-years", "by-subject", or names of eCRF pages like "Treatment Termination" page.

5 Objectives and Endpoints

Objectives	Endpoints	Ref. #
Primary		
To evaluate whether evobrutinib administered as a single oral dose (as solution) of 45 mg or 225 mg prolongs QT/QTc in comparison to placebo control	ΔΔQTcF (placebo-corrected change from baseline QTcF) for evobrutinib; with concentration-QTc analysis as primary analysis	1
Secondary		
To demonstrate QTc assay sensitivity	ΔΔQTcF (placebo-corrected change from baseline QTcF) for moxifloxacin	2
To assess the safety and tolerability of evobrutinib	Nature, occurrence, and severity of TEAEs Absolute values and changes in safety laboratory tests Vital signs assessed from time of first dose to end of study participation Single 12-lead ECGs evaluated by Investigator	3
To assess the effect of evobrutinib on other ECG parameters	QT, QTcB, QTcI, PR, QRS, RR, HR, cardiologist assessment including T-wave morphology, and U-wave.	4
To determine the PK of evobrutinib and its major metabolite at 45 mg and 225 mg oral dose (solution) under fasting conditions and moxifloxacin at 400 mg oral dose	AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for evobrutinib and major metabolite AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for moxifloxacin	5

6 Overview of Planned Analyses

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

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

Not applicable.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study. The analysis of subject disposition will be based on this analysis set.
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. All safety analyses and by timepoint and categorical analysis of secondary objectives will be based on this analysis set.
PK	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance. With evaluable PK data, i.e. nonmissing values for primary endpoints. If participants received prohibited concomitant therapy or medicines, as specified in protocol Section **6.8** they will be excluded from the PK population. All PK analyses will be based on this analysis set.
ECG	The ECG Analysis Set will be the basis of the C-QTc analysis and will be a subset of the SAF. Only participants who had a baseline Holter ECG in triplicate and at least one post-baseline Holter ECG in triplicate with a time-matched concentration will be retained for C-QTc analysis. Participants with protocol deviations likely to affect the comparability of ECG measurements or PK concentrations will not be considered in the C-QTc analysis.

8.2 Subgroup Definition and Parameterization

Not applicable.

9 General Specifications for Data Analyses

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

Listings

In the individual participant data listing all individual data will be listed as measured. Repeated and unscheduled measurements will be included in the listings. All listings will be sorted by subject ID and nominal time point, if not stated otherwise.

Tables and Descriptive Statistics

All safety data will be summarized overall and study intervention by nominal time point, as appropriate. All PK data will be summarized by study intervention and nominal time point. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), the number of participants with missing values (nmiss), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values the number of participants with missing values should be indicated by a 0. Mean, Median, Q1, Q3, Min, Max will have the same precision as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest that received the respective study intervention for safety, QTc and PK summaries and for all other evaluations the analysis set of interest [N]. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Study day 1 for this study is defined as the start date of study intervention.

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

Placebo:	Placebo
400 mg Moxifloxacin:	400 mg Moxifloxacin tablet
45 mg Evobrutinib:	45 mg Evobrutinib solution
225 mg Evobrutinib:	225 mg Evobrutinib solution

All statistical analyses will be performed using SAS® Software version 9.2 or higher and R version 4.1 or higher.

9.1 Definition of Baseline and Change from Baseline

If not otherwise specified, ‘baseline’ refers to the last scheduled measurement before administration of study intervention in each period.

However, if a participant is missing the baseline collection, the previous non-missing evaluation could become the baseline value (e.g. from Screening). If no baseline or previous to baseline evaluations exist, then the baseline value will be treated as missing.

For the ECG measurements, ’baseline’ refers to the average of the derived ECG intervals from the three ECG timepoints prior to dosing on day 1 within each respective period.

Absolute changes from baseline are defined as

absolute change = visit value – baseline value

9.2 Study Day / Study Intervention Day

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

9.3 Definition of Duration and 'Time Since' Variables

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

- Duration of AE (in days hh:mm) = end date and time - start date and time of the AE, if missing time for either the beginning or end then = end date – start date + 1; in case of multiple records for the same AE, the duration will be calculated over all these records
- Days hh:mm from dosing (onset post administration) = start date and time of the event - date and time of last dose administration of study intervention (calculated for each intervention, for TEAEs), if missing time for either the dosing or event then days hh:mm from dosing = event start date – date of dose administration + 1
- Relative (Rel.) Day in period of AE = start date of the event – date of admin in period + 1 (for AEs on or after the day of dosing within a period)
- Relative Day in study of AE = start date of the event – date of first admin + 1 (for AEs on or after the first day of dosing)
- Rel. Day in study of AE = start date of the event – date of first admin (for events before the first day of dosing of the study only)

9.4 Imputation of Missing Data

In this Phase I thorough QT study, missing observations will be assumed to be missing completely at random (MCAR) if not stated otherwise. No action will be taken to handle missing data. A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

The following will be presented in a summary table:

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of screened participants who discontinued from the study prior to first dosing overall and grouped by the main reason for discontinuation:
  - Participant did not meet all eligibility criteria

  - Withdrew consent
  - Other (e.g., COVID-19-related and COVID-19-non-related)
- Number of treated participants
- Number and percentage of treated participants who completed study
- Number and percentage of treated participants who discontinued the study or study intervention, with the primary reason of discontinuation:
  - Adverse event
  - Lost to follow-up
  - Protocol non-compliance
  - Death
  - Withdrew consent
  - Other (e.g., COVID-19-related and COVID-19-non-related)

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

A listing of discontinued participants will be provided.

A listing of participants affected by the COVID-19 related study disruption by unique participant identifier will also be provided.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing in the relevant period. A distinction will be made between important protocol deviations due to COVID-19 versus not due to COVID-19. The respective important protocol deviations will be flagged accordingly.

Important protocol deviations or important events that might influence PK and QTcF analysis include, but may not be limited to the following:

- Adverse events, diarrhea etc. (these instances will be discussed on a case-by case basis)
- Vomiting after administration following oral dosing (these instances will be discussed in alignment with applicable regulatory guidelines on a case-by-case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g., dose administration delayed, dose change or missed doses)

- Predose or trough sample collected after the actual dosing
- Non-compliance with food and drink requirements (e.g., non-fasted, incomplete meal consumption, caffeine intake)
- Concomitant medication, vitamins, dietary or herbal supplements
- Missing baseline Holter ECG in triplicate or post-baseline Holter ECG in triplicate

Should one or more of these events be available at the Data Review Meeting, its implication for PK and QTcF evaluation will be discussed and agreed amongst relevant study team members (e.g., Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team/Pharmacometrics representative). Appropriate action will be taken such as flagging individual values to be excluded from analysis.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

If participants are excluded from the PK Analysis Set and/or ECG Analysis Set, the reasons for exclusion will be listed.

Reasons for excluding individual PK concentrations from PK analysis as well as C-QTc analysis will also be listed separately and flagged in the main listing.

11 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be presented for the SAF.

11.1 Demographics

Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and ethnicity. The summary will be performed overall.

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

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

11.2 Medical History

Medical history will be coded using the MedDRA, most current version at time of data base lock, and listed.

The medical history will be listed by participant including PT as event category and SOC body term as Body System category.

11.3 Other Baseline Characteristics

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

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

12 Previous or Concomitant Therapies/Procedures

Medications will be presented for the Safety Analysis Set.

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

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

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

13 Study Intervention: Compliance and Exposure

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

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

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

All safety analyses will be performed for the Safety Analysis Set and will be presented by study intervention and nominal timepoint, as appropriate.

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

15.1 Adverse Events

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

TEAEs are those events with onset dates on or after the first administration of study intervention on Day 1. Any AE occurring before the administration of study intervention on Day 1 and resolved before administration of study intervention or not worsening after administration of study intervention on Day 1 will be included in the AE listings but will not be included in the summary tables (unless otherwise stated). These will be referred to as "pre-treatment" AEs.

In case AE-related dates are partial, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent.

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

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

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

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

15.1.1 All Adverse Events

TEAEs and participants experiencing TEAEs will be summarized by study intervention and overall with:

- The number and percentage of participants with any TEAE, any related TEAE, any serious TEAE, any related serious TEAE, any severe TEAE, any related severe TEAE, any AESI, any TEAE leading to death, any related TEAE leading to death, any TEAE leading to study discontinuation

- The number and percentage of participants with at least one TEAE and the number of events by SOC and PT.
- The number and percentage of participants with TEAEs excluding SAEs and the number of events, with frequency ≥ 5% in any study intervention arm by SOC and PT
- The number and percentage of participants with at least one TEAE and the number of events by severity, SOC, and PT
- The number and percentage of participants with at least one related TEAE, evobrutinib-related TEAE, moxifloxacin-related TEAE, and placebo-related TEAE and the number of events by SOC and PT
- The number and percentage of participants with at least one AESI recorded and the number of events by SOC and PT.

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

For determining incidence counts, within each level of TEAE term, if a participant experiences more than one occurrence, the participant will only be counted once for that TEAE.

AEs related to any study intervention are those events with relationship missing, unknown or yes.

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

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

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

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

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

15.2.1 Deaths

A listing of deaths, if any, will be provided.

15.2.2 Serious Adverse Events

A listing of SAEs, if any, will be provided.

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

15.2.3 Other Significant Adverse Events

The following AESI were defined:

- Infections (serious, severe, and opportunistic, ≥ Grade 3)
- Seizures
- Elevated lipase, elevated amylase, pancreatitis
- Liver-related events

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

AESIs will be flagged based on an external excel file which includes the precise descriptions of the AESIs (SMQs, PTs and laboratory constellations) and will be used to retrospectively identify AESIs in the AE listings. Summary table of the number and percentage of participants with at least one AESI by SOC and PT will also be provided.

In addition to the AESIs defined above, the preferred term including “Syncope” or “Pre-syncope”, if any, will also be flagged and summarized.

15.3 Clinical Laboratory Evaluation

Listings and summary statistics at each assessment time will be presented using SI units. Normal ranges will be provided by the laboratory department, and out of range flags will be calculated based on the normal ranges. Laboratory data not transferred from the central laboratory in SI units will be converted to SI units before processing. Both original units and SI units will be provided in the SDTM domain.

Safety laboratory parameters are separated into:

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

Hematology (including coagulation) and biochemistry will be summarized by treatment and time point using descriptive statistics.

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

15.4 Vital Signs

Vital signs data will be summarized by treatment 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 vital sign data will be provided.

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

15.5 Other Safety or Tolerability Evaluations

15.5.1 Standard Safety ECG

Standard safety ECG data include ventricular rate, PR interval, QRS duration, QT interval (uncorrected) and QTcB and QTcF and will be summarized by treatment and time point using descriptive statistics for baseline (see definition in Section 9). A listing of safety ECG data will be provided.

Safety standard ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed.

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

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

PK evaluation will be performed by Nuvisan GmbH.

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

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements of evobrutinib CCI as well as moxifloxacin will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

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

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

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. In export datasets, as well as in the SDTM PC domain, PK concentrations will be provided with full precision and will not be rounded.

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

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

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data of each analyte will be summarized using: number of non-missing observations (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For PK parameters related to time (e.g. t_{max}, t_{lag}, t_{last}), only n, Min, Median, and Max may be reported.

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

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

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

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

16.1.3 Statistical Analysis of PK Parameter Data

Analysis of Primary Endpoints

All PK parameters will be analyzed descriptively as described above.

16.1.4 General Specifications for PK Concentration and PK Parameter Data

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

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

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

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

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

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

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

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

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

16.1.5 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., Overlook Center, Suite101, Princeton, NJ 08540) will be used to derive PK parameters applying NCA.

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) will be used to generate additional PK parameters and produce tables, listings, and figures.

16.1.5.1 Estimation of Pharmacokinetic Parameters in Plasma

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

The following PK parameters will be calculated, when appropriate: PK parameters will be calculated for all analytes and unless otherwise noted.

Symbol	Definition
AUC_{0-24}	The partial AUC from time zero (= dosing time) to 24 hours.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
AUCextra%	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$.
C_{max}	Maximum observed concentration.
CL/F	The apparent total body clearance following extravascular administration (parent only).
λz	Terminal first order (elimination) rate constant.
t_{max}	The time to reach the C_{max} in a dosing interval.
$t_{1/2}$	The terminal half-life.
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration (parent only).

Additional PK parameters may be calculated where appropriate.

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

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

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

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

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

If $AUC_{extra\%} > 20\%$ and/or the coefficient of correlation (Rsq adj) of λ_z is < 0.8 and/or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL/F, etc.) will be

listed, flagged and included in the parameter outputs. Should more than 10% of subjects be flagged for AUCextra and/or Rsq adj (for a particular analyte), a sensitivity analysis excluding flagged parameters may be performed after discussion with the Sponsor.

16.1.6 Presentation of PK Concentration and PK Parameter Data

16.1.6.1 Listings and Tables

The following PK tables will be produced (PK Analysis Set):

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

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

- Individual concentrations, nominal time by participant, analyte, and study intervention sorted in chronological order
- Individual PK parameters by participant, analyte, and day sorted in chronological order
- PK Sampling date, actual time, nominal time, deviation from time, percentage time deviation by participant, analyte, and study intervention sorted in chronological order
- Phoenix WinNonlin NCA Core Output

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

The following graphical summaries and individual plots will be provided:

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

16.2 Pharmacodynamics

Not applicable.

16.3 QTc Analysis

For QTc analysis, the ECG analysis set will be used.

As a first step, ECG assay sensitivity will be demonstrated via C-QTc analysis of data following administration of moxifloxacin as described in Section 16.3.4.

Subsequently, the relationship between observed evobrutinib CCI plasma concentrations and time-matched, triplicate QTc intervals will be evaluated in a C-QTc analysis as described below in Section 16.3.3. The correction of the observed QT intervals will be based on the Fridericia correction (QTcF). If adequate correction of the observed QT data for heart rate is not obtained with the Fridericia correction and there is a meaningful effect of evobrutinib and MSC2729909A on HR (i.e. greater than 10 bpm as described in Section 16.3.3.1), individual-optimized RR correction methods (QTcI) may be applied in a supplemental analysis.

CCI

Primary and secondary endpoints will be summarized by timepoint as described in Section 16.3.4.3.

16.3.1 Data Selection for C-QTc Analysis

For the C-QTc analysis, PK samples and ECG measurements will be matched by nominal time point, unless the ECG and PK sample times are more than 15 minutes apart, in which case the ECG record will be flagged for exclusion from the analysis.

Parameters to be considered in the C-QTc analysis include QTcF intervals, uncorrected QT intervals, and heart rate (HR). In addition, QTcI may be considered based on correction factors derived from predose and placebo data.

A NONMEM-formatted analysis dataset will be constructed based on data from ECG analysis set. The dataset will include information on participant ID, period identifier, nominal and actual date and time of PK sample collections, evobrutinib plasma concentrations, MSC2729909A plasma concentrations, and time-matched ECG measurements, as well as relevant covariates (age, body weight, sex, and race). As a general principle, missing concentration and ECG data will not be imputed. Concentration values below the limit of quantification will be treated as 0. The exact format of the dataset will be described and agreed upon through a data specification document.

Assembly of the C-QTc dataset will be performed using SAS® Software version 9.2 or higher. C-QTc analysis will be performed using NONMEM 7.3 or higher or R version 4.1 or higher. Model diagnostics, evaluation, and model predictions will be performed using R version 4.1 or higher. Actual software versions will be reported. Quality control (QC) of the dataset programming will be performed per Certara standard operating procedures.

16.3.2 C-QTc Analysis Dataset Summary and [redacted]

Absolute and baseline-corrected ECG measurements and evobrutinib, MSC2729909A, and moxifloxacin plasma concentrations will be summarized by period/time point, a summary of participants and observations in the analysis dataset will be provided, and a listing of participants and data records flagged for exclusion from the C-QTc analysis will be created.

The mean observed evobrutinib, MSC2729909A, and moxifloxacin plasma concentrations and absolute and baseline-corrected ECG measurements will be shown vs nominal time point for each treatment group (placebo, moxifloxacin, 45 mg evobrutinib, 225 mg evobrutinib), and baseline-corrected ECG measurements will be shown vs time-matched PK data. In addition, plots of QT, QTcF, and QTcI vs RR will be created to illustrate the heart rate correction of the available QT data.

16.3.3 Primary Objective Analysis: C-QTc analysis

The relationship between evobrutinib, MSC2729909A, and moxifloxacin plasma concentration and QT intervals will be carried out based on heart rate-corrected QT data (QTc). QTc should be independent of HR or RR interval (HR=60/RR) in the evaluation of drug-induced QT prolongation. Fridericia-correction shown in **Equation 1** is considered the gold standard, however, the adequacy of the Fridericia correction will be assessed by a linear regression of QTcF interval on the RR interval.

$$QT_cF = \frac{QT}{RR^{1/3}} \qquad \textbf{Equation 1}$$

[redacted]

A linear mixed effects modeling approach will be used to quantify the relationship between evobrutinib (and metabolite) and moxifloxacin plasma concentration and ΔQTcF, provided that QTcF is independent of RR interval and no evidence of drug-induced heart rate changes, no hysteresis, and no clear indication of nonlinearity in the concentration-ΔQTcF relationship is identified [**1**, **2**]. Data-driven C-QTc models will be developed when one or more of the assumptions discussed in Section 16.3.3.1 are violated.

The standard linear mixed-effects model is described in Section 16.3.3.2. A covariate analysis will be performed to refine the developed structural model by including covariates that have a statistically significantly effect on QTc as described in Section 16.3.3.3.

16.3.3.1 Evaluation of Assumptions

Assessment of Drug Effect on HR

The potential of evobrutinib and MSC2729909A to increase or decrease heart rate by more than 10 bpm will be assessed graphically by plotting the mean observed ΔHR with 90% confidence interval versus timepoint for each treatment group and visually inspecting the trend of consistence with time and treatment group and, if applicable, based on model predicted ΔHR with 90% confidence versus corresponding evobrutinib and/or MSC2729909A plasma concentrations (see Section 16.3.4.2). Treatment groups with a small number of participants may be grouped together for this purpose. The ΔHR-concentration relationship may be further evaluated by scatter plots of individual time-matched ΔHR vs concentration pairs.

Hysteresis

To assess visually whether there is a time lag (a hysteresis effect) between evobrutinib plasma concentration and ΔQTc interval, mean concentration and mean ΔQTc will be plotted versus timepoint for each treatment group in a single plot and visually inspected for differences between t_{max} for concentration and t_{max} for ΔQTc. In addition, individual and mean plots showing ΔQTc and concentration connected in the order of ECG measurements/PK sampling will be shown for each study participant and evobrutinib treatment group, respectively. If the relationship between ΔQTc and evobrutinib plasma concentration appears independent of time, this suggests no hysteresis. If the exploration shows that the value of ΔQTc for a given value of concentration differs as time evolves, and the values of ΔQTc observed before t_{max} consistently differ from the values observed at a similar concentration at a timepoint after t_{max} , this suggests presence of hysteresis [1,3].

CCI [redacted]

Assessment of Linearity

The relationship between observed ΔQTc and evobrutinib and MSC2729909A plasma concentrations will be visualized by decile plots showing mean observed ΔQTc with 90% confidence intervals placed at the midpoint of each concentration decile, as well as scatter plots of ΔQTc versus concentration for all timepoints from all treatment groups. Locally estimated scatterplot smoothing (LOESS) curve and linear regression lines will be included in the scatter plots.

CCI [redacted]

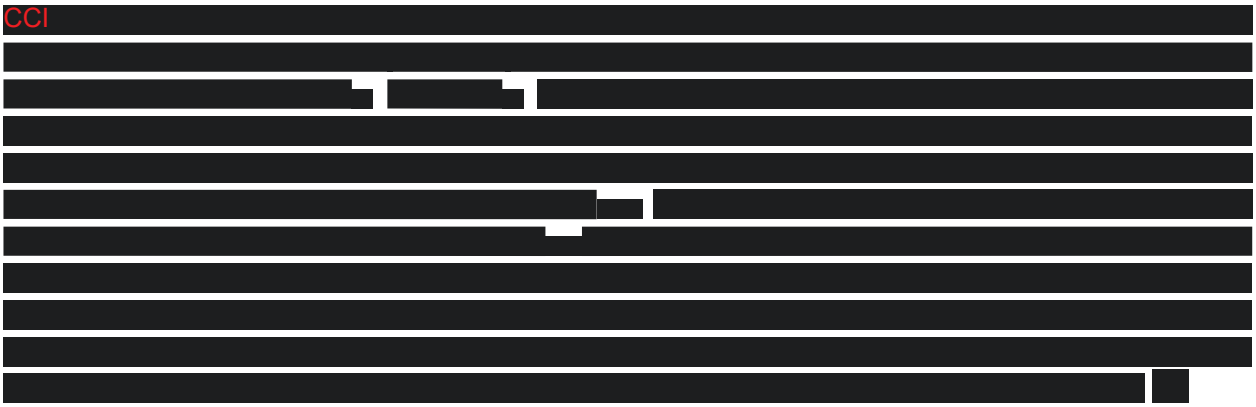
[redacted]

16.3.3.2 Standard Linear Mixed-Effects Model of QTc

The recommended linear mixed effects model described by Garnett et al. [1] will be applied in the C-QTc analysis to quantify the relationship between evobrutinib and CCI [redacted]

CCI [redacted]

[redacted]



Similar methodology will be applied in the C-QTc analysis of ECG measurements following administration of moxifloxacin or placebo in the evaluation of assay sensitivity, as described in Section 16.3.4.

16.3.3.3 Covariate Analysis

Covariates of interest for the C-QTc models are (apart from nominal time) age, body weight, sex, race, and study period. Covariates will only be evaluated as predictors of parameters with random effects.

For a covariate to be included in the formal covariate analysis, it should be available in at least 80% of participants. For categorical covariates, if a category constitutes less than 10% of the total participants, it will be combined with the most prevalent category. Multiple low proportion categories may be grouped together as a single category.

Covariate analysis will only be performed if a statistically significant C-QTc relationship is found ($P<0.01$). A multivariable forward addition of significant covariates ($P<0.01$) followed by backward elimination of not significant covariates ($P>0.001$) will be performed on univariable significant covariates ($P<0.01$). Only one of a highly correlated pair of univariable significant covariates will be included in the multivariable analysis. The model emerging from the multivariable covariate evaluation may be refined to ensure model identifiability and plausibility of included covariate relations.

In the covariate evaluation, the maximum likelihood (ML) estimation option will be selected instead of the restricted maximum likelihood (REML) option. A REML criterion is inappropriate to compare models differing in fixed effects while ML is consistent with the likelihood-ratio test used in the covariate evaluation. Final run results will use the "REML" option; results will be compared with "ML" results to confirm minimal differences.

16.3.3.4 Model Selection and Evaluation

The standard model shown in Equation 5 will be considered the primary model of ΔQTcF. If the assessment of QT interval correction indicates that the Fridericia-correction is not adequate (see Section 16.3.3), the standard model may be fitted to ΔQTcI in an additional supplemental analysis. If indicated by model diagnostics, additional models may be evaluated, and a data-driven model may be presented.

For nested models, a log-likelihood criterion at the 0.01 level of significance will be used for model selection; for non-nested models, the Akaike Information Criterion will be used. The final model will be selected based on the statistical comparisons described above, diagnostic plots, and clinical plausibility and relevance. A model building summary and parameter estimates (with 95% confidence intervals (CIs) and relative standard errors) for the standard and (if applicable) empirical models will be provided.

Diagnostic plots will include plots of observed vs. model-predicted ΔQTc, observed and model-predicted ΔQTc intervals versus time, quantile-quantile plots of standardized residuals, and plots of standardized residuals vs. predicted ΔQTc, concentration, time after dose within period, and treatment (placebo, 45 mg evobrutinib, 225 mg evobrutinib). Distributions of random effects will be shown in histograms and quantile-quantile plots, and correlations between random effects will be shown in a pairwise scatterplot. Correlations between random effects and covariates will be shown in scatter plots with LOESS (continuous covariates) or box-whisker plots (categorical covariates). The predicted concentration-ΔQTc relationship will be overlaid on corresponding observed data on a continuous concentration scale and summarized by concentration bins (e.g. deciles). The 90% CI of the observed mean ΔQTc will be based on a normality assumption.

The predictive performance of the developed final C-ΔQTc model will be evaluated using visual predictive checks (VPC). The distribution of observed data will be compared to corresponding simulated data to demonstrate the model's ability to adequately predict the data on which the model is based. VPC will show data vs time after first dose and vs concentration. VPCs will be based on 1000 simulations.

The model diagnostics and evaluation will be based on the overall dataset and stratified by subject covariates included in the final model. If the final model includes both evobrutinib and MSC2729909A, two alternative individual models based on only evobrutinib and only MSC2729909A will be estimated and used for figures representing the underlying data (scatter plots for C-QTc model, decile plots, and prediction plots).

For data-driven, non-linear C-QTc models, a non-parametric bootstrap with subject identifier used as the unit for resampling may be carried out to confirm model robustness, as well as for computing confidence intervals on model predictions (see Section 16.3.3.5).

16.3.3.5 Model-Based Predictions

The predicted placebo- and baseline-corrected QTc will be denoted ΔΔQTc and calculated as the difference between the model-predicted ΔQTc at relevant evobrutinib and MSC2729909A plasma concentrations and ΔQTc predicted for participants treated with placebo [1]. CCI [redacted]

CCI [redacted]

Predictions based on additional and/or data-driven models (if relevant, see Section 16.3.3.4) will be calculated based on corresponding model equations.

CCI [redacted]

16.3.4 Secondary Objective Analysis

16.3.4.1 QTc Assay Sensitivity

The evaluation of assay sensitivity based on the data from the positive control will be based on estimates and model predictions based on the standard linear mixed-effects model of QTcF fit to data obtained following administration of moxifloxacin (see Section 16.3.3.2). Predictions of ΔΔQTc following moxifloxacin exposure will follow the methodology described in Section 16.3.3.5. The evaluation of assay sensitivity will be based on the assumption that the assumptions described in Section 16.3.3.1 (no evidence of drug-induced heart rate changes, adequate correction of QTcF for heart rate , no hysteresis, and no clear indication of a nonlinear relationship between concentration and ΔQTc) are met.

CCI [redacted]

16.3.4.2 Assessment of the Effect of Evobrutinib on other ECG Parameters

The effect of evobrutinib and MSC2729909A plasma concentrations on baseline-corrected measurements of uncorrected QT intervals, PR and QRS intervals, and HR will be visually assessed by plots of the ECG measurements versus time-matched evobrutinib and MSC2729909A plasma concentrations with trend lines.

CCI [redacted]

16.3.4.3 By Timepoint and Categorical Analysis

The Safety analysis set will be used for the analysis.

Triplicate 10 s ECGs from continuous Holter recordings for central evaluation will also be extracted and evaluated statistically similar to standard safety ECG described in section 15.5.1. For the evaluation of continuous variables, the mean of each assessment at each time point with triplicates will be used in summary tables and for the evaluation of qualitative variables, the worst assessment will be used in summary tables, if not stated otherwise. Change from baseline will also be calculated and summarized.

This Holter ECG assessment include the parameters QT, QTcB, PR, QRS, RR, HR, and cardiologist assessment including T-wave morphology, and U-wave.

QTcI will be derived by log-linear regression. Individual correction factors (mi) for log-transformed QT vs. log-transformed RR data for each subject at predose (-1 h, -30 min, -10 min) and from the placebo period will be fitted. QTcI will then be calculated as shown in **Equation 2**

ΔΔQTcF, ΔΔQTcI, ΔΔHR, ΔΔPR, ΔΔRR, ΔΔQRS, will be calculated as the difference between the change from baseline of active treatment (evobrutinib or moxifloxacin) and the time-matched change from baseline of placebo.

For ΔΔQTcF, the postdose timepoint with the maximum mean for each active study intervention will be selected and tabulated together with the mean value and its 2-sided 90% confidence intervals (CI).

QT values will be categorized for each time point using the following groups

- ≤ 500 ms
- > 500 ms

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

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

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

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

The number and percentage of subjects by these categories at each postdose assessment will be tabulated by study intervention.

A categorical analysis for outliers will be performed in order to identify the frequency of postdose categorical outliers for ECG parameters by study intervention:

The categorical outliers for HR parameters will be categorized as:

- HR changes reflecting at least a 25% decrease from baseline to a HR < 50 beats per minute (bpm) (Bradycardic event)
- HR changes with a 25% increase from baseline reflecting a HR > 100 bpm (Tachycardic event)

The categorical outliers for PR and QRS parameters will be categorized as:

- PR change from baseline: at least a 25% increase when PR > 200 msec
- QRS change from baseline: at least a 25% increase when QRS > 100 msec

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

The results for T-wave morphology (abnormal+finding) and U-wave (abnormal) will be summarized in frequency tables with counts and percentages for number of subjects.

17 References

1. Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, Mehrotra D, Riley S, Sager P, Tornoe C, Wang Y. Scientific white paper on concentration-QTc modeling. *J Pharmacokinet Pharmacodyn.* 2018;45:383-397.
2. Darpo B, Benson C, Dota C et al. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. *Clin Pharmacol Ther*. 2015;97:326-35.
3. Tornøe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol*. 2011;51:1035-42.
4. Sparve E, Quartino AL, Luttgen M, Tunblad K, Teiling Gardlund A et al. Prediction and modeling of effects on the QTc interval for clinical safety margin assessment, based on single-ascending-dose study data with AZD3839. *J Pharmacol Exp Ther*. 2014;350:469-478.

18 Appendices

Not applicable.