TRIAL STATISTICAL ANALYSIS PLAN

c34211779-01

BI Trial No.:	1402-0016
Title:	Investigation of pharmacokinetics and absolute bioavailability of BI 1358894 administered orally as tablet co-administered with an intravenous microtracer dose of [C-14]-BI 1358894 in healthy male volunteers via a non-randomised, open-label, fixed-sequence trial (part 1) followed by a randomised, open-label, single dose, two-period, two-sequence cross-over relative bioavailability trial in BI 1358894 oral suspension (part 2) Revised Protocol #01
Investigational Product:	BI 1358894
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Date of statistical analysis plan:	09 FEB 2021 SIGNED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis dataset
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{0-312}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 312 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BP	Blood pressure
C_{max}	Maximum measured concentration of the analyte after oral administration
COVID	Coronavirus disease
CV	Arithmetic coefficient of variation
ECGPCS	ECG plasma concentration set
gCV	geometric coefficient of variation
gMean	Geometric mean
IQRMP	Integrated quality and risk management plan
MedDRA	Medical Dictionary for Regulatory Activities
PKS	Pharmacokinetic parameter set
PR	Pulse rate
RAGe	Report appendix generator
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
ULN	Upper limit of normal range

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the revised CTP and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the CTP and its amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 'Statistical Methods and Determination of Sample Size'. Therefore, TSAP readers may consult the revised CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

The trial is divided into two parts, with the same patients included in both parts. The analyses of both parts are described in the TSAP.

Study data will be stored in a trial database within the RAVE EDC system.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods planned in the revised CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary PK endpoints are as defined in Section 2.1.2 of the CTP.

Primary endpoints in Part 1 are $AUC_{0-\infty}$ for (C-14) BI 1358894 i.v. and $AUC_{0-\infty}$ for BI 1358894 p.o.

Primary endpoint of Part 2 is AUC_{0-312} of BI 1358894.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable

5.2.2 Secondary endpoints

Secondary PK endpoints will be as defined in Section 2.1.3 of the CTP.

Secondary endpoint in Part 1 is C_{max} of BI 1358894.

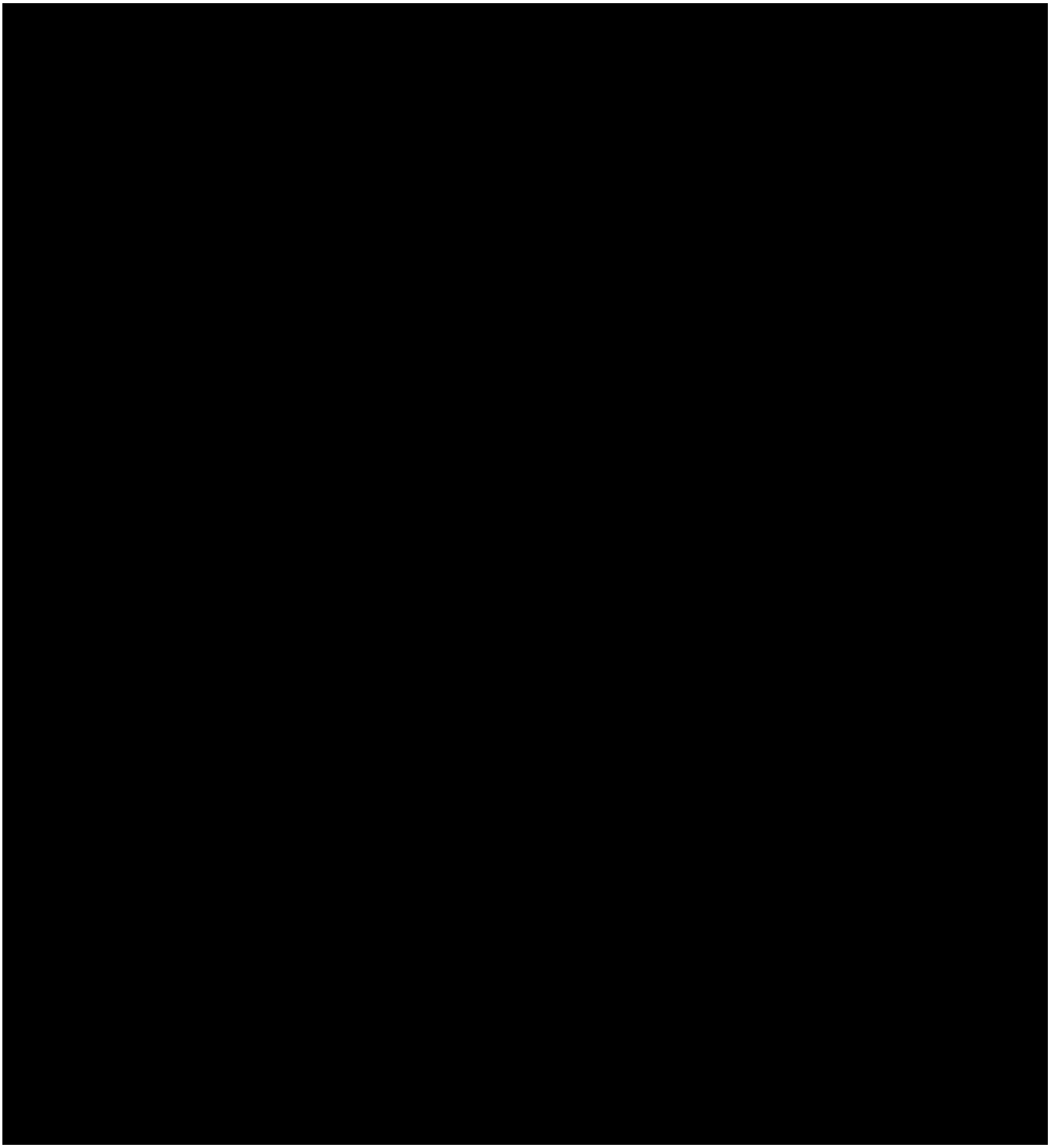
Secondary endpoints in Part 2 are C_{max} and $AUC_{0-\infty}$ of BI 1358894.

[redacted]

Further safety parameters of interest will be as defined in **Section 2.2.2.2 of the CTP**:

- AEs (including clinically relevant findings from the physical examination)

[redacted]



5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

Section 5.2.1 of the CTP: *At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, a physical examination and a neurological examination.*

Body mass index will be calculated as weight (kg) / [height (m)]^2.

5.4.2 Treatment compliance and treatment exposure

Treatment compliance will not be analysed as a specific endpoint, cf. Section 4.3 of the CTP.

Treatment exposure is defined as the number of doses and the total dose of BI 1358894 per treatment and per subject.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

The trial is divided into two parts, with the same patients included in both parts.

In **Part 1**, each subject is planned to be treated with a single oral dose (two non-radiolabelled tablets) of BI 1358894 (T1) on Day 1. Five hours after the administration of the tablet, the subjects will receive an i.v. microtracer dose of [C-14]-BI 1358894 (R1).

In **Part 2**, each subject is planned to be treated with a single oral suspension of BI 1358894 either under fasted (R2) or fed (T2) conditions on Day 1 in each period separated by a washout period of at least 17 days between the two drug administrations. The subjects will be randomly allocated to the two treatment sequences T2-R2 or R2-T2.

Single oral drug administrations of each period are separated by a washout period of at least 17 days.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs

Analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of BI 1358894 in Part 1
On-treatment	**BI Tab**	Date/time of first administration of BI 1358894 tablet in Part 1	Date/time of start of infusion of BI 1358894 (C-14) in Part 1
On-treatment	**BI Tab/C14**	Date/time of start of infusion of BI 1358894 (C-14) in Part 1	Date/time of end of infusion of BI 1358894 (C-14) in Part 1 + REP (11*24h)
Follow-up	**F/U BI**	Date/time of end of infusion of BI 1358894 (C-14) in Part 1 + REP (11*24h)	Date/time of first administration of BI 1358894 in Part 2
On-treatment	**BI fasted**	Date/time of administration of BI 1358894 under fasted conditions in Part 2	Date/time of administration of BI 1358894 under fasted conditions in Part 2 + REP (11*24h)
Follow-up	**F/U BI fasted**	Date/time of administration of BI 1358894 under fasted conditions in Part 2 + REP (11*24h)	Date/time of administration of BI 1358894 under fed conditions in Part 2 or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
On-treatment	**BI fed**	Date/time of administration of BI 1358894 under fed conditions in Part 2	Date/time of administration of BI 1358894 under fed conditions in Part 2 + REP (11*24h)
Follow-up	**F/U BI fed**	Date/time of administration of BI 1358894 under fed conditions in Part 2 + REP (11*24h)	Date/time of administration of BI 1358894 under fasted conditions in Part 2 or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier

Analysis phases for statistical analysis of AEs are defined for each subject as described in the Table 6.1: 1.

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phases only.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- "**Total BI**", defined as the total over all on-treatment phases involving BI

In disposition, demographics and baseline characteristics, all subjects will be analysed together (i.e., one "Total" column).

Safety laboratory data, vital signs and ECG will be analysed by treatment (BI, BI fasted, BI fed) with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 1.

The following labels will be used for the comparison of treatments:

Table 6.1: 2 Overview of treatments for intra-individual comparison

Treatment		**Short label**
R1	100 µg BI 1358894 (C-14)	BI (C-14) 100 ug iv
T1	100 mg BI 1358894	BI 100 mg tablet
R2	100 mg BI 1358894 under fasted conditions	BI 100 mg fasted
T2	100 mg BI 1358894 under fed conditions	BI 100 mg fed

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in the analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2). Additionally, all iPDs will be documented in the DV sheet.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other iPDs, the definition in the IQRMP and the table below will be supplemented accordingly by the time of the RPM.

iPDs will be summarized and listed. Table 6.2: 1 below specifies which kind of iPDs could potentially lead to exclusion from which analysis set (cf. Section 6.3). The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will only be listed.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
A1	Inclusion Criteria Not Met	PKS
A2	Exclusion Criteria Violated	PKS
B1	Informed consent not available/not done	TS, PKS
B2	Informed consent too late	None
C1	Incorrect trial medication intake	PKS
C2	Randomisation not followed	PKS
C3	Non-compliance	PKS
C4	Medication code broken inappropriately	PKS
C5	Incorrect intake of trial medication	PKS
C6	Improper washout between treatments	PKS
D1	Prohibited medication use	PKS
D2	Mandatory medication not taken	PKS
D3	Improper washout of prohibited concomitant medication	PKS
E1	Certain violations of procedures used to measure primary or secondary data	PKS
F1	Certain violations of time schedule used to measure primary or secondary data such as incorrect duration of infusion	PKS
G1	Incorrect intake of meal	PKS

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in the **Section 7.3 of the CTP**:

- *Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or*

secondary and was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

In addition, the following subject set for a certain analysis of ECG data will be used.

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

- ECG plasma concentration set (ECGPCS):
  This subject set includes all subjects from the TS who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the RPM before data base lock.

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	TS	PKS	ECGPCS
Disposition	X		
IPDs	X		
Primary endpoints		X	
Secondary endpoints		X	
Further PK endpoints		X	
Safety parameters (except for exposure-response analyses of ECG data)	X		
Exposure-response analyses of ECG data			X
Demographic/baseline conditions	X		
Exposure	X		

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because the trial is performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR.

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal reported in the CTR.

CTP Section 7.5.1: *It is not planned to impute missing values for safety parameters.*

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic mean per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

Missing data and outliers of PK data are handled according to BI standards (4) and (5).

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

A separate baseline is defined for each treatment period: Baseline is the last available off-treatment value before administration of the respective treatment (BI, BI fasted, BI fed). Off-treatment in this context means that a value measured within an on-treatment phase, as defined in Table 6.1: 1, will not be used as baseline for any study treatment.

There will be a centralised evaluation of 12-lead ECG recordings at the time points specified in Table 6.7: 1.

Three triplicate ECGs will be recorded as the baseline before the each oral drug administration, but only all 3 single ECGs of the first of the 3 triplicates will be transferred to the database. Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all on-treatment time points with centralised ECG evaluation.

The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to first study drug administration. For all on-treatment assessments, only the first of the three replicate ECG at a single assessment time will be centrally evaluated.

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation

Visit	Day	Planned time [hh:mm] - relative to respective drug administration	Study phase
2/3/4	1	-01:00	Baseline
		01:00	On-treatment
		04:00	
		08:00[1]	
		12:00	
	2	24:00	

[1] in Part 1 only

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g., the HR change from baseline and the plasma concentration measured at planned time 01:00 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big for a reliable assessment and the pair has to be excluded from the analysis will be decided no later than at the RPM.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Standards for Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment sequence ("Tab/C14-fasted-fed" and "Tab/C14-fed-fasted"), subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For plasma concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant, if it

- is ongoing at the time of first study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

Only descriptive statistics are planned for this section of the CTR.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analyzed as a specific endpoint. Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

The analysis of primary endpoints will be based on the PKS.

7.4.1 Primary analysis of the primary endpoints

Part 1

The statistical model for the primary endpoint $AUC_{0-\infty}$ is an analysis of variance (ANOVA) model on the logarithmic scale including “formulation” as fixed effect and “subject” as random effect (cf. CTP Section 7.3.1).

Absolute bioavailability will be estimated by the ratios of the geometric means of $AUC_{0-\infty}$ for BI 1358894 p.o. (T1) versus $AUC_{0-\infty}$ for (C-14) BI 1358894 i.v. (R1). The point estimates for the ratios of the geometric means and their two-sided 90% CIs will be provided.

Part 2

The statistical model for the primary endpoint AUC_{0-312} is an ANOVA model on the logarithmic scale including “treatment”, “sequence” and “period” as fixed effects and “subject within sequence” as random effect (cf. CTP Section 7.3.1).

Relative bioavailability will be estimated by the ratios of the geometric means of BI fed (T2) versus BI fasted (R2) of AUC_{0-312} of BI 1358894. The point estimates for the ratios of the geometric means and their two-sided 90% CIs will be provided.

Part 1 and 2

Section 7.3.1 of the CTP:

For study part 1 and part 2, point estimates for the ratios of the geometric means (test/reference) for the primary endpoints […] and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to “ALL CALC”, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to “DESC STATS” the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition “TIME VIOLATION” or “TIME DEVIATION”, the value can be used for further analyses based on actual times. If ACEXCO is set to “HALF LIFE”, the value will be excluded from half-life calculation only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to “Included”.

Further details are given in “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (4) and “Description of Analytical Transfer Files and PK/PD Data Files” (5).

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

The analysis of secondary endpoints will be based on the PKS.

The secondary endpoints will be statistically analysed in the same way as for the primary endpoints. [redacted]

See Section 7.4 of this TSAP for details regarding exclusion of PK parameters and plasma concentrations.

[redacted]

7.6.2 Safety parameters

Safety endpoints and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to screening, on-treatment or follow-up phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.

CTP Section 5.2.6.1.4: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (8), in addition to deaths and SAEs, "other significant" AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related will be

summarised separately. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. AEs will also be summarized by maximum intensity.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

If the subject reports headaches during the treatment period further information about the duration of headache, location, characteristics, and signs and symptoms were recorded. The information will be summarized with descriptive statistics.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

Analyses will be based on normalised values, which mean transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Descriptive statistics of absolute values and change from baseline from laboratory parameters over time (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement. Descriptive statistics will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of absolute values and change from baseline from vital signs over time (see Section 6.7) will be provided.

Unscheduled measurements of vital signs will be assigned to planned time points as follows:

- Unscheduled measurements prior to the first scheduled measurement within a visit will be assigned to the planned time point of the first scheduled measurement of that visit.
- Other unscheduled measurements will be assigned to the planned time point of the previous, most recent scheduled measurement.

Unscheduled measurements of vital signs will be used in calculation of descriptive statistics by planned time point as follows:

- If an unscheduled measurement is the last available off-treatment value before study drug administration, this unscheduled measurement will be used in the statistical analysis as baseline (as this is in accordance with the definition of baseline, cf. Section 6.7).
- At post-baseline time points, descriptive statistics by planned time point will be calculated based on the last value of the subject within 20 minutes of the scheduled measurement of that planned time point. The rationale for this rule is that these measurements are interpreted to be repeat measurements of the scheduled measurement (e.g. for confirmation of a particular value).

  An unscheduled measurement more than 20 minutes after the time of the scheduled measurement of that planned time point will be listed, but will not be used in calculation of descriptive statistics. These measurements are interpreted as off-schedule vital signs measurements, taken for other reasons.

  If an unscheduled measurement is taken at exactly the same time as the scheduled measurement, this unscheduled measurement will be considered to be done after the scheduled measurement, and will potentially qualify to be the “last value of the subject within 20 minutes of the scheduled measurement of that planned time point”.

  If the time of measurement is missing for a scheduled measurement, the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).
  If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (from first study drug administration onwards) if judged clinically relevant by the investigator.

The ECG exposure response analysis will be based on the ECGPCS. All other descriptive analysis of ECG endpoints will be based on the TS.

Generally, ECG measurements will not be included in the statistical analysis if one of the following applies:

- No date or time available for ECG measurement
- Pre-dose measurement done after first drug administration
- On-treatment measurement done before first drug administration
- Measurement is a repeated measurement
- More than 3 single ECGs (i.e., measurements from 4th single ECG onwards will not be included)
- Unscheduled measurements

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR, only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by renal function group.

Exposure-response assessment

To assess the relationship between changes from baseline in QTcF and HR and the time-matched plasma concentrations of each subject group, several plots will be provided. For a list

of time points with scheduled ECG assessments and a time-matched plasma concentration, refer to Table 6.7: 1.

For the handling of missing values, see Section 6.6.

The remaining section describes the analysis for QTcF only, however the same plots will be performed for HR.

To investigate if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF, a general visual impression will be provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline. These figures will be generated for each subject (presented in the Statistical Appendix of the CTR), as well as for means per subject group (presented in the End-of-Text part of the CTR).

For a visual inspection of the relationship between BI 1358894 plasma concentration and QTcF changes from baseline, a scatterplot of the individual values of BI 1358894 plasma concentration against QTcF changes from baseline will be created with separate symbols for each subject group. For QTcF a horizontal reference line at 60 msec will be added. Vertical lines at the gMean of C_{max} of the respective subject group will also be added.

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying a random coefficient model using all time points. A scatterplot of ln(QTcF) vs ln(RR) including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

7.8.5 Others

Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.5.1 of the CTP, results will only be listed. No further analysis will be prepared. Findings will also be reported as AEs.

Physical and neurological examinations

Physical and neurological examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical or neurological examination findings will be prepared.

8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
5	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042: "*Display and Analysis of Laboratory Data", current version; KMED

9. ADDITIONAL SECTIONS

9.1 DETAILED DESCRIPTION OF ENDPOINTS FOR ECG

QT, PR, QRS and RR baseline and on-treatment measurements (see Table 6.7: 1) are included in the centralised ECG evaluation.

For each single ECG, measurements of QT, PR, QRS and preceding RR interval of four cardiac cycles will be determined and stored in the database as raw data. Their mean values will be used as the QT, PR, QRS, and RR interval values, respectively, for this ECG.

QTcF, HR and QTcB will be calculated based on the derivation rules as follows:

From the four cardiac cycles of a single ECG, the HR (measured in beats per minute, beats/min) will be calculated as

$$HR\ [beats/min] = \frac{60\ 000}{\overline{RR}}$$

where $\overline{RR}$ is the mean of the four RR intervals (measured in msec).

Similarly, the QT interval corrected for HR according to Fridericia's formula (QTcF) for a single ECG will be derived as

$$\overline{QTcF}\ [msec] = \left(\frac{1000}{\overline{RR}}\right)^{1/3} * \overline{QT}[msec],$$

where $\overline{\mathrm{QT}}$ is the mean of the four QT intervals and $\overline{\mathrm{RR}}$ is the mean of the corresponding preceding RR intervals of the four cardiac cycles for this ECG.

Likewise, the HR-corrected QT interval according to Bazett's formula (QTcB) for a single ECG is given by

$$\overline{QTcB}\ [msec] = \left(\frac{1000}{\overline{RR}}\right)^{1/2} * \overline{QT}[msec].$$

In case of triplicate ECGs at a time point, the respective ECG variable will be averaged over the triplicate ECG measurements at this time point (arithmetic mean). Note that in case of missing values the averaging is simply done for the available values.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**09-FEB-2021**	[redacted]	None	This is the final TSAP