TRIAL STATISTICAL ANALYSIS PLAN

c27807278-01

BI Trial No.:	1402-0002
Title:	Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1358894 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects Final protocol (including protocol revision 1 (c21808436-02), 2 (c21808436-03), 3 (c21808436-04) and 4 (c21808436-05))
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	 Phone: Fax:
Date of statistical analysis plan:	12 AUG 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24h
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a dosing interval τ
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CV	Arithmetic coefficient of variation
ECGPCS	ECG plasma concentration set
gCV	geometric coefficient of variation
HR	Heart rate
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available
PKS	Pharmacokinetic parameter set
PR	Pulse rate
QRS complex	Combination of the Q, R, and S waves
QT interval	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
RAGe	Report appendix generator
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SD	Standard Deviation
SOC	System Organ Class
TS	Treated Set
ULN	Upper limit of normal range

Term	Definition / description
VAS	Visual analogue scale

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 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.

Study data will be stored in a trial database within the Medidata Rave 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).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, Certara USA Inc., Princeton, NJ, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number of subjects with drug-related AEs, as defined in Section 5.2.1 of the CTP.

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 5.5.1.1 of the CTP.

BI 1358894

Secondary endpoints are AUC_{0-24} and C_{max} of BI 1358894 in plasma after the first dose, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1358894 in plasma after the last dose.

Midazolam

Secondary endpoints are AUC_{0-tz} and C_{max} of midazolam after each of the three doses.

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.

Each subject is planned to be treated with 75 µg q.d. of midazolam (solution for injection) as single dose on Day -1, Day 1, and Day 14.

Starting on Day 1, the subjects will receive 10 mg, 25 mg, 50 mg, 100 mg, or 200 mg q.d. of BI 1358894 or placebo (orally) as multiple doses every 24 hours over 14 days.

On Day 1 and Day 14, BI 1358894 will be administered immediately prior to midazolam.

All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made for placebo subjects).

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

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of Midazolam
On-treatment	**MDZ**	Date/time of first administration of Midazolam	Date/time of first administration of BI 1358894/Placebo or date/time of first administration of midazolam + 1 day (1 * 24 h) whichever occurs earlier
On-treatment	**Pbo+MDZ,** **10 mg BI+MDZ**, **25 mg BI+MDZ**, **50 mg BI+MDZ**, **100 mg BI+MDZ** or **200 mg BI+MDZ** respectively	Date/time of first administration of BI 1358894/Placebo together with Midazolam (e.g. planned on Day 1 and Day 14)	Date/time of first administration of BI 1358894/Placebo together with Midazolam (e.g. planned administration on Day 1 and Day 14) + 1 day (1 * 24 h)
On-treatment	**Pbo,** **10 mg BI**, **25 mg BI**, **50 mg BI**, **100 mg BI**, or **200 mg BI**, respectively	Date/time of first administration of BI 1358894/Placebo together with Midazolam (e.g. planned administration on Day 1 and Day 14) + 1 day (1 * 24 h)	Date/time of last administration of BI 1358894/Placebo + REP (14 * 24 h) or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U Pbo,** **F/U 10 mg BI**, **F/U 25 mg BI**, **F/U 50 mg BI**, **F/U 100 mg BI**, or **F/U 200 mg BI**, respectively	Date/time of last administration of BI 1358894/Placebo + REP (14 * 24 h)	12:00 a.m. on day after subject's trial termination date

In addition, follow-up period "F/U MDZ" may be applicable if BI+Midazolam was not administered within 24 h after first administration of Midazolam.

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 phase 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
- "**Total on-trt**", defined as the total over all on-treatment phases, including placebo

CTR Appendix 16.1.13.1.8.1 displays will present results for the screening, on-treatment and follow-up phases.

Additionally to the totals defined above, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total**", defined as the total over all study phases (screening + on-treatment + follow-up)

Safety laboratory data, vital signs, VAS and ECG will be analysed based on dose groups (Pbo, 10 mg BI, 25 mg BI, 50 mg BI, 100 mg BI, or 200 mg BI).

Analysis phases for statistical analysis of safety laboratory data, vital signs, VAS and ECG are defined for each subject as described in the table below.

Table 6.1: 2 Flow chart of analysis phases for statistical analysis of safety laboratory, vital signs, VAS and ECG – based on dose groups

Study analysis phase	Start (inclusive)	End (exclusive)
Screening	Date of informed consent at 12 a.m.	Date/time of first administration of BI 1358894 or Placebo
On-treatment	Date/time of first administration of BI 1358894 or Placebo	Date/time of last administration of BI 1358894 or Placebo+ REP (14 * 24 h)
Follow-up	Date/time of last administration of BI 1358894 or Placebo+ REP (14 * 24 h)	12:00 a.m. on day after subject's trial termination date

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects entered and randomised who did not fail during screening.

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 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 BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2). Each decision which was agreed during the RPM will be documented in the decision log.

If any iPDs are identified, they are to be summarised into categories and will be captured in an accompanying excel spreadsheet. 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 will be supplemented accordingly by the time of the RPM. Table 6.2: 1 specifies which kind of iPDs should be excluded from which analysis set.

Table 6.2: 1 Handling of iPDs

Category / iPD Code		Description	Excluded from which analysis set
A		**Entrance criteria not met**	
	A1	Inclusion criteria not met	None
	A2	Exclusion criteria met	None
B		**Informed consent**	
	B1	Informed consent not available/not done	Treated set
	B2	Informed consent too late	None
C		**Trial medication and randomisation**	
	C2	Randomisation not followed	None
	C3	Non-compliance	PKS, ECGPCS
	C4	Medication code broken inappropriately	PKS, ECGPCS
	C5	Incorrect intake of trial medication	PKS, ECGPCS
D		**Concomitant medication**	
	D1	Prohibited medication use	PKS, ECGPCS
E		**Missing data**	
		Certain violations of procedures used to measure primary or secondary data	None
F		**Incorrect timing**	
	F1	Certain violations of time schedule used to measure primary or secondary data	PKS, ECGPCS
G		**Other trial specific important deviation**	
	G1	Incorrect intake of meal	PKS, ECGPCS
	G2	Not conducted CSSRS at discharge and EOT	None

Deviations C1, C2, C5 and G1 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not protocol deviations

iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

All entered subjects who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP.

The following subject sets will be defined for statistical analysis:

- Treated set (TS):
  This subject set includes all subjects who received at least one dose of study drug. This is the full analysis set population in the sense of ICH E9 (1). It will be used for analysis of safety, demographic data and baseline characteristics.

- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the TS who provide at least one PK parameter that was not excluded due to a protocol deviation relevant to the statistical evaluation of PK endpoints or due to PK non-evaluability.

  Section 7.3.2 of the CTP: *Plasma and urine concentration data and parameters of a subject are included in the statistical PK analyses, if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR*

  Refer to the CTP Section 7.3.2 for further details.

- PKS-Midazolam (PKS-MDZ)
  The PKS-Midazolam (PKS-MDZ) includes all subjects from the TS receiving BI 1358894 or Placebo and Midazolam who provide at least one secondary PK parameter for Midazolam that was not excluded according to the description above. It is used for investigation of relative bioavailability.

All ECG analyses are performed on the TS,

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to analysis sets will be made at RPM prior to DBL.

Table 6.3: 1 Subject sets analysed

	Subject set			
Class of endpoint	**TS**	**PKS**	**PKS-MDZ**	**ECGPCS**
Disposition	X			
Exposure	X			
IPDs	X			
Demographic/baseline endpoints	X			
Primary endpoint	X			
Other safety parameters	X			
ECG endpoints and plasma concentrations				X
ECG endpoints in other analyses	X			
Secondary PK endpoints (BI 1358894)		X		
Secondary PK endpoints (Midazolam)			X	
Further PK endpoints (BI 1358894)		X		
Further PK endpoints (Midazolam)			X	

6.5 POOLING OF CENTRES

This section is not applicable, because the study was 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 recorded in the CTR.

Section 7.4.1 of the CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

The only exceptions 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 (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

Section 5.2.4.1 of the CTP: *ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart of the CTP.*

At predose (Visit 2, Day 1, planned time point -01:00), three triplicate ECGs (9 single ECGs) will be recorded.

All ECGs performed on Days 1 through 20 are transferred to the central ECG lab for evaluation.

Section 5.2.4.1 of the CTP: *Central ECG lab evaluation (of Visit 2 Days 1 to 20 ECGs only) will be performed for the first of three replicate ECGs per time point given in the Flow Chart.*

For the 3 predose triplicates, only the first of the 3 replicate ECGs at a single assessment time will be evaluated centrally.

For ECGs recorded as triple, only the first single ECG is evaluated and transferred. Therefore, for each post-baseline time point only a single ECG record will be analysed, including the ones which were measured as triple.

The baseline value of an ECG variable is defined as the mean of the first single ECG measurement of each triple ECG prior to first drug administration.

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	1	-01:00	Baseline
		01:00	On-treatment
		02:00	
		04:00	
		08:00	
		12:00	
	2	24:00	
	3	48:00	
	4	72:00	
		76:00	
		80:00	
	5	96:00	
	6	120:00	
	7	144:00	
		148:00	
		152:00	
	8	168:00	
	9	192:00	
	10	216:00	
	11	240:00	
	12	264:00	
	13	288:00	
	14	311:00	
		313:00	
		314:00	
		316:00	
		320:00	
		324:00	
	15	336:00	
	17	384:00	
	19	432:00	
	20	456:00	

In all other analyses (except for analyses of ECG variables), the last non-missing value determined prior to the first dosing of BI 1358894 or Placebo will be defined as baseline.

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

Unscheduled measurements of laboratory data, vital signs or VAS 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 of laboratory data 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).

For vital signs and VAS, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (5).

The individual values of all subjects will be listed. Listings will generally be sorted by dose group, 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 to 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. These will be based on the TS.

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 World Health Organisation – Drug Dictionary, version March 2018.

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

A medication will be considered concomitant to a treatment, if it

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the number of subjects with drug related AEs, which is the primary endpoint of this trial.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

Not applicable.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

The analysis of secondary endpoints of BI 1358894 will be based on the PKS and the analysis of the secondary endpoints of Midazolam will be based on the PKS-MDZ.

Analysis of secondary endpoints of BI 1358894

Dose proportionality will be evaluated as defined in the CTP, Section 7.3.2, by use of a power model for the secondary endpoints AUC_{0-24} and C_{max} of BI 1358894 in plasma after the first dose and $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1358894 in plasma after the last dose.

Section 7.3.2 of the CTP: *Attainment of steady state will be explored by using the trough concentrations of BI 1358894 $C_{pre,9}$, $C_{pre,11}$, $C_{pre,13}$, $C_{pre,14}$ and the concentrations taken directly at the end of the first and the last dosing interval (C_{24}, $C_{24,14}$) for each dose level. […].*

Attainment of steady state of BI 1358894 will be explored as defined in the CTP, Section 7.3.2, by use of a repeated measures linear model on the logarithmic scale. The model will be estimated using an unstructured covariance matrix. In case convergence criteria are not met when using this covariance structure, another structure (Huynh-Feldt, Toeplitz or AR(1)) will be used. The information criterion of Akaike (AIC) will be used to select the best fitting structure. Results will only be presented for the best fitting structure. A compound symmetry structure of the covariance matrix will not be considered, as this structure already postulates a steady state.

Section 7.3.2 of the CTP: *Comparisons which reveal CIs (for the adjusted ratio) not including 100% will be inspected to determine if the differences between time points are resulting from not yet attaining steady-state.*

Analysis of secondary endpoints of Midazolam

Analysis of relative bioavailability of the secondary endpoints AUC_{0-tz} and C_{max} of midazolam in plasma on Day 1 and on Day 14 will be performed as defined in Section 7.3.2 of the CTP. The endpoints will be compared between the second dose of midazolam (Test 1) and third dose of midazolam (Test 2) and the first dose of midazolam (Reference). The relative bioavailability will be analysed separately for each dose group.

The statistical model for the relative bioavailability analysis defined in the CTP is an ANOVA model on the logarithmic scale including "treatment" ("midazolam" and "midazolam + Placebo/BI") as fixed effect and "subject" as random effect. The analysis will be performed separately for Day 1 and Day 14.

CTP Section 7.3.2: *The effect of BI 1358894 on midazolam will be estimated by the ratios of geometric means (with the second and the last doses of midazolam respectively as the test and the first dose of midazolam as the reference) and their two-sided 90% confidence intervals (CIs) for C_{max} and AUC_{0-tz}. CIs will be calculated based on the residual error from ANOVA. These quantities will then be back transformed to the original scale to provide the point estimate and 90% Cis for each secondary endpoint.*

In addition, a sensitivity analysis will be performed for the secondary endpoints $AUC_{0\text{-}tz}$ and C_{max} of midazolam in plasma on Day 1 and on Day 14 including all subjects who were treated with BI 1358894. The model will include "subject" as a random effect, "time point" as fixed effect and the logarithm (base 2) of the dose (10 mg, 25 mg, 50 mg, 100mg und 200 mg) as covariate. The ANCOVA model is described by the following equation:

$Y_{ij} = \mu + \tau_i + s_j + \beta D_j + e_{ij}$, where

Y_{ij} = logarithm of response measured on subject j at time point i,

μ = the overall mean,

s_j = (random) effect associated with the j^{th} subject, j = 1, 2, ..., 40

τ_i = the effect associated with the time point i, i = 1 (Day -1) and i=2 (Day 1 or Day 14)

β = fixed effect regression coefficient for dose effect

D_j = the logarithm (base 2) of the dose level of subject j

e_{ij} = the random error associated with the j^{th} subject at time point i

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".

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.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS except the exposure response ECG analysis which will be based on the ECGPCS.

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 analysis, multiple AE occurrence data on the eCRF will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended)

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 the screening, on-treatment or follow-up phase 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 other significant AEs according to ICH E3 (8) and for the class of AESIs.

Section 5.2.2.1 of the CTP: *The AESI for this trial is hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*

- *an elevation of aspartate transaminase (AST) and/or alanine aminotransferase (ALT)≥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), AEs classified as "other significant" need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

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 (primary endpoint) will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (8)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

The system organ classes and preferred terms within system organ classes will be sorted by descending frequency overall 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 summarised by dose group.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term. The number of subjects included by country and the number of subjects inside (member states) and outside the EU (third countries) will also be summarised by dose group.

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). The assessments will include testing for faecal occult blood and faecal calprotectin.

Analyses will be based on normalised values, which means 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 laboratory values over time and for the difference from baseline (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.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM prior to DBL at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings. 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 (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) and orthostatic tests will be descriptive in nature. Descriptive statistics of each parameter over time and for the difference from baseline (see Section 6.7) will be provided.

Orthostatic change will be defined as the difference between standing and supine blood pressure (calculated as standing minus supine), and will be calculated separately for systolic and diastolic blood pressure. Orthostatic change will be summarized in the same way as vital signs parameter.

Clinically relevant findings in vital signs and orthostatic test data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

12-lead ECG

ECG data will be analysed based on dose groups.

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluation of ECG data except of exposure response analysis will be based on the TS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. Occurrences of notable findings (as defined in Section 5.3.2) will be flagged.

For QTcB and RR, only listings will be provided.

For all subjects with any notable finding in quantitative ECG recordings, 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.

Comments regarding the ECGs will be listed.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

For subjects with notable findings, the individual time courses of QTcF, QT, HR, PR and QRS of these subjects will be presented in figures.

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 treatment group for PR and QRS.

No plots are planned for QT.

7.8.5 Others

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	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
6	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
7	*KM Asset BI-KMED-BDS-HTG-0041:* "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
10	Bond A, Lader M. The use analogue scales in rating subjective feelings. Br J Med Psychol. 1974. 47: 211-218. [R98-0752]
11	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018. 45(3): 383-397. [R18-0143]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**12-AUG-19**		None	This is the final TSAP