TRIAL STATISTICAL ANALYSIS PLAN

c26550915-01

BI Trial No.:	1402-0001
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) and effect of food on the relative bioavailability of BI 1358894 (open-label, randomised, two-way cross-over) Including Protocol Amendment 1 to 9 [c13880029-10]
Investigational Product:	BI 1358894
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	18 MAR 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Dataset
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
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 time point tz
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below Limit of Quantification
BMI	Body mass index
BWC	Bioavailability/Bioequivalence, Within-Subject Design, Time-Controlled
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
C-SSRS	Columbia Suicidal Severity Rating scale
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DB	Dose Proportionality, Between-Subject Design
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
ECG	Electrocardiogram

Term	Definition / description
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FE	Food Effect
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
iPD	Important Protocol Deviation
ISF	Investigator Site File
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non missing observations
O*C	Oracle Clinical
P10	10^{th} percentile
P90	90^{th} percentile
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set
PT	Preferred Term
Q1	1^{st} quartile
Q3	3^{rd} quartile
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SRD	Single rising dose
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

Term	Definition / description
XPKISTAT	Library of SAS® Macros for PK analysis

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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol 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 Oracle Clinical™ (O*C) system.

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

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 as planned in the CTP will be performed and are described in more detail in this TSAP. The following changes compared to the protocol will be made:

According to the Reference Document 3 of the Boehringer Ingelheim (BI) Statistical Position Paper on Statistical Methods for PK (13), the 90% confidence intervals (CI) should be considered for all described PK analyses. Therefore, the 90% CI will be used instead of the 95% CI.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 5.2.1 of the CTP*: Primary endpoint to assess safety and tolerability of BI 1358894 is the number [N (%)] of subjects with drug- related adverse events.*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 5.5.1.1 of the CTP:

- *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 time point t_z)*
- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

It is planned that 64 healthy male subjects will enter the SRD part (8 per dose group, 6 on active and 2 on placebo) and 24 healthy males will enter the FE part (12 per dose group, all on active) of the study.

For details of dosage and formulation see Tables 6.1:1 and 6.1:2 below.

Table 6.1: 1 Labels for treatments for use in the CTR (SRD Part)

Treatment		Short label
P*	Placebo, tablet, qd	Placebo
AA	BI 1358894, 3*1 mg tablet, po, qd	BI 3mg
CA	BI 1358894, 6*1 mg tablet, po, qd	BI 6mg
AB	BI 1358894, 2*5 mg tablet, po, qd	BI 10mg
AC	BI 1358894, 1*25 mg tablet, po, qd	BI 25mg
AD	BI 1358894, 2*25 mg tablet, po, qd	BI 50mg
AE	BI 1358894, 1*100 mg tablet, po, qd	BI 100mg
AF	BI 1358894, 2*100 mg tablet, po, qd	BI 200mg
CD	BI 1358894, 2*100 mg tablet, po, qd, fed	BI 200mg fed

*: The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated.

Table 6.1: 2 Labels for treatments for use in the CTR (FE Part)

Treatment		Short label
W	BI 1358894, 2*25 mg tablet, po, qd, fed	BI 50mg fed
X	BI 1358894, 2*25 mg tablet, po, qd, fasted	BI 50mg fast
Y	BI 1358894, 1*100 mg tablet, po, qd, fed	BI 100mg fed
Z	BI 1358894, 1*100 mg tablet, po, qd, fasted	BI 100mg fast

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00 h on day of informed consent until administration time of study drug)

- **On treatment**
  (SRD part: separately for each treatment, ranging from the time of first administration of BI / Placebo until 0:00h on the day after trial termination date;
  FE part: separately for each treatment, ranging from the time of first administration of BI until administration time of next study drug dose or 0:00h on the day after trial termination date)

Please note that all AEs reported between start of trial drug administration and the last per-protocol contact will be considered on treatment (i.e. no follow-up period is considered in this trial).

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 and Table 6.1: 2 above.

Two types of AE displays will be provided in the report:

A) Section 15.3 (separately for SRD and FE part) and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only but combined for SRD and FE part) of the CTR displays:

In these displays, the on treatment phase will be analysed by dose group (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis. The following totals will be provided in addition:

- a total over all on treatment phases included in this analysis ("**Total on treatment**") (Section 15.3 only)
- SRD part: a total over all BI treated phases ("**BI Total**")

B) Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))

In Section 16.1.13.1.8 AE tables (separately for SRD and FE part), the following totals will be provided in addition:

- a total over all study phases ("**Total**")
- SRD part: a total over all BI treated phases ("**BI Total**")

Tables of vital signs and laboratory values will present results by the above mentioned screening and on treatment phase. Tables of ECG values will present results by the above mentioned on treatment phase

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Consistency check listings (for identification of deviations of 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, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM minutes via an accompanying Excel spreadsheet (3). The following Table 6.2: 1 contains the categories which are considered to be iPDs in this trial. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM/DBLM at the latest.

Protocol deviations will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category/Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Incorrect intake of trial medication
	C5	Improper washout between treatments
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
	D2	Improper washout of concomitant medication
E		**Missing data**
	E1	Certain deviations from procedures used to measure secondary data
F		**Incorrect timing**[1]
	F1	Certain deviations from time schedule used to measure secondary data
G		**Other trial specific important deviations**
	G1	Incorrect intake of meal before administration of treatment
	G2	Protocol deviations affecting safety and rights

[1] Time deviations will only be flagged as iPD, when leading to exclusion of the entire subject from an analysis set

6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This is the full analysis set population in the sense of ICH-E9 (1). It is used for safety analysis.

Section 7.3.2 of the CTP: *Plasma and urine concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol* deviation *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.*

Relevant protocol deviations *may be*

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*
- *The subject has a protocol deviation relevant to the evaluation of relative bioavailability. (Whether a protocol deviation is relevant, will be decided no later than the Report Planning Meeting.)*

Plasma and urine concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *missing samples/concentration data at important phases of PK disposition curve.*

- PK parameter analysis set (PKS):
  The PK parameter analysis set (PKS) includes all subjects from the TS receiving BI 1358894 who provide at least one secondary PK parameter (AUC or C_{max}) that was not excluded according to the description above.
  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 (FE part).
  It is used for assessment of dose proportionality (SRD part/FE part) and for assessment of the food effect (FE part).

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Table 6.3: 1 Analysis sets for endpoints/data description

	Analysis set	
Endpoint/data description	TS	PKS
Primary endpoint / Safety assessments (incl. ECG)	X	
Secondary and further PK endpoints		X
Demographic/baseline data	X	
Important Protocol Deviations	X	
Disposition	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

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

For placebo subjects the missing plasma concentration values will be replaced by 0 for the exposure response analysis. For subjects on active drug, missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ (post treatment values) or by 0 (pre dose values).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For the analysis of vital signs and VAS the baseline value is defined as the last measurement before trial drug administration (SRD part) / before trial drug administration in each treatment period (FE part).

For laboratory analysis the baseline is defined as the last measurement before trial drug administration in the first period.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation from the scheduled time for vital signs, orthostatic testing and ECG will be ± 10 min and laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter.

[…] *The acceptable deviation from the scheduled time for standardized neurological tests (conducted in Dose Group 200 mg fed) is ± 45 min on day 1, and ± 90 min from day 2 onwards.*

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

Section 5.2.4 of the CTP: *With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECGs at a single assessment time will be evaluated.*

7. PLANNED ANALYSIS

The SRD and FE part will be evaluated separately.
The placebo group in the safety evaluation of the SRD part will consist of all placebo treated subjects, regardless of the dose group in which they were treated.

Safety analysis (refer to Section 7.8) will be performed by and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by the department of Translational Medicine and Clinical Pharmacology at BI and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of Clinical Trials and Project Summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations.

In the SRD part, the individual values of all subjects will be listed, sorted by treatment group, subject number, and visit.
In the FE part, the individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate).
The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

For analyte concentrations, 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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile

Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of 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 (%) for each treatment group/sequence. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) 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 will include parameters if they are not flagged for exclusion; that is APEXC is equal to “Included”.

Exclusion of PK 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” [001-MCS-36-472_RD-01] (5) and “Description of Analytical Transfer Files and PK/PD Data Files” [001-MCS-36-472_RD-03] (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

SRD part: The data will be summarised by treatment group and in total.
FE part: The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1358894.

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

Assessment of dose proportionality

Dose proportionality of the PK endpoints $AUC_{0-\infty}$, C_{max}, AUC_{0-tz} in plasma of BI 1358894 will be explored using the power model that describes the functional relationship between dose and PK endpoints. The basic model consists of a regression model applied to log-

transformed data (log-transformation refers to using the natural logarithm). The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

The model is described by the following equation:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …,n, j = 1, 2, …, m,
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

Section 7.3.2 of the CTP: *This equation can be fit as a linear regression model.*

Based on the estimate for slope parameter (β), a 2-sided 90% *CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.*

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Dose proportionality will be assessed separately for film-coated tablet after fasted (treatment groups of SRD part only) *and fed conditions* (combination of treatment groups of SRD and FE part).

This analysis will be accomplished by using the XPKISTAT macro (design DB), based on the PKS.

A regression plot will be performed, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality (β=1).

<u>Investigation of relative bioavailability (food effect evaluation – FE part)</u>

Section 7.3.2 of the CTP: *Relative bioavailability is primarily to be determined on the basis of the parameters AUC* ($AUC_{0-\infty}$, AUC_{0-tz}) *and* C_{max} *[...] for the dose levels […] 50mg, 100mg. […] Those parameters will be ln-transformed (natural logarithm) prior to fitting the model.*

The statistical model used for the analysis of $AUC_{0-\infty}$, AUC_{0-tz} *and* C_{max} *will be an ANOVA (analysis of variance) model on the logarithmic scale. […] This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences',*

'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. The model is described by the following equation

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ *the overall mean,*

ζ_i *the* i^{th} *sequence effect, i = 1, 2*

s_{im} *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m =1, 2, ...,* p_i; p_i=number of subjects in i^{th} sequence

π_j *the* j^{th} *period effect, j = 1, 2*

τ_k *the* k^{th} *treatment effect, k = 1, 2*

e_{ijkm} *the random error associated with the* m^{th} *subject in sequence i who received treatment k in period j.*

The difference between the expected means for test treatments (tablets under fed conditions T1) and reference treatment (tablets under fasted conditions R) log(T1)-log(R), will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

The analysis will be accomplished by using the XPKISTAT macro, based on PKS (design BWC).

In addition, a sensitivity analysis will be performed by fitting the model described above, but using all effects as fixed. This analysis will be done using PROC GLM.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, separately for SRD and FE part.

If not stated otherwise, the safety results will be sorted by treatment group (SRD part) or by actual treatment (FE part).

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

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 and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [001-MCG-156] (9).

The standard AE analyses 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 CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence)

For further details on summarization of AE data, please refer to [001-MCG-156] (9).

Section 5.2.2.1 of the CTP: *The following are considered as AESI in this trial:*

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

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

The analysis of adverse events will be based on the concept of treatment emergent adverse events.

Section 5.2.2.2 of the CTP: *The REP for BI 1358894, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment […].*

According to ICH E3 (10), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the RPM at the latest.

An overall summary of AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with other significant AEs according to ICH E3 (10), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.
The SOC and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (11).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM/DBLM at the latest).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate), as well as respiratory rate (RR) and orthostatic tests (SRD part only).

7.8.4 ECG

Continuous safety ECG monitoring (by investigator) – (SRD part only)

Clinically relevant abnormal findings will be reported as adverse events.
No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG (SRD part + FE part)

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

The descriptive evaluation of ECG data will be based on the TS, separately for the SRD part and the FE part.

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.

7.8.5 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.
No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Neurological examination

Neurological examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.
No separate listing or analysis of neurological examination findings will be prepared.

7.8.5.3 Visual Analogue Scale (VAS) - Bond & Lader and Bowdle

The VAS will be used at screening and at end of trial examination, as well as on predose at visit 3 (FE part only) and planned times -1:00 (dose groups 3mg to 50mg), -0:30 (dose groups 100mg, 200mg and 200mg fed), 2:00, 4:00, 8:00, 24:00, 34:00 and 48:00 (SRD part only).
The last VAS assessments before drug administration will be considered as baseline.
The results of both VAS will be listed and descriptive statistics over time including change from baseline will be performed.

Visual analogue scale – Bond and Lader

For Bond and Lader VAS, three factors will be calculated using the loadings (regression weights) from the factor analysis in (12), which are shown in Table 7.8.5.3:1 below. The individual scores on each scale will be multiplied by the scale's factor loading and totaled within the three factors. The summed scores will then be divided by the sum of loadings for each factor.

Alertness $= F_1 = 1/ \Sigma w_{1i} * \Sigma(w_{1i}*VAS_i)$

Contentment $= F_2 = 1/ \Sigma w_{2i} * \Sigma(w_{2i}*VAS_i)$

Calmness $= F_3 = 1/ \Sigma w_{3i} * \Sigma(w_{3i}*VAS_i)$

where

VAS_i measured scale i; where i = 1, ... , 16

w_{fi} factor loading for factor f and scale i; where f = 1, 2, 3 and i = 1, ... , 16,

Since some scales for these loadings are reversed compared to the scales in the questionnaire the corresponding individual scores have to be reversed (100– measured score value (mm)) before multiplication. Descriptive statistics of the three factors over time and for the difference from baseline will be provided. Furthermore, for the SRD part, the change from

baseline of the three factors will be presented graphically over time (arithmetic means + standard deviation).

Table 7.8.5.3: 1 Factor loadings for Bond and Lader VAS

Measured score value		**Factor loadings to**		
		Alertness	**Contentment**	**Calmness**
Alert / Drowsy	1. Alert	0.827	0.088	0.008
Calm / Excited	2. Calm	0.049	0.029	0.845
Strong / Feeble	3. Strong	0.618	0.142	0.328
Muzzy / Clear-headed *	4. Clear-headed	0.755	0.149	0.080
Well-coordinated / Clumsy	5. Well-coordinated	0.642	0.122	0.424
Lethargic / Energetic *	6. Energetic	0.776	0.174	-0.019
Contented / Discontented	7. Contented	0.233	0.677	0.278
Troubled / Tranquil *	8. Tranquil	0.133	0.697	0.429
Mentally slow / Quick-witted *	9. Quick-witted	0.635	0.340	-0.138
Tense / Relaxed *	10. Relaxed	0.031	0.445	0.677
Attentive / Dreamy	11. Attentive	0.792	0.179	0.098
Incompetent / Proficient *	12. Proficient	0.593	0.328	0.027
Happy / Sad	13. Happy	0.270	0.823	0.051
Antagonistic / Amicable *	14. Amicable	0.159	0.738	0.172
Interested / Bored	15. Interested	0.614	0.412	-0.006
Withdrawn / Gregarious *	16. Gregarious	0.343	0.594	-0.217

* Measured score value will be reversed

Visual analogue scale – Bowdle

Descriptive statistics of the 13 individual Bowdle scales at screening and post examination and for the difference from baseline (=screening) will be provided. Other assessments will be listed only.

Furthermore, for the SRD part, the change from baseline of the individual scales will be presented graphically over time (arithmetic means + standard deviation).

7.8.5.4 Suicidality assessment - Columbia Suicidal Severity Rating scale (C-SSRS)

The C-SSRS will be done at

- screening and PTM 144:00 and end of trial examination in dose group 200mg fed
- screening and end of trial examination in dose groups 3mg to 200mg
- screening, predose at visit 3 and end of trial examination in FE part.

The results will be listed only.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
4.	*001-MCG-156_RD-01:* "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.
5.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6.	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
7.	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
8.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
9.	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", Version 8; IDEA for CON.
10.	*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
11.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
12.	Bond A, Lader M. "The use of analogue scales in rating subjective feelings." Br J Med Psychol 1974;47:211-218. [R98-0752]
13.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn 2017 [R18-0143]
14.	BI Statistical Position Paper - Statistical Methods for PK - Reference Document 3: Regulatory recommendations for BA/BE trials and implementation instructions in clinical trial documents, version 1.0 (2017).

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	18-MAR-19		None	This is the final TSAP without any modification