TRIAL STATISTICAL ANALYSIS PLAN

c26500341-01

BI Trial No.:	1400-0001
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 473494 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) Including Protocol Amendment 1 [c11760893-02]
Investigational Product:	BI 473494
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	29 JAN 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug Antibody
ADS	Analysis Dataset
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analyis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under The Concentration-Time Curve
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
CARE	Clinical Analysis and Reporting Environment
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
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
EudraCT	European Union Drug Regulating Authorities Clinical Trials

Term	Definition / description
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart Rate
ICH	International Conference On Harmonisation
ISF	Investigators Site File
iPD	Important Protocol Deviation
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing observations
O*C	Oracle Clinical
P10	10th percentile
P90	90th percentile
PD	Pharmacodynamics
PDS	Pharmacodynamic Analysis Set
PK	Pharmacokinetics
PKS	PK Parameter Analysis Set
PR	Pulse Rate
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
QRS	Complex of three closely related waves on the ECG (Q, R and S wave)
QT	Time between start of the Q-wave and the end of the T-wave on the ECG
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SAS®	Statistical Analysis System

Term	Definition / description
SD	Standard Deviation
SOC	System Organ Class
TMCP	Translational Medicine and Clinical Pharmacology
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary
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 ClinicalTM (O*C) system.

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

The statistical analyses will be performed within the validated Clinical Analysis and Reporting 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 Clinical trial Report (CTR) appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the TSAP are outlined in the CTP. The following changes compared to the protocol will be made:

Dose escalation was stopped after the second dose group (75 µg BI 473494). Therefore, all analyses will be performed for the first and second dose group only.

- As there are only two dose groups available, no dose proportionality analysis will be done. Secondary endpoints (AUC_{0-tz} and C_{max} of BI 473494) will be analysed descriptively only.

- As there are only two dose groups available and only little exposure levels expected, no ECG exposure-repsonse analyses will be done.

As an abbreviated CTR will be written, the change from baseline in body weight will be analysed descriptively only.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 5.2.1 of the CTP: *Primary endpoint to assess safety and tolerability of BI 473494 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: *The following pharmacokinetic parameters will be determined for BI 473494 if feasible:*

- *$AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

It was planned that in total 88 healthy male subjects participate in the trial, according to 11 sequential groups comprising 8 subjects per group (6 on active drug and 2 on placebo).

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

Table 6.1: 1 Labels for treatments for use in the CTR

Treatment		Short label
P*	Placebo solution, sc, qd	Placebo
A	BI 473494, solution for injection, 35 ug	BI 35 ug
B	BI 473494, solution for injection, 75 ug	BI 75 ug
C	BI 473494, solution for injection, 150 ug	BI 150 ug
D	BI 473494, solution for injection, 300 ug	BI 300 ug
E	BI 473494, solution for injection, 550 ug	BI 550 ug
F	BI 473494, solution for injection, 1.0 mg	BI 1.0 mg
G	BI 473494, solution for injection, 1.6 mg	BI 1.6 mg
H	BI 473494, solution for injection, 2.6 mg	BI 2.6 mg
I	BI 473494, solution for injection, 4.0 mg	BI 4.0 mg
J	BI 473494, solution for injection, 6.0 mg	BI 6.0 mg
K	BI 473494, solution for injection, 8.5 mg	BI 8.5 mg

*: 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.

Dose escalation was stopped after the second dose group (Treatment B / 75µg BI 473494). Therefore, all analyses will be performed for the first and second dose group only (treatments Placebo, 35µg BI 473494 and 75µg BI 473494).

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 (BI 473494 or Placebo))
- **On treatment**
  - **BI 473494/Placebo treatment** (separately for each treatment, ranging from the time of administration of BI 473494 / Placebo until 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 Placebo, 35µg BI 473494 and 75µg BI 473494.

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

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis.
The following total will be provided in addition (Section 15.3 only):

- a total over all BI 473494 treated phases ("**BI Total**")
- a total over all on treatment phases included in this analysis ("**Total on treatment**") (Section 15.3 only)

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, the following totals will be provided in addition:

- a total over all BI 473494 treated phases ("**BI Total**")
- a total over all study phases ("**Total**")

Tables of vital signs and laboratory 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 and database lock meeting (RPM/DBLM). 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/DBLM 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.

The iPDs 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
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial 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	Appropriate fasting condition not met prior to study drug administration
	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 demographics, baseline characteristics, and safety analyses.
  The ECG analyses are performed on the TS.

Section 7.3.2 of the CTP: *Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol* deviation *relevant for the evaluation. Whether a protocol* deviation *is important will be decided no later than in the Report Planning Meeting.*

Reasons for exclusion of single pharmacokinetic parameters may be:

- *The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be determined for the test product excluding the subjects experiencing emesis.*
- *The subject experiences emesis at any time during the labelled dosing interval.*
- *Time deviations*
- *Use of restricted medications*

The subject set for the evaluation of PK endpoints […] will include all treated subjects that provide at least one observation for at least one secondary endpoint without important protocol deviations *with respect to the statistical evaluation of PK endpoints.*

- PK parameter analysis set (PKS):

  The PK parameter analysis set (PKS) includes all subjects from the TS receiving BI 473494 who provide at least one secondary PK parameter that was not excluded according to the description above.

Section 7.3.2 of the CTP: *It will be decided in the Report Planning Meeting which subjects are to be included in the PKS.*

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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

Table 6.3: 1 Analysis sets for endpoints/data description

Endpoint/data description	Analysis set		
	TS	PKS	PDS
Primary and further safety endpoints (incl. ECG)	X		
Secondary 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).

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on-treatment QTc/QT intervals into “no new onset” / “new onset” categories, a missing value is obtained only in case that

(i) all on-treatment values are missing and
(ii) the baseline value is less than or equal to 500 msec, or missing.

If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as ‘no new onset’. If baseline is missing and the maximum on treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a ‘new onset’ in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as ‘no new onset’. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For vital signs or laboratory measurements, baseline is defined as the last measurement before drug administration (BI or Placebo).

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 of Visits 2 or 3 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK

Starting from 96 h post administration a deviation from the scheduled time for PK sampling ECG and blood sampling for ADA of ± 70 min is acceptable. However, ECGs should always be time-matched with blood PK sampling.

The acceptable deviation from the scheduled time for vital signs and laboratory tests will be ± 30 min for the first 72 h after trial drug administration. Starting from 96 h post

administration a deviation from the scheduled time for vital signs and laboratory tests of ± 70 min is acceptable.

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

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

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

Visit	**Day**	**Planned time [hh:mm] (relative to drug administration)**	**Study phase**	**Central evaluation**
1	-21 to -2		Screening	NA
2	-1	-24:00		NA
3	1	-1:00		first of three replicate ECG
		-0:45		first of three replicate ECG
		-00:30		first of three replicate ECG
		06:00	On treatment	first of three replicate ECG
		09:00		first of three replicate ECG
		12:00		first of three replicate ECG
	2	24:00		first of three replicate ECG
		28:00		first of three replicate ECG
		34:00		first of three replicate ECG
	3	48:00		first of three replicate ECG
		60:00		first of three replicate ECG
	4	72:00		first of three replicate ECG
	5	96:00		first of three replicate ECG
	6	120:00		first of three replicate ECG
	8	168:00		first of three replicate ECG
	11	240:00		first of three replicate ECG
	15	336:00		first of three replicate ECG
	22	504:00		first of three replicate ECG
	29	672:00		first of three replicate ECG
4	33 to 40		End of trial examination	NA

Triple ECGs (3 single ECGs of 10 sec duration each, recorded within 180 sec) will be recorded at all time points, except for Screening, planned time -24:00h and End-of-trial visit.

At these time-points single ECGs will be recorded. Three pre-dose triplicate ECGs within 60 minutes are to be recorded as baseline.

Section 6.1 of the CTP: *Only the first of the three replicate ECGs at a single time point or at baseline will be evaluated.*

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.

7. PLANNED ANALYSIS

The placebo group in the safety evaluation 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.

Descriptive data analysis of PK parameters and concentrations will be performed by the department Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 and 15.7 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.

The individual values of all subjects will be listed, sorted by treatment group, subject number, and visit.
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. 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 analysis data set (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 will include parameters if they are not flagged for exclusion, that is APEXCO 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 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (11).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The data will be summarized by treatment group 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 latest version of 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 of investigational and non-investigational medicinal products and urinary excretion of BI 473494 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 ENDPOINTS

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 473494.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

Descriptive statistics of plasma concentrations and PK endpoints will be done by the department TMCP at BI and will be presented in Section 15.6 of the CTR.

The analysis of PK parameters as well as the tables and graphs for the pharmacokinetic non-compartmental analyses will follow specific definitions of this TSAP or, otherwise, the BI standard procedure "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" [001-MCS-36-472] (7).

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.

If not stated otherwise, the safety results will be sorted by treatment group. 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] (8).

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 (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] (8,4).

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

- *Hepatic injury: A hepatic injury is defined by the following alterations of hepatic laboratory parameters:*
    - *an elevation of AST* (aspartate aminotransferase) *and/or ALT* (alanine aminotransferase) *≥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 473494, 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 […].*

For more details see the TSAP ADS plan.

According to ICH E3 (9), 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 summarised 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 (9), 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] (10).

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 body weight).

7.8.4 ECG

12-lead ECG

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

All evaluations of ECG data 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. 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 treatment.

7.8.5 Others

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.

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*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8.	*001-MCG-156*: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version; IDEA for CON.
9.	*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.
10.	*001-MCG-157*: “Handling, Display and Analysis of Laboratory Data”, current version; IDEA for CON.
11.	*001-MCS-36-472_RD-03*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON.
12.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 2010 [R10-2920]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**29-JAN-19**		None	This is the final TSAP without any modification