TRIAL STATISTICAL ANALYSIS PLAN

c25347677-01

BI Trial No.:	1305-0017
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled, parallel group design) Including Protocol Amendment 1 [c19450453-02]
Investigational Product:	BI 1015550
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	09 AUG 2019 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
website: glossary

Term	Definition / description
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
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
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
FU	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
P10	10th percentile
P90	90th percentile
PK	Pharmacokinetics
PKS	PK parameter analysis set
Q1	1st quartile
Q3	3rd quartile
RAGe	Report Appendix Generator system

Term	Definition / description
REP	Residual effect period
SD	Standard deviation
SOC	System organ class
TEAE(s)	Treatment emergent adverse event(s)
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated set
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

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

In the protocol, it was stated that events after the REP but prior to end of trial examination will be summarised as 'post-treatment', those after the end of trial examination will be assigned to 'post-study'. However, in contrast to the protocol, events which occurred after the residual effect period (REP) will be considered as follow-up events and there will be no assignment to the time interval 'post-study' in the planned analysis of this study.

Dose escalation was stopped after the second dose group (24mg BI 1015550). Therefore, all analyses will be performed for the first and second dose group only.

- Secondary endpoints ($AUC_{0-\infty}$ and C_{max} of BI 1015550) will be analysed descriptively only.
- As there are only two dose groups available, no ECG exposure-response analyses will be done.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 5.2.1 of the CTP: *Primary endpoint to assess safety and tolerability of BI 1015550 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

The following secondary endpoints will be determined for BI 1015550

Section 5.5.1.2 of the CTP:

- *$AUC_{0-\infty}$ (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)*

Safety:

Section 5.2.1 of the CTP: *Further criteria of interest:*

- *TEAEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests, including fecal occult blood and fecal calprotectin testing and urinalysis*
- *12-lead ECG*
- *Abnormal findings in the Continuous ECG monitoring if rated as AE*
- *Vital signs (blood pressure, pulse rate, respiratory rate and body temperature)*

For detailed information (formula) please refer to Section 7.8.

Details on ECG measurements and endpoints:

12-lead ECG endpoints

For the definition of baseline and a summary of time points scheduled for ECG recording and central evaluation please refer to Section 6.7.

Quantitative ECG endpoints

The following quantitative ECG endpoints will be determined for the ECG variables QTcF, heart rate (HR), QT, PR, QRS, RR and QTcB derived as described in additional Section 9.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints:

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present any time at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment.
  For assignment of a particular subject to one of the above categories, all time points on treatment (refer to Table 6.7: 1) will be considered.
- Maximum change from baseline in QT interval ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be considered as 'notable findings':

- New onset (not present any time at baseline) of uncorrected QT interval > 500 msec at any time on treatment
- New onset of QTcF interval > 500 msec at any time on treatment
- Change from baseline of QTcF interval > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on treatment value of HR is < 50 beats/min, at any time on treatment
- Percent change from baseline of PR ≥ 25%, when corresponding on treatment value of PR interval is > 200 msec, at any time on treatment
- Percent change from baseline of QRS complex ≥ 10%, when corresponding on treatment value of QRS complex is > 110 msec, at any time on treatment

5.4 OTHER VARIABLES

Section 5.2.5.2 of the CTP: *At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body temperature and respiratory rate), 12-lead ECG, laboratory tests including fecal occult blood and fecal calprotectin testings and a physical examination.*

Age [years] will be determined as the difference between year of informed consent and year of birth.

BMI will be calculated as weight [kg] / (0.01 * height [cm])^2.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatment sequences and selection of doses, please see CTP, Sections 3 and 4.

Section 3.1 of the CTP: *This single-rising dose trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups.*

It was planned that in total 24 healthy Japanese male subjects participate in this study, according to 3 sequential groups comprising 8 subjects per group (6 on active and 2 on placebo).

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

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		**Short label**
P*	Placebo	Placebo
A	BI 1015550, 2*6 mg tablet, qd	BI 12mg
B	BI 1015550, 4*6 mg tablet, qd	BI 24mg
C**	BI 1015550, 6*6 mg tablet, qd	BI 36mg

'qd' means here a single drug administration, not a regular drug administration per day.

*: 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
**: This dose group was cancelled.

Dose escalation was stopped after the second dose group and the trial was closed per protocol (CTP Section 3.3.4.2). Therefore, all analyses will be performed for the first two dose groups only.

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 first administration time of study drug (BI 1015550 or Placebo))
- **On treatment**
  BI 1015550/Placebo treatment (separately for each treatment, including REP, i.e. ranging from the time of administration of BI 1015550 / Placebo until 168 hours thereafter)

- **Follow-up** (separately for each treatment, ranging from end of on treatment phase until 0:00h (midnight) on the day after trial termination date) – labelled with FU Plc, FU 12mg and FU 24mg

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) 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 and follow-up periods will not be included in this analysis.
The following total will be provided in addition:

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

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

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up (“FU Plc”, “FU 12mg” and “FU 24mg”)

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

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

Tables of vital signs, ECG 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 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 combined report planning 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 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 / not done
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Medication code broken inappropriately
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	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).
  The treated set will be used for demographics, baseline characteristics, and safety analyses, as well as for the ECG analyses

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 violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) 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 violations 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.*

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 1015550 who provide at least one secondary PK parameter ($AUC_{0-\infty}$ or C_{max}) that was not excluded according to the description above.
  It is used for the descriptive analyses of PK parameters.

The following Table 6.3: 1 contains the information which subject is used for which endpoint/data description:

Table 6.3: 1 Subject sets analysed

	Analysis set	
Endpoint/data description	TS	PKS
Primary and further safety endpoints (incl. ECG)	X	
Demographic/baseline data	X	
Important protocol deviations	X	
Disposition	X	
Secondary PK endpoints		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 exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards.

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (4).

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean per 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. In case of a missing qualitative ECG finding at baseline, a finding observed on treatment will be categorized as 'new onset'.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of BI 1015550 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* 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 3 h-period prior to the trial drug administration (including blank values for PK

The acceptable deviation on profile days from the scheduled time for vital signs and ECG will be -15 min and for laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter.

Fecal occult blood and calprotectin testing will be done as indicated and described in the Flow Chart.

The tolerance for drug administration will be ± 1 min on Days 1.

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	-28 to -1		Screening	NA
2	1	-03:00	Baseline	First (of three) triplicate ECG
		00:30	On-treatment	first of three replicate ECG
		01:00		first of three replicate ECG
		01:30		first of three replicate ECG
		02:00		first of three replicate ECG
		04:00		first of three replicate ECG
		08:00		first of three replicate ECG
		10:00		first of three replicate ECG
	2	24:00		first of three replicate ECG
	3	48:00		first of three replicate ECG
	4	72:00		first of three replicate ECG
	5	96:00		NA
	6	120:00		NA
3	8 to 9		End of trial examination	NA

At Visits 1 and 3, single ECGs will be recorded.
At Visit 2 on Days 1 to 4, triple ECGs will be recorded (three single ECGs within 180 sec), except for the pre-dose measurements, where three triplicates are recorded.
At Visit 2, on Days 5 and 6, single ECGs will be recorded.

Section 5.2.4.1 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 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 endpoints and concentrations will be performed by Clinical PKPD and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the BI standards with the exception of those generated for PK-calculations (7).

The individual values of all subjects will be listed, sorted by treatment group, subject number and visit.
The listings except PK/PD evaluations performed by Clinical PKPD 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 sequence/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 ADS ADPP (PK parameters) contains column variables 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 and 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 λz) 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” (4) and 001-MCS-36-472_RD-03

"Description of Analytical Transfer Files and PK/PD Data Files" (7).

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 summarised 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 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/PD 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 ENDPOINTS

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1015550.

7.4.1 Primary analysis of the primary endpoints

Analysis of safety and tolerability is described in TSAP Section 7.8.

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

This section is not applicable as no further analysis of the primary endpoints is planned.

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 CTP.

7.5.2 Secondary endpoints

Descriptive statistics of plasma concentrations and PK parameters will be done by Clinical PKPD 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] (5).

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.

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 case report form (CRF) will be collapsed into one 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).

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

- *Hepatic injury:*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *an elevation of AST 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*

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 1015550, when measurable drug levels or PD effects are still likely to be present, is defined as 7 days after the last administration of BI 1015550. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment […].Events which occurred after the REP will be considered as follow-up-events.*

For more detail see the TSAP ADS plan.

According to ICH E3 (6), AEs classified as 'other significant' need 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 investigator or Clinical Trial Leader.

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 (6), 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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards.

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 significantly abnormal or not (at the RPM/DBLM at the latest).

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).

The mean normalised values and SD over time for all laboratory parameters, except for parameters that are measured at a single time point will be displayed graphically. The time span is from baseline to post examination.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate and respiratory rate).

For vital signs, 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).

7.8.4 ECG

12-lead ECG

Abnormal findings, irrespective of whether they originate from central or local evaluation, 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.

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1 using all time points. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in this plot.

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, IDEA for CON.
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; IDEA for GEN.
4.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
5.	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6.	*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.
7.	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
8.	
9.	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	**09-AUG-2019**		None	This is the final TSAP without any modification