TRIAL STATISTICAL ANALYSIS PLAN

c23386906-02

BI Trial No.:	1371-0001
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 894416 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design) Including Protocol Amendment 9 [c12098812-09]
Investigational Product(s):	BI 894416
Responsible trial statistician(s):	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	17 OCT 2018 REVISED
Version:	2.0 “Revised”

1. TABLE OF CONTENTS

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3. INTRODUCTION

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

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

Study data will be stored in a trial database within the Oracle Clinical™ system.

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

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, Certara USA Inc., Princeton, NJ, USA) and SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

Additionally a sensitivity analysis will be performed for relative bioavailability with subject as fixed effect.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number of subjects with drug-related AEs in the SRD (single rising dose) part of the trial, as defined in Section 5.2.1 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary endpoints of this trial are $AUC_{0-\infty}$ and C_{max} of BI 894416 in plasma for the SRD part and AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} of BI 894416 in plasma for rel. BA (relative bioavailability) part, as defined in Section 5.5.1.1 of the CTP.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Subjects were planned to be treated with

SRD part:

- either a single dose of 3, 10, 20, 30, 40, 54 or 70 mg of BI 894416 (test treatments)
  or
- a single dose of placebo (reference treatment)

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

Rel BA part:

- a single dose of 10 mg BI 894416 as tablet formulation (treatment X)
  and
- a single dose of 10 mg BI 894416 as oral solution formulation (treatment Y)
  and
- a single dose of 40 mg BI 894416 as tablet formulation (treatment Z)

In treatment periods 1 and 2, the sequence of administration of treatments X and Y is assigned in a randomised manner. In the last (third) treatment period, subjects will receive a single dose of 40 mg BI 894416 as tablet formulation. This treatment period follows in a fixed sequence after the first two treatment periods for all subjects.

Analysis phases for statistical analysis of AEs, safety laboratory data, vital signs and ECG are defined for each subject as described in Table 6.1: 1.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, vital signs and ECG

SRD part:

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Pbo,** **3 mg BI**, **10 mg BI**, **20 mg BI**, **30 mg BI,** **40 mg BI**, **54 mg BI** or **70 mg BI**, respectively	Date/time of administration of study drug	12:00 a.m. on day after subject's trial termination date

rel. BA part:

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**10 mg BI tablet** **10 mg BI PfOS** **40 mg BI tablet**	Date/time of administration of study drug	Drug administration of study drug in next period or 12:00 a.m. on day after subject's trial termination date

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

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

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

rel. BA part:
- "**Total on-trt**", defined as the total over all on-treatment phases

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

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

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

- "**Study Total**", defined as the total over all study phases (screening +on-treatment) for the SRD and rel. BA part combined (only for disclosure outputs)

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of violations 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 RPM/DBLM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an IPD. For definition of IPDs, and for the process of identification of these, refer to the BI reference document " Identify and Manage Important Protocol Deviations (iPD)", " (2).

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
	C5	Improper washout between treatments
	C6	Incorrect dose of trial medication
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**
		None[1]
G		**Other trial specific important violations**
	G1	Certain violations of procedures used to measure secondary PK data

Deviations C1, C2 and G1 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not IPDs
Source: BI reference document " 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 table above contains the categories which are considered to be IPDs in this trial. IPD C5 is only applicable

for the SRD part. If the data show other IPDs, this table will be supplemented accordingly by the time of the RPM/DBLM.

IPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

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

The following subject sets will be defined for statistical analysis:

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

- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the TS who provide at least one PK parameter that was not excluded because of IPDs relevant to the statistical evaluation of PK endpoints as defined in Section 7.3 of the CTP.

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

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Disposition	X	
Exposure	X	
IPDs	X	
Demographic/baseline endpoints	X	
Primary endpoint	X	
Other safety parameters	X	
Secondary PK endpoints		X
Further 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

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

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

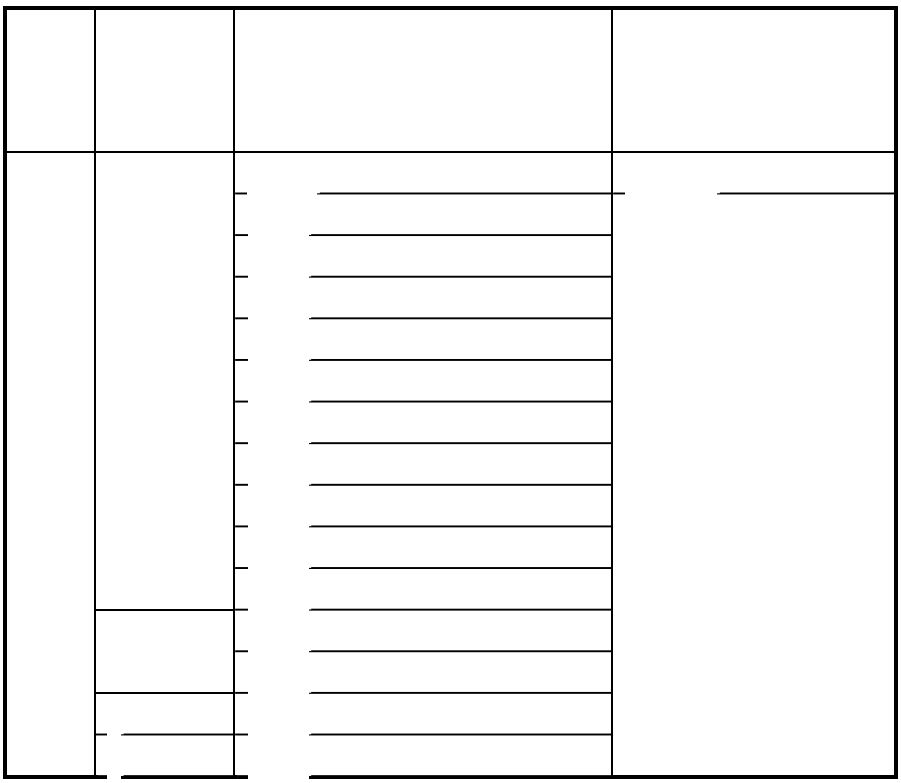
CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (4).

Missing data and outliers of PK data are handled according to BI standards (5). **CTP**: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).*

CTP: *For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS



In all other analyses the last non-missing value determined prior to the first dosing of trial medication will be defined as baseline.

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

7. PLANNED ANALYSIS

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

In general, the SRD and rel. BA part will be analysed separately, unless stated otherwise.

The individual values of all subjects will be listed. Listings will generally be sorted by dose group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

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

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

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

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

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

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

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

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

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

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

rel. BA part:

Analysis of relative BA of secondary endpoints AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} of BI 894416 in plasma will be performed as defined in Sections 7.1.1 and 7.3.2 of the CTP.

The statistical model for the main analysis defined in the CTP is an ANOVA model on the logarithmic scale including "sequence", "period" and "treatment" as fixed effects and "subject within sequence" as random effect.

A sensitivity analysis will be performed with the same model as described above but with subject as fixed effect.

Exclusion of PK parameters

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

Exclusion of plasma concentrations

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

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5) and "Description of Analytical Transfer Files and PK/PD Data Files" (7).

7.7 EXTENT OF EXPOSURE

Only listings are planned for this section of the CTR.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

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

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

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

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)

- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended)

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (8) and "Handling of missing and incomplete AE dates" (4).

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

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 and for the class of AESIs.

CTP: *The following are considered as AESIs 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*
- *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

According to ICH E3 (9), AEs classified as "other significant" need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related (primary endpoint) will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (9)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

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

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

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

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (10).

Analyses will be based on original values.

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

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

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

7.8.3 Vital signs

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

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

7.8.4 ECG

12-lead ECG

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

7.8.5 Others

Clinically relevant physical and 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 or neurological examination findings will be prepared.

8. REFERENCES

1 *CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trialss, current version

2 *001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON

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-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*: "Display and Analysis of Laboratory Data", current version; IDEA for CON

11 Garnett C, Needleman K, Liu J, Brundage R, Wang Y. Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther 2016;100 (2):170-178 [R17-0553]

10. HISTORY TABLE

Table 10: 1 History table

This is a revised TSAP including the following modifications to the final TSAP

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**04-JUL-2018**		None	This is the final TSAP without any modification
Revised	**17-Oct-2018**		Sections 5,6 and 7	Rel. BA part included and description of analysis of rel. BA part added. IPVs are now iPDs according to new SOP