TRIAL STATISTICAL ANALYSIS PLAN

c26699071-01

BI Trial No.:	1346-0015
Title:	Investigation of pharmacokinetics and absolute oral bioavailability of BI 425809 administered as an oral dose with an intravenous microtracer dose of [C-14]-BI 425809 in healthy male volunteers Including Protocol Amendment 1 [c21363182-03]
Investigational Product:	BI 425809
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	01 APR 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity
BLQ	Below the lower limit of quantification
BMI	Body mass index
BI	Boehringer Ingelheim
BP	Blood pressure
CARE	Clinical data analysis and reporting environment
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
eCRF	Electronic case report form
Fp.o.	Absolute bioavailability after oral administration
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviation
IV	Intravenous
LLT	Lower level term
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PO	Per os
PR	Pulse rate
Q1	Lower quartile

Term	Definition / description
Q3	Upper quartile
RAGe	Report appendix generator
RPM	Report planning meeting
SD	Standard deviation
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range

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

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

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Regarding the safety analysis, only one on-treatment phase will be defined, combining BI tablet and BI tablet/infusion. No separate analyses will be done for the two phases as described in the CTP.

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is $AUC_{0-\infty}$ of BI 425809 and [^{14}C]-BI 425809 in plasma after oral and after intravenous administration, respectively.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoint is C_{max} in plasma for BI 425809 after oral administration.

5.3 FURTHER ENDPOINTS

5.3.2 Safety parameters

Further safety parameters will be used as defined in Section 2.2.2.2 of the CTP:

CTP:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

All subjects were planned to be treated with

- a non-radiolabelled film-coated tablet on Day 1 containing 25 mg of BI 425809 (test treatment)
  and
- a single microtracer infusion of 30 µg BI 425809 (C-14) on Day 1 (reference treatment)

For statistical analysis of AEs, safety laboratory data and vital signs, the following analysis phases are defined for each subject:

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

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**BI 425809**	Date/time of first administration of study drug	Date/time of last administration of study drug + 11 * 24 h (i.e., REP of 11 days) or 0:00 AM on day after subject's trial termination date whatever occurs earlier
Follow-up	**F/U**	Date/time of last administration of study drug + 11 * 24 h	0:00 AM on day after subject's trial termination date

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. CTR Section 15 will present results for the screening, on-treatment and follow-up phases.

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 total will be provided in addition:

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

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).

If any IPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an Excel spreadsheet (3). Categories which are considered to be IPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other IPDs, the definition in the IQRMP will be supplemented accordingly by the time of the RPM/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 primary or secondary 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 characteristics	X	
Safety parameters	X	
Primary PK endpoints		X
Secondary PK endpoint		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 treated subjects who failed to complete 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: *It is not planned to impute missing values for safety parameters.*

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

Missing data and outliers of PK data are handled according to BI standards (5) [001-MCS-36-472_RD-01] and (7).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last non-missing value determined prior to the first study drug administration 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).

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

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

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

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

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of 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 are actually 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 report. 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 report.

A medication will be considered concomitant to a dose group, if it

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

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

Treatment compliance will not be analysed as a specific endpoint (cf. Section 5.4.2). 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

Analysis of absolute bioavailability (Fp.o.) of the dose-normalised primary endpoint will be performed as defined in Section 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP is an analysis of variance (ANOVA) model on the logarithmic scale. The absolute bioavailability is calculated as the ratio of the two gMeans of $AUC_{0-\infty}$ after oral and intravenous administration, that originate from the statistical model.

A sensitivity analysis will be performed with subject as fixed effect. If there are no missing values a STATDOC will be sufficient since the analysis will be identical to the main analysis. If there are missing values a table will be presented displaying the results from the ANOVA.

Primary PK endpoints will also be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (5) [001-MCS-36-472_RD-01].

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 CTP trial 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).

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

The endpoint will only be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (5) [001-MCS-36-472_RD-01].

See Section 7.4 of this TSAP for details regarding exclusion of PK parameters and plasma concentrations.

7.6 FURTHER ENDPOINTS

7.6.1 Safety endpoints

Safety endpoints will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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 electronic case report form (eCRF) will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (LLT, 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 treatment phases 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 (9) and for the class of AESIs.

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 transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

According to ICH E3 (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 system organ class and preferred term. AEs which were considered by the investigator to be drug related 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)). AEs will also be summarised by maximum intensity.

The system organ classes will be sorted by total frequency, preferred terms will be sorted by total frequency (within system organ class).

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 system organ class 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 standard "Display and Analysis of Laboratory Data" (10).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range.

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 on the eCRF 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 will not be applied in this study.

Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.

7.8.3 Vital signs

The analysis of vital signs 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

Abnormal findings in 12-lead ECG 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. No separate listing or analysis of ECG data will be prepared.

7.8.5 Others

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of first 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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version*
2	*001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	"Template Domain DV", current version; Section "Resources and Key User Emails" on ICBI homepage
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*

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**01-APR-19**		None	This is the final TSAP without any modification