TRIAL STATISTICAL ANALYSIS PLAN

c12282163-01

BI Trial No.:	1339.1
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design) Including protocol amendments 1, 2, and 3 [c02155664-05]
Investigational Product(s):	BI 655088
Responsible trial statistician(s):	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	25 MAR 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European union drug regulating authorities clinical trials
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics
PKS	PK analysis set
PV	Protocol violation
R	Reference treatment
RAGe	Report Appendix Generator system
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation

Term	Definition / description
T	Test treatment
TS	Treated set
TSAP	Trial statistical analysis plan

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 Clinical Trial Protocol (CTP), 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 revised CTP. 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 (Clinical data Analysis and Reporting Environment), 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 adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

Pharmacokinetic (PK) parameters will be calculated using WinNonlin™ software (professional Network version Phoenix 6.3, Pharsight Corporation, Mountain View, CA 94041-1530, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Section 7.3 of the CTP specifies an analysis set of all randomised subjects, whether treated or not. This subject set will be identical to the analysis set of all treated subjects (cf. Section 6.3), since Section 3.3.4.1 of the CTP specifies that, if "a subject is removed from or withdraws from the trial prior to the administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR)". Therefore, it was considered to be sufficient to use the analysis set of all treated subjects in statistical analysis, and not to additionally use an analysis set of all randomised subjects.

Section 7.3.3 of the CTP suggests the time point of the end-of-trial examination to be the end of the on-treatment phase. This phase is used for statistical analysis of AEs, laboratory values and vital signs. Section 7.3.3 says that “These assignments including the corresponding time intervals will be defined in detail in the TSAP”. This TSAP defines the time point of subjects’ trial termination date to be the end of the on-treatment phase. The trial termination date is the last contact with the subject and more appropriately defines the end of the study. There is no post-treatment or follow-up period defined for this trial.

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number of subjects with drug-related AEs, 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 C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ of BI 655088 in plasma, 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, assignments of dose groups, and selection of doses, cf. Section 4 of the CTP.

Subjects were planned to be treated either with

- single dose of of BI 655088 (test treatments)
  or
- single doses 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).

Analysis phases for statistical analysis of AEs, safety laboratory data, and vital signs are defined for each subject as described in the table below.

Table 6.1: 1 Flow chart of analysis phases for adverse events, laboratory tests and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of start of infusion of BI 655088 or placebo
On treatment	**Pbo,**	Date/time of start of infusion of BI 655088 or placebo	12:00 a.m. on day after subject's trial termination date
	respectively		

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 phases 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:

- "**Total BI**", defined as the total over all on-treatment phases involving BI
- "**Total on-trt**", defined as the total over all on-treatment phases, including placebo

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)

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects entered and treated who did not fail during screening.

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 report planning and database lock meeting (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 important protocol deviation (iPD). For definition of iPDs, 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. The following table (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.

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 administered
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Incorrect administration of trial medication
	C5	Incorrect dose of trial medication administered
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**[1]
		None
G		**Other trial specific important deviations**
	G1	Certain deviations of procedures used to measure secondary PK endpoint data

Violations C1, C2, C4 and G1 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not PDs
Source: BI SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

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 were documented to have received at least one dose of study drug. It will be used for analysis of safety, demographic data, baseline characteristics, and disposition.

- PK analysis set (PKS):
  This subject set includes all subjects from the TS on active treatment who provide at least one PK endpoint value that was not excluded according to the description in Section 7.3.2 of the CTP.

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

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Disposition, exposure	X	
iPDs	X	
Demographic/baseline endpoints	X	
Primary endpoint	X	
Other safety parameter	X	
Secondary PK endpoints		X
Further PK endpoints		X

6.5 POOLING OF CENTRES

This section is not applicable, because the study will be performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects, who discontinued from the trial due to screening failures prior to administration of any trial medication, will not be included in the CTR. The safety data of treated subjects who were withdrawn from the trial prematurely will be reported as far as available. All withdrawals will be documented and the reason for withdrawal recorded.

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 (3).

Missing data and outliers of PK data are handled according to BI standards (4)REF5.

CTP: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), 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

For oral glucose tolerance test (i.e. further plasma glucose and serum insulin measurements), baseline is defined for each oral glucose tolerance test as the last measurement prior to the glucose intake. For all other analyses, baseline is defined as the last measurement before study drug administration.

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" (5).

The individual values of all subjects will be listed, sorted by treatment 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

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 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 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.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (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 based on the TS.

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

- is ongoing at the time of administration of the respective treatment or
- starts within the on-treatment phase of the respective treatment (see Section 6.1).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete drug administration 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 frequency of subjects with drug related AEs, 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.

Dose proportionality will be evaluated as defined in the CTP, Section 7.3.2, by use of the power model for the secondary endpoints C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ of BI 655088 in plasma.

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"(4)REF5 and "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the CTR. Exposure will be presented by treatment groups.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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 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, AE of special interest (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" (7) and "Handling of missing and incomplete AE dates" (3).

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 (8) 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 in the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (8), 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 (primary endpoint of this trial). Separate tables will also be provided for subjects with serious AEs (SAEs), subjects with AESIs and subjects with other significant AEs (according to ICH E3 (8)). 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 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 standards "Display and Analysis of Laboratory Data" (9).

Analyses will be based on normalised values, which mean transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

CTP: *Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated.*

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.

The results of the oral glucose tolerance test (i.e. further plasma glucose and serum insulin measurements) will be presented separately using descriptive statistics.

Additionally, individual time-course and (geometric) mean time profiles will be presented for plasma glucose and insulin. The change in the area under the curve for glucose and insulin from baseline to post-treatment will be presented descriptively by treatment and compared between BI 655088 and placebo. An ANOVA model including “treatment” as a fixed effect will be applied on the log-transformed AUCs for the comparison.

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 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 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

ECG data will not be listed but clinically relevant abnormal findings will be reported as adverse events.

7.8.5 Others

7.8.5.1 Bleeding time

Descriptive statistics of bleeding time and for the difference from baseline will be provided by time point.

7.8.5.2 Local tolerability

A frequency table will present the results of the local tolerability assessments by visit.

7.8.5.3 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before administration 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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version*
2	*001-MCS-40-413: "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON*
3	*001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON*
4	*001-MCS-36-472_RD-01: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON*
5	*001-MCG-159: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON*
6	*001-MCS-36-472_RD-03: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON*
7	*001-MCG-156: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON*
8	*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*
9	*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	**25-MAR-19**		None	This is the final TSAP without any modification