TRIAL STATISTICAL ANALYSIS PLAN

c21342784-01

BI Trial No.:	1368.3
Title:	Safety, tolerability, and pharmacokinetics of two dose strengths of a single subcutaneous dose of BI 655130 and one single intravenous dose of BI 655130 in healthy male and female subjects (open-label, parallel group design).
Investigational Product:	BI 655130
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	06 FEB 2018 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADPC	Proper name of the analysis dataset containing PK concentrations per time-point or per time-interval
ADPP	Proper name of the analysis dataset containing calculated PK parameters
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
CI	Confidence interval
Cmax	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Exploratory reference treatment
EudraCT	European union drug regulating authorities clinical trials
gCV	Geometric coefficient of variation

Term	Definition / description
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPV	Important protocol violation
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available
on-trt	on-treatment
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
R	Reference treatment
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SDL	Subject data listing
SOC	System Organ Class
T	Test treatment
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 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. 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 6.3, Certara USA Inc., Princeton, NJ, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints as defined in Section 5.5.1.1 of the CTP:

- *AUC_{0-tz} (area under the concentration-time curve of BI 655130 in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of BI 655130 in plasma)*

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoint is $AUC_{0-\infty}$ (area under the concentration-time curve of BI 655130 in plasma over the time interval from 0 extrapolated to infinity).

5.3 FURTHER ENDPOINTS

5.3.2 Safety parameters

CTP:

Safety and tolerability of the investigational drug will be assessed based on:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous ECG monitoring*
- *Vital signs (blood pressure, pulse rate)*
- *Local tolerability*
- *Oral body temperature*

Local tolerability will be assessed as absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings".

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

CTP: *At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy* […].

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

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

5.4.2 Treatment compliance and treatment exposure

Treatment compliance will not be analysed as a specific endpoint, cf. Section 4.3 of the CTP.

Treatment exposure is defined as the total dose of BI 655130 per subject.

Additionally, the duration of infusion per subject is calculated for the treatment group of subjects who receive BI 655130 intravenously.

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 one single dose of

- as subcutaneous (SC) injection (exploratory reference treatment (ER))

  or
- as intravenous (IV) infusion (reference treatment (R))

  or
- as SC injection (test treatment (T)).

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 administration of study drug
On-treatment	**BI SC**, or **BI IV** or **BI SC**, respectively	Date/time of administration of study drug	0:00 AM on day after subject's trial termination date

CTR Section 15, Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE tables), the following total will be provided in addition:

- "**Total on-trt BI**", defined as the total over all on-treatment phases involving BI 655130

CTR Appendix 16.1.9.2.8.1 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 16.1.9.2.8.1 AE tables:

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

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

6.2 IMPORTANT PROTOCOL VIOLATIONS

Consistency check listings (for identification of violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration) will be provided to be discussed at the RPM/DBLM. At this meeting, each protocol deviation must be assessed to determine whether it is an IPV. For definition of IPVs, and for the process of identification of these, refer to the BI reference document "Protocol Violation Handling Definitions" (2).

If any IPVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be IPVs in this trial. If the data show other IPVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

IPVs will be summarised and listed.

Table 6.2: 1 Important protocol violations

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
C3	Non-compliance
C5	Incorrect intake of trial medication
D	**Concomitant medication**
D1	Concomitant medication with the potential to affect the assessment of the trial medication
E	**Missing data**
	None[1]
G	**Other trial specific important violations**
G1	Certain violations of procedures used to measure primary PK data

Violations C1, C2, C5 and G1 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not PVs
Source: BI reference document "Protocol Violation Handling Definitions" [001-MCS-50-413_RD-01] (2).

6.3 SUBJECT SETS ANALYSED

The following subject sets will be defined for statistical analysis:

- Treated set (TS):
  This subject set includes all subjects who received study drug.

- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects of the TS who provide at least one observation for at least one primary or secondary PK endpoint without important PVs with respect to the statistical evaluation of PK endpoints, as defined in Section 7.3.1 and Section 7.3.2 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	
IPVs	X	
Demographic/baseline endpoints	X	
Other safety parameters	X	
PK endpoints		X

6.4 SUBGROUPS

A subgroup analysis is not planned.

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

CTP: If a subject is removed from or withdraws from the trial prior to first 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). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported 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 (see 001-MCG-156_RD-01 (4)).

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

For safety measurements 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" (001-MCG-159) (10).

The individual values of all subjects will be listed. Listings will generally be sorted by treatment group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned analysis phase (see Table 6.1: 1 for a definition of analysis phases). 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

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. 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.

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 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, but will be assessed for the treatment group receiving BI 655130 intravenously based on the duration of infusions (descriptive statistics of duration) and dose per infusion (descriptive statistics of the administered dose per infusion). Any deviations from complete intake will be addressed in the RPM/DBLM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Analysis of relative BA of primary endpoints $AUC_{0\text{-}tz}$ and C_{max} of BI 655130 in plasma will be performed as defined in Sections 7.1.3 and 7.3.1 of the CTP.

The statistical model for the primary analysis (comparison of subcutaneous versus intravenous administration of of BI 655130) is an ANOVA model on the logarithmic scale including an effect for "treatment group" as defined in Sections 7.1.3 and 7.3.1 of the CTP.

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.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoint

The secondary PK endpoint $AUC_{0-\infty}$ will be analysed in the same way as described for the primary PK endpoint.

Descriptive analyses of the secondary PK endpoint will be 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.

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the CTR, see also Section 7.3.

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 Trial" (7) [001-MCG-156] and "Handling of missing and incomplete AE dates" (4) [001-MCG-156_RD-01].

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 phase or on-treatment phase as defined in Section 6.1.

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 AESI in this trial is 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*
- *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 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 SOCs and preferred terms within SOCs will be sorted by descending frequency overall 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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). If possible, analyses will be based on original values. If multiple reference ranges apply for a parameter (e.g. due to different age groups), 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 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, pulse rate, body temperature) 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.

Body weight will only be listed.

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 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 study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination will be prepared.

Matching pairs for subjects included in the BI SC and BI IV treatment group will be summarized in a table and a listing displaying the matching criteria.

7.8.6 Local tolerability

Local tolerability (absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings") will be summarized with counts and percentages overall (i.e. over all time points) as well as by time point.

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.

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. HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
Final	**06-FEB-18**	( ), ( )	None	This is the final TSAP without any modification