TRIAL STATISTICAL ANALYSIS PLAN c15047157-01

BI Trial No.:	1368-0009
Title:	Safety, tolerability and pharmacokinetics of single rising intravenous dose and single subcutaneous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled design) Protocol Amendment 3 1368-0009-protocol-amendment-3 [c08998695-03]
Investigational Product:	BI 655130
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Date of statistical analysis plan:	01 FEB 2018 SIGNED
Version:	final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Ati-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CTP	Clinical Trial Protocol
DBL	Dtabase lock
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PKS	Pharmacokinetic set
PV	Potocol violation
RPM	Report planning meeting
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

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

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 ’Statistical Methods and Determination of Sample Size‘. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

SAS® Version 9.4 (or later version) will be used for all analyses.

This initial version of the TSAP is defining important protocol violations in Section 6.2.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There will be no changes in the planned analysis of the study.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

CTP 5.2.1 defines the frequency [N(%)] of subjects with drug-related AEs as primary endpoint.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There are no key secondary endpoints in this trial.

5.2.2 Secondary endpoint(s)

CTP 5.5.1.1 defines the following pharmacokinetic parameters for BI 655130 as secondary endpoints:

IV administration:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)
- CL (total clearance of the analyte in the plasma after intravenous administration)
- V_{ss} (Volume of distribution at steady state after intravenous administration)

SC administration:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

All subjects on active treatment will be analysed according to their actual treatment group. All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made).

The following separate study phases will be defined for analyses of adverse events (AEs), laboratory tests, and vital signs:

- **Screening** (ranging from 0:00 h on day of informed consent until first administration of study drug)
- **On-treatment** (separately for each treatment, ranging from the time of first administration of the respective treatment until study termination date)

Displays of AEs, laboratory tests and vital signs will account for the treatments (Table 6.1: 1) during on-treatment phase.

A) High-level analysis (for CTR Section 15.3 and Appendix 16.1.9.2.8.2 displays)

In this analysis screening and post-study periods will not be included. In Section 15.3 AE tables (but not in Appendix 16.1.9.2.8.2 AE tables), the following totals will be provided in addition to the by treatment display:

- a total over all active treatments during on-treatment phase, excluding placebo ("**Total BI**")
- a total over the on-treatment phase and placebo ("**Total**")

B) Low-level analysis (for Appendix 16.1.9.2.8.1 displays)

Results will be presented separately for the following phases:

- Screening
- On-treatment (labelled with the name of the study drug administered at the start of the on treatment phase)

In Section 16.1.9.2.8.1 AE tables, the following totals will be provided in addition:

- a total over all active treatments during on-treatment phase, excluding placebo ("Total BI")
- a total over all phases ("Total")

Table 6.1: 1 Treatment Set-up

	Treatment	Short label
A	BI 655130, [redacted] iv	[redacted] iv
B	BI 655130, [redacted] iv	[redacted] iv
C	BI 655130, [redacted] iv	[redacted] iv
I	Placebo, iv	Placebo
D	BI 655130, [redacted] sc injection	[redacted] sc
S	Placebo, sc injection	Placebo

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects and subjects with serious AE (SAE) which the investigator considered related to the screening procedure). 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 meeting (RPM). 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 violation (PV). For definition of important PVs, and for the process of identification of these, refer to the Boehringer Ingelheim reference document 'Protocol Violation Handling Definitions' (1).

If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM minutes via an accompanying Excel spreadsheet (2). The following table contains the categories which are considered to be important PVs in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM. If substantial numbers of PVs are reported at the RPM, a decision about summarising the PVs in a tabular format will be made. Otherwise, only a PV listing will be provided.

The following Table 6.2: 1 gives the important PVs for this trial.

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 administered
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Medication code broken inappropriately
	C5	Incorrect administration of trial medication
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**
	E1	Certain violations of procedures used to measure primary or secondary data
F		**Incorrect timing**
	F1	Certain violations of time schedule used to measure primary or secondary data.

6.3 SUBJECT SETS ANALYSED

- Randomised set (RS):

  This subject set includes all randomised subjects, whether treated or not.

- Treated set (TS):

  This set includes all subjects who were provided with study medication and were documented to have taken at least one dose.

Section 7.3.1 of the CTP:

Plasma concentration data and parameters of a subject will be included in the statistical PK analysis if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below).

Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violation may be:

- *Incorrect trial medication administrated, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication administrated*
- *Use of restricted medications.*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *Missing samples/concentration data at important phases of PK disposition curve.*

The PK parameter analysis set (PKS) includes all subjects in the treated set who provide at least one PK parameter that was not excluded according to the description above.

- Pharmacokinetic set (PKS):

  The PKS includes all subjects in the treated subjects who provide at least one PK parameter that was not excluded according to the description above.

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.

The following table summarises which subject sets will be used for the different analyses.

Table 6.3: 1 Subject sets analysed

Class of endpoint	RS	TS	PKS
Disposition, exposure	X		
Important PVs	X		
Primary endpoints		X	
Secondary endpoints and further parameters of interest in PK analyses			X
Safety endpoints		X	
Demographic/baseline 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 discontinued from the trial due to screening failures prior to administration of any trial medication, will not be included in the CTR except for those with SAEs which the investigator considered related to the screening procedures. 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.

Handling of missing data is according to the CTP, Section 7.4. Additionally, handling information of missing data is shown as follows:

- Missing data and outliers of PK data are handled according to (3).
- Missing or incomplete AE dates are imputed according to BI standards (see 'Handling of missing and incomplete AE dates'). (5)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline values of laboratory data and vital signs for safety analysis will be defined as the last values before first drug infusion or administration.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM/database lock (DBL) meeting.

7. PLANNED ANALYSIS

In general, a set of descriptive statistics to be displayed for continuous variables in the clinical trial report will be as follows:

Non-pharmacokinetic variables:

For End-Of-Text tables, the set of summary statistics is: N, mean, standard deviation (SD), min, median, and max.

Tabulation of frequencies for categorical or categorised data will include all possible categories and display numbers of observations (subjects) with the percentage relative to the respective treatment sequence / regimen. 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.

Pharmacokinetic variables:

The analysis of standard PK parameters will be performed according to (3).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics by group 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.

A respective listing only is planned for this section of the report. The data will be summarised in total.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

A medication will be considered concomitant to a treatment, 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).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete administration of the trial medication will be addressed in the RPM and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

The analysis will be performed as defined in the CTP, Section 7.3.1.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

There are no key secondary endpoints in this trial.

7.5.2 (Other) Secondary endpoint(s)

The analysis will be performed as defined in the CTP, Section 7.3.2.

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 (3, 4).

7.7 EXTENT OF EXPOSURE

A respective listing only is planned for this section of the report.

7.8 SAFETY ANALYSIS

The analysis will be performed as defined in the CTP. 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, 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)

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

For further details on summarisation of AEs data, please refer to (5, 6).

According to ICH E3 (7), AEs classified as ‘other significant’ need to be reported and will include those non-serious with

(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a RPM/DBLM.

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by group, primary system organ class (SOC) and preferred term (PT) (MedDRA levels to be displayed in the tables).

Separate tables will be provided for subjects with other significant AEs according to ICH E3 (7), for subjects with drug-related AEs, for subjects with significant non-serious AEs (only if these were defined for the project) and for subjects with serious AEs.

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 PT. The frequency of subjects with SAEs will also be summarised.

The SOCs will be sorted by default alphabetically. PTs will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8), descriptive statistics with original values will be provided by group for baseline, on-treatment values and for changes from baseline. Clinically relevant findings in laboratory data were to be reported as AEs and will be analysed as part of AE analysis. Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of subjects within and outside the reference range at baseline and the last measurement on treatment. Frequency tables for categorical laboratory values categorised by value at baseline and last value on treatment will be shown.

7.8.3 Vital signs

Only descriptive statistics by group and planned visit are planned for this section of the report. Clinically relevant findings in vital signs data were to be reported as AEs and will be analysed as part of AE analysis.

7.8.4 ECG

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

7.8.5 Others

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

8. REFERENCES

1	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version; IDEA for CON.
2	*001-MCS-50-413_RD-02*: "Important Manual Protocol Violations Spreadsheet", current version; IDEA for CON.
3	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON;
4	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON;
5	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version IDEA for CON;
6	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", Version 5; IDEA for CON.
7	*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
8	*001-MCG-157*: "Handling, 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
Initial	**22-MAY-17**		None	This is the initial TSAP with necessary information for trial conduct.
Final	**01-FEB-18**		Section 5, 6 and 7	Details for analysis are specified.