TRIAL STATISTICAL ANALYSIS PLAN

c27982603-01

BI Trial No.:	1368-0029
Title:	Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design). Including Protocol Amendment 2 [c21745299-03]
Investigational Product:	BI 655130
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	14 JUN 2019 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
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
$AUC_{0-\infty}$	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
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviation
IQRMP	Integrated quality and risk management plan
LLT	Lower level term
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics

Term	Definition / description
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
Q1	Lower Quartile
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

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.
CTP Section 7.3.1 states that the TS includes all subjects from the “RS” who were documented to have received one dose of study drug. “RS” was not explained, but in this context certainly refers to a randomized set. Since there is no randomization in this trial, it is clear that there is no randomized set and this must be a typo in the CTP and that the CTP actually intends the TS to include all subjects who were documented to have received one dose of study drug. The TS was defined in this TSAP accordingly, and this was considered to be in accordance with the intention of the CTP (despite of the typo).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

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

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoint is $AUC_{0\text{-}\infty}$ in plasma for BI 655130.

5.4 OTHER VARIABLES

5.4.3 Safety parameters

Further safety parameters of interest will be used as defined in Section 5.2.1 of the CTP:

CTP:

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *Vital signs (blood pressure, pulse rate)*
- *Local tolerability*

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

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.

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 single dose of BI 655130 injected subcutaneously in the abdominal region or into the thigh. See Table 6.1: 1 for details on the treatment schedule.

Table 6.1: 1 Dosage and treatment schedule

Dose Group	Total dose	Concentration of solution	Application volume	Injection site
1 (reference treatment R)				Periumbilical
2 (test treatment T1)				Periumbilical (left and right)
3 (test treatment T3)				Periumbilical (left and right)
4 (test treatment T2)				Thigh

The analysis phases specified in Table 6.1: 2 will be defined for each subject for use in the statistical analysis of AEs, safety laboratory data, local tolerability and vital signs.

Table 6.1: 2 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, local tolerability 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 pmbl,** **BI pmbl (l+r),** **BI pmbl (l+r),** **BI thigh** respectively	Date/time of administration of study drug	Date/time of administration of Study drug + 113 * 24 h (i.e., REP of 112 days (16 weeks) + 1 day) or 0:00 AM on day after subject's trial completion or discontinuation date whatever comes first
Follow-up[1]	**F/U BI pmbl,** **F/U BI pmbl (l+r),** **F/U BI pmbl (l+r),** **F/U BI thigh** respectively	Date/time of administration of study drug + 113 * 24 h (i.e., REP of 112 days (16 weeks) + 1 day)	0:00 AM on day after subject's trial completion or discontinuation date

[1] If the trial completion or discontinuation date is earlier than 113 days after date of administration of study drug, the follow-up phase does not exist for the respective subject.

CTR Section 15.3.1, 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. Appendix 16.1.13.1.8.1 will present results for the screening, on-treatment and follow-up phase.

In CTR Section 15.3.1 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 on-trt**", defined as the total number of subjects with AEs over all on-treatment phases

Additionally, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total**", defined as the total number of subjects with AEs 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. 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 domain "DV" of the database via an Excel spreadsheet (3). Categories which are considered to be IPDs in this trial are defined in the following table, along with the information which kind of IPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses, and will be documented in the decision log. If the data show other IPDs, this table will be supplemented accordingly by the time of the RPM.

IPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Excluded from which analysis set
A		**Entrance criteria not met**	
	A1	Inclusion criteria violated	PKS
	A2	Exclusion criteria violated	PKS
B		**Informed consent**	
	B1	Informed consent not available	Treated set
	B2	Informed consent too late	None
C		**Trial medication and randomisation**	
	C1	Incorrect trial medication taken	PKS
	C2	Incorrect administration of trial medication	PKS
	C3	Incorrect dose of trial medication administered	PKS
D		**Concomitant medication**	
	D1	Concomitant medication with the potential to affect the assessment of the trial medication	PKS
G		**Other trial specific important deviations**	
	G1	Certain deviations from procedures used to measure primary PK data	PKS

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, or because of non-evaluability, as described in Section 7.3.1 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. These decisions will be documented in the decision log.

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 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 Section 7.4.1: *With respect to safety evaluations, it is not planned to impute missing values.*

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]. **CTP** Section 7.4.2**:** *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 Section 7.4.3: *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

The last non-missing value determined prior to the 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.

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 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.

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 (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Analysis of relative bioavailability of the primary endpoints will be performed as defined in Sections 7.1.3 and 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP Section 7.1.3 is an analysis of variance (ANOVA) model on the logarithmic scale. For each matched pair a pair number will be assigned and included in the model as random effect.

The following comparisons will be analysed: T1/R, T2/R and T3/R.

CTP Section 7.3.1**:** *Further comparisons may be investigated if appropriate (e.g. T1 vs. T2) […].*

A sensitivity analysis will be performed with matched pair as fixed effect.

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 CTR associated with an appropriate flag.

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

7.5 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 secondary PK endpoint will be analysed in the same way as the primary endpoints. A sensitivity analysis will also be performed with matched pair as fixed effect.

The endpoint will also 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 parameters

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

7.7 EXTENT OF EXPOSURE

Treatment exposure will only be listed by subject and date and time of drug administration.

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 one 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, treatment or follow-up phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 2.

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 Section 5.2.2.1**:** *The AESI in this trial is hepatic injury, as 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 summarized 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 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) and will be analysed as such.

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.

Body weight at end of trial examination will be listed, including its change from baseline.

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 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 on-treatment time points, cf. Section 6.1) as well as by time point.

7.8.6 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 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	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
5	*001-MCS-36-472_RD-01:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
8	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
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	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**14-JUN-2019**		None	This is the final TSAP without any modification

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5. ENDPOINTS

5.1 PRIMARY ENDPOINT

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

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoint is $AUC_{0\text{-}\infty}$ in plasma for BI 655130.

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 single dose of BI 655130 injected subcutaneously in the abdominal region or into the thigh. See Table 6.1: 1 for details on the treatment schedule.

Table 6.1: 1 Dosage and treatment schedule

Dose Group	Total dose	Concentration of solution	Application volume	Injection site
1 (reference treatment R)				Periumbilical
2 (test treatment T1)				Periumbilical (left and right)
3 (test treatment T3)				Periumbilical (left and right)
4 (test treatment T2)				Thigh

The analysis phases specified in Table 6.1: 2 will be defined for each subject for use in the statistical analysis of AEs, safety laboratory data, local tolerability and vital signs.

Table 6.1: 2 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, local tolerability 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 pmbl,** **BI pmbl (l+r),** **BI pmbl (l+r),** **BI thigh** respectively	Date/time of administration of study drug	Date/time of administration of Study drug + 113 * 24 h (i.e., REP of 112 days (16 weeks) + 1 day) or 0:00 AM on day after subject's trial completion or discontinuation date whatever comes first
Follow-up[1]	**F/U BI pmbl,** **F/U BI pmbl (l+r),** **F/U BI pmbl (l+r),** **F/U BI thigh** respectively	Date/time of administration of study drug + 113 * 24 h (i.e., REP of 112 days (16 weeks) + 1 day)	0:00 AM on day after subject's trial completion or discontinuation date

[1] If the trial completion or discontinuation date is earlier than 113 days after date of administration of study drug, the follow-up phase does not exist for the respective subject.

CTR Section 15.3.1, 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. Appendix 16.1.13.1.8.1 will present results for the screening, on-treatment and follow-up phase.

In CTR Section 15.3.1 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 on-trt**", defined as the total number of subjects with AEs over all on-treatment phases

Additionally, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total**", defined as the total number of subjects with AEs 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. 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 domain "DV" of the database via an Excel spreadsheet (3). Categories which are considered to be IPDs in this trial are defined in the following table, along with the information which kind of IPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses, and will be documented in the decision log. If the data show other IPDs, this table will be supplemented accordingly by the time of the RPM.

IPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Excluded from which analysis set
A		**Entrance criteria not met**	
	A1	Inclusion criteria violated	PKS
	A2	Exclusion criteria violated	PKS
B		**Informed consent**	
	B1	Informed consent not available	Treated set
	B2	Informed consent too late	None
C		**Trial medication and randomisation**	
	C1	Incorrect trial medication taken	PKS
	C2	Incorrect administration of trial medication	PKS
	C3	Incorrect dose of trial medication administered	PKS
D		**Concomitant medication**	
	D1	Concomitant medication with the potential to affect the assessment of the trial medication	PKS
G		**Other trial specific important deviations**	
	G1	Certain deviations from procedures used to measure primary PK data	PKS

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, or because of non-evaluability, as described in Section 7.3.1 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. These decisions will be documented in the decision log.

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 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 Section 7.4.1: *With respect to safety evaluations, it is not planned to impute missing values.*

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]. **CTP** Section 7.4.2**:** *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 Section 7.4.3: *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

The last non-missing value determined prior to the 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.

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 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.

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 (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Analysis of relative bioavailability of the primary endpoints will be performed as defined in Sections 7.1.3 and 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP Section 7.1.3 is an analysis of variance (ANOVA) model on the logarithmic scale. For each matched pair a pair number will be assigned and included in the model as random effect.

The following comparisons will be analysed: T1/R, T2/R and T3/R.

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 CTR associated with an appropriate flag.

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

7.5 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 secondary PK endpoint will be analysed in the same way as the primary endpoints.

The endpoint will also 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.

7.7 EXTENT OF EXPOSURE

Treatment exposure will only be listed by subject and date and time of drug administration.

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 one 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, treatment or follow-up phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 2.

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 Section 5.2.2.1**:** *The AESI in this trial is hepatic injury, as 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 summarized 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 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) and will be analysed as such.

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.

Body weight at end of trial examination will be listed, including its change from baseline.

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 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 on-treatment time points, cf. Section 6.1) as well as by time point.

7.8.6 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 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	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
5	*001-MCS-36-472_RD-01:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
8	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
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	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**14-JUN-2019**		None	This is the final TSAP without any modification