Trial Statistical Analysis Plan

c19081897-01

BI Trial No.:	1368.2
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects Final Protocol (including protocol revisions 1, 2 and 3 (c09105854-05))
Investigational Product:	BI 655130
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted] [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	07 SEP 2017 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
AIC	Akaike's information criterion
ALT	Alanine aminotransferase
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
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
$AUEC_{above}$	Area above the biomarker effect vs. time curve above the baseline during the treatment interval
$AUEC_{below}$	Area under the biomarker effect vs. time curve below the baseline during the treatment interval
$AUEC_{diff}$	Difference between $AUEC_{below}$ and $AUEC_{above}$
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BMS	Biomarker set
CARE	Clinical data analysis and reporting environment
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma after administration of the first dose
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CRF	Case report form

Term	Definition / description
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
E_{base}	Baseline effect of biomarker
ECG	Electrocardiogram
ECGPCS	Electrocardiogram plasma concentration set
eCRF	Electronic case report form
EMA	European Medicines Agency
E_{max}	Maximum effect of biomarker
EudraCT	European union drug regulating authorities clinical trials
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPV	Important protocol violation
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
on-trt	on-treatment
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PR interval	ECG interval from the onset of P wave to the beginning of the QRS
PV	Protocol violation
QRS complex	Combination of the Q, R, and S waves
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave

Term	Definition / description
QTcB	QT interval, heart rate corrected according to Bazett's formula
QTcF	QT interval, heart rate corrected according to Fridericia's formula
QTcN	QT interval, heart rate corrected according to study population formula
RAGe	Report appendix generator
RPM	Report planning meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SD	Single dose [in dose group labels] Standard deviation [otherwise]
SDL	Subject data listing
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range

3. INTRODUCTION

As per 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 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 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.

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

[redacted]

Deviating from CTP Section 7.3.2, the secondary analysis of relative bioavailability for single intravenous dose of 20 mg/kg weight based on secondary endpoints will not be conducted, since this analysis was considered not to be relevant.

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoint is the number [N (%)] of subjects with drug-related AEs, as defined in Section 5.2.1 of the CTP.

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoints in the single dose part of this trial are $AUC_{0-\infty}$ and C_{max} of BI 655130 in plasma.

Secondary endpoints in the multiple dose part of this trial are $AUC_{\tau,1}$, C_{max}, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 655130 in plasma, as defined in Section 5.5.1.1 of the CTP.

[redacted]

5.3.2 Safety parameters

CTP: *Further criteria of interest:*

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

In addition, body temperature is a further parameter of interest.

Local tolerability is a further parameter of interest, and will be assessed as absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings".

12-lead ECG endpoints

For the definition of baseline and a summary of time points please refer to Section 6.7.

Quantitative ECG endpoints:

The following quantitative ECG endpoints will be determined for the ECG variables QTcN, QTcF, QT, HR, PR, QRS, RR, and QTcB derived as described in Additional Section 9.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present at baseline) of maximum QTcN interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment (and similar for QTcF).
  For assignment of a particular subject to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered. A missing value is obtained only in case that (i) all on-treatment values are missing and (ii) all baseline values are less than or equal to 500 msec or missing. If condition (i) is fulfilled but at least one baseline value is greater than 500 msec, this case will be categorized as "no new onset". If baseline is missing, but the maximum absolute QTcN interval falls in a category other than normal (i.e. when QTcN > 450 ms), then this is categorized as a new onset in the respective category. If baseline is missing, but the maximum absolute QTcN interval is normal, then it is categorized as "No new onset" (similar for QTcF).
- Maximum change from baseline in QT interval ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcN interval ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment (similar for QTcF)

The occurrence of any of the following will be viewed as "notable findings":

- New onset (not present at baseline) of uncorrected QT interval > 500 msec at any time on treatment
  If baseline is missing, any occurrence of QT interval > 500 msec at any time on treatment will be a notable finding
- New onset of QTcN interval > 500 msec at any time on treatment (and similar for QTcF)
  If baseline is missing, any occurrence of QTcN interval > 500 msec at any time on treatment will be a notable finding (similar for QTcF)
- Increase in QTcN interval from baseline by > 60 msec at any time on treatment (similar for QTcF)
- Increase in HR from baseline by ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or decrease in HR by ≥ 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Increase in the PR interval from baseline by ≥ 25%, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment

- Increase in the QRS complex from baseline by ≥ 10%, when corresponding on-treatment value of QRS complex is > 110 msec, at any time on treatment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

CTP: *At the screening visit, 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 exposure is assessed by means of

- the total infused dose of BI 655130 [mg] per subject, the
- infused dose of BI 655130 [mg/kg body weight] per subject and infusion,
- the duration of infusion per subject and infusion, and
- the number of infusions per subject.

The total dose of BI 655130 [mg] received is calculated as the total infusion volume [mL], as documented on the eCRF, times the drug concentration in the infusion solution (which is 5 mg/mL for subjects in the 3 mg/kg dose group, 10 mg/mL for subjects in the 6 mg/kg dose group, and 20 mg/mL for subjects in the 10 mg/kg and 20 mg/kg dose groups). The dose of BI 655130 [mg/kg body weight] will be calculated as the total dose of BI 655130 received divided by the body weight [kg] of the patient on Day -2.

The duration of the infusion of BI 655130 [minutes] will be calculated as the end of the infusion date/time minus the start of the infusion date/time.

Treatment compliance will be assessed based on the actual number of infusions, duration of infusions and dose per infusion.

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

- four intravenous doses of 3 mg/kg, 6 mg/kg, 10 mg/kg or 20 mg/kg body weight of BI 655130 (test treatment)
  or
- four intravenous doses of placebo (reference treatment)
  or
- a single intravenous dose of 20 mg/kg body weight of BI 655130 (test treatment)
  or
- a single intravenous dose of placebo (reference treatment).

All placebo subjects from multiple dose groups will be analysed in one pooled placebo group (i.e. no distinction between multiple dose groups will be made for placebo subjects). Placebo subjects from the single dose group will be analysed separately.

In displays of disposition, demographics and safety, results of statistical analysis for multiple dose groups will be presented side by side with those for the single dose group in the same tables.

For statistical analysis of AEs, safety laboratory data, vital signs and ECG, 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, vital signs and ECG

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Placebo MD**, **Placebo SD**, **BI 3 mg/kg MD**, **BI 6 mg/kg MD**, **BI 10 mg/kg MD**, **BI 20 mg/kg MD**, or **BI 20 mg/kg SD**, respectively	Date/time of first administration of study drug	12:00 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 MD**", defined as the total over all on-treatment phases involving BI multiple dose treatment only, ignoring placebo and single dose BI

CTR Appendix 16.1.9.2.8.1 displays will present results for the screening and on-treatment phases.

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" (1).

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 (2). 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
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Medication code broken inappropriately
	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 secondary PK data

Violations C1, C2, C4, 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] (1).

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 secondary PK endpoint without important PVs with respect to the statistical evaluation of PK endpoints, as defined in Section 7.3.2 of the CTP.

[redacted]

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

- ECG PC set (ECGPCS):
  This subject set includes all subjects from the TS who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analysis. For placebo subjects, the plasma concentration is set to 0 and hence always valid. For subjects treated with BI 655130, the decision about concentration value validity needs to be assessed within the Clinical Pharmacology group. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the RPM before data base lock.

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	BMS	ECGPCS
Disposition	X			
Exposure	X			
IPVs	X			
Demographic/baseline endpoints	X			
Primary endpoint	X			
ECG endpoints and plasma concentrations used in exposure-response analysis				X
ECG endpoints in other analyses	X			
Other safety parameters	X			
Secondary PK endpoints		X		
Further PK endpoints		X		
Biomarkers			X	

[redacted]

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 (3)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (4). **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

6.7.1 Time points and baseline for analysis of 12-lead ECG

There will be a centralised evaluation of all 12-lead ECG recordings at the time points specified in Table 6.7: 1 below:

Table 6.7.1: 1 Time schedule of 12-lead ECG recordings with centralised evaluation

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Comment[2]	Study phase
2	1, 8[1], 15[1] and 22[1]	-02:00		Baseline/on-trt[3]
		00:30	only for BI 3 mg/kg MD, 6 mg/kg MD and BI 20 mg/kg SD	On-treatment
		01:00	only for BI 10 mg/kg MD and BI 20 mg/kg SD	
		01:30	only for BI 20 mg/kg MD and BI 20 mg/kg SD	
		02:00		
		03:00	only for BI 20 mg/kg SD	
		04:00	only for BI 20 mg/kg SD	
		06:00		
		08:00	only for BI 20 mg/kg SD	
		12:00		
	2, 9[1], 16[1] and 23[1]	24:00		
		32:00	only for BI 20 mg/kg SD	
	3, 10[1], 17[1] and 24[1]	48:00		

[1] These days are only applicable to dose groups with multiple dosing
[2] If no comment is given, time point is applicable to all dose groups in this trial
[3] ECG recording at relative time -2:00 h prior to next dosing is considered to be baseline on Day 1 and to be on-treatment on other days

Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all time points with centralised ECG evaluation (as listed in the table above). On all other time points, single ECGs will be recorded.

The value of an ECG variable at each of the time points with triple ECG is defined as the arithmetic mean of the 3 single ECG measurements. In particular, the baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to first drug administration.

For the exposure-response analysis, ECG measurements and corresponding plasma concentrations building pairs using the same planned time points will be used (e.g., QTcN change from baseline and plasma concentration for planned time 0:30 will build one pair.) Whether a time deviation between a PK sample and the corresponding ECG recording is too big and the respective pair has to be excluded, or whether a value has to be matched to another time point, will be decided no later than at the RPM/DBLM.

6.7.2 Baseline in all other analyses

In all other analyses (except for analyses of ECG variables), the last non-missing value determined prior to the first dosing of BI 655130 will be defined as baseline.

6.7.3 Time windows for measurements

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM/DBLM.

6.7.4 Pooled time points for comparison of endpoints at end of infusion

The duration of infusion varies between dose groups, as shown in the table below.

Table 6.7.4: 1 Duration of infusion

Dose group	Duration of infusion
BI 3 mg/kg MD and matching placebo	30 min
BI 6 mg/kg MD and matching placebo	30 min
BI 10 mg/kg MD and matching placebo	60 min
BI 20 mg/kg MD and matching placebo	90 min
BI 20 mg/kg SD and matching placebo	60 min

Therefore, the planned time of measurements taken at the end of infusion also varies between dose groups (e.g., 0:30 h, 1:00 h or 1:30 h after infusion on Day 1). In order to allow comparison between dose groups at the end of infusion, the following time points will be defined for use in statistical analysis of vital signs, body temperature, ECG results and biomarkers. They will be created by pooling the time points at the end of infusion of all dose groups.

Table 6.7.4: 2 Time points for statistical analysis of vital signs, body temperature, ECG and biomarkers

			Planned time [hh:mm] (relative to first drug administration)				
Visit	**Day**	**Time point label**	**BI 3 mg/kg MD**	**BI 6 mg/kg MD**	**BI 10 mg/kg MD**	**BI 20 mg/kg MD**	**BI 20 mg/kg SD**
2	1	Day 1, end of inf.	0:30	0:30	1:00	1:30	1:00
2	8	Day 8, end of inf.	168:30	168:30	169:00	169:30	NA
2	15	Day 15, end of inf.	336:30	336:30	337:00	337:30	NA
2	22	Day 22, end of inf.	504:30	504:30	505:00	505:30	NA

NA = Not applicable.

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) (9).

The individual values of all subjects will be listed. Listings will generally be sorted by dose 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 first 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 based on the actual number of infusions (counts and percentages of subjects with a total of 1, 2, 3 or 4 infusions), 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

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the frequency of subjects with drug related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

The analysis of secondary endpoints will be based on the PKS.

Dose proportionality of secondary endpoints will be evaluated as defined in the CTP, Section 7.3.2, by use of the power model, excluding the BI 20 mg/kg SD group.

Exclusion of PK parameters

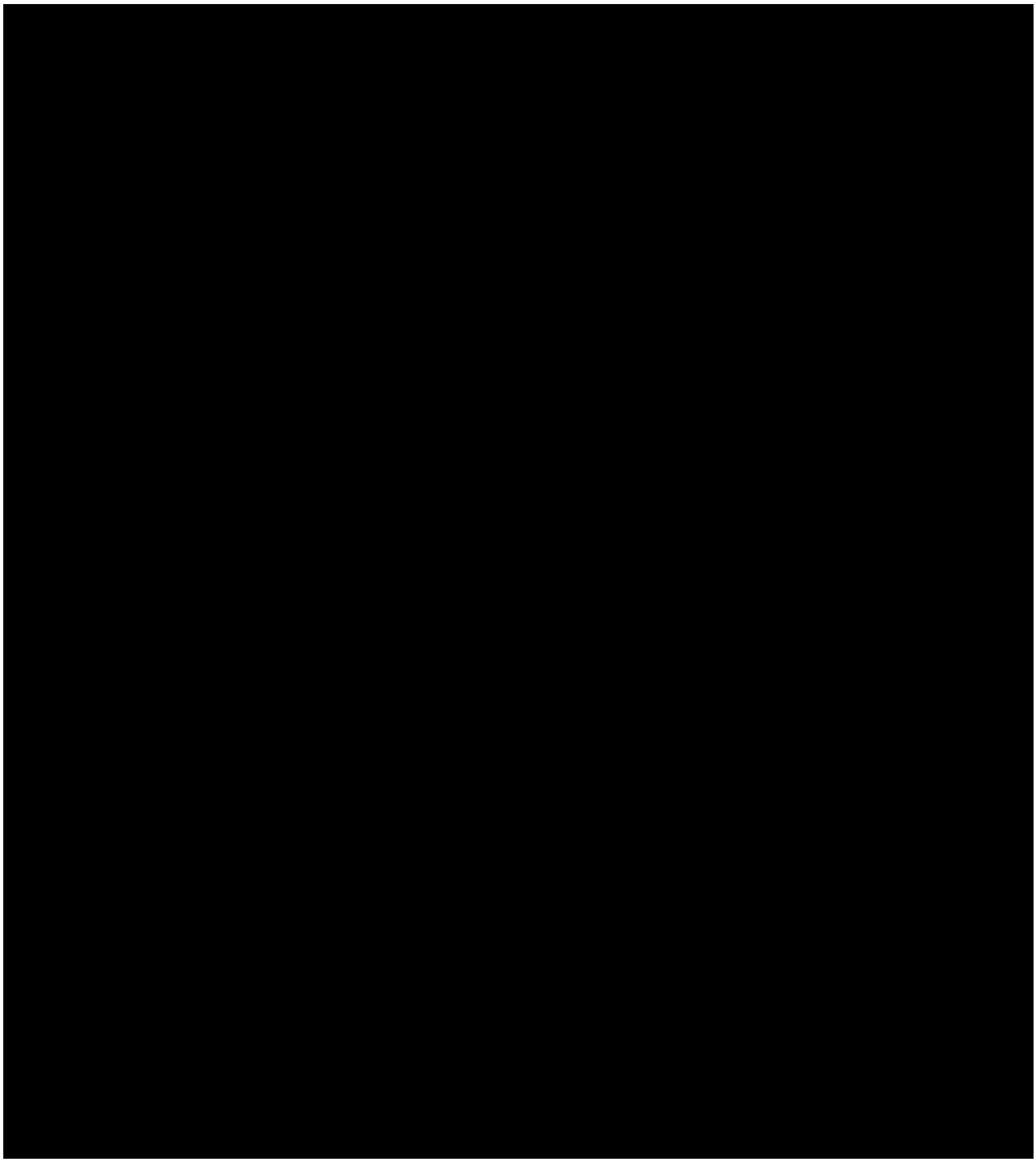
The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

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" (4) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (5).



7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For analysis, multiple AE occurrence data on the 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 "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (6) [001-MCG-156] and "Handling of missing and incomplete AE dates" (3) [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 following are considered as AESIs in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*
  - *an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or*
  - *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.*

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

According to ICH E3 (8), AEs classified as "other significant" need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related (primary endpoint) 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 (8)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

The SOCs will be sorted according to the standard sort order specified by the EMA, preferred terms will be sorted by total frequency (within SOC).

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 (7). 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

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluation of ECG data except of exposure response analysis will be based on the TS. The exposure-response analysis will then be done on the ECGPCS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. Occurrences of notable findings (as defined in Section 5.3.2) will be flagged.

For all subjects with any notable finding in quantitative ECG recordings, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Comments regarding the ECGs will be listed.

Descriptive analysis

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time in all quantitative ECG variables, and time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

Plasma concentrations and relationship to QTcN, QTcF, QT interval and HR change from baseline

For the following analyses, all time points with ECG recordings with centralised evaluation and corresponding plasma concentrations will be included.

The changes from baseline in QTcN (ΔQTcN) will be investigated as response variable. The placebo subjects will be included in the analysis, with zero plasma concentrations. Time points with plasma concentrations "BLQ" in subjects in active dose groups will be ignored in this analysis.

As a first step, it will be investigated if there is a potential delayed or accelerated (e.g. metabolites) effects of the drug on QTcN. A general visual impression of the PK-QT relationship is provided by overlaying time profiles of plasma concentrations and QTcN changes from baseline (ΔQTcN). All figures will be generated for each subject (presented in Appendix 16.1.9.2 of the CTR), as well as for means per active treatment (presented in Section 15.3 of the CTR).

In case of non-linearity or if there is evidence for a delayed effect, further models will be explored that better characterise the PK/ECG relationship (effect compartment, non-linear model etc.).

If there is no non-linearity or delayed effect seen, the relationship between BI 655130 plasma concentrations and QTcN changes from baseline will be investigated in an exploratory manner using a random coefficient model approach to estimate the QTcN change from baseline and its 90% confidence interval at the geometric mean of the C_{max} for each dose (multiple dose groups as well as single dose group). Additionally, the estimated slope with its 90% confidence interval will be provided. The used random coefficient model is based on Garnett et al. 2016 [R17-0553] (10):

```
PROC MIXED DATA=myDATA METHOD=REML;
CLASS subject active(ref=FIRST) time;
MODEL ECGep = conc active time / NOINT CL ALPHA=0.1 ALPHAP=0.1 DDFM=KR
      OUTPREDM=pred;
RANDOM INT conc / TYPE=UN SUBJECT=subject;
ESTIMATE 'Pred. value at conc. xx.xx' conc xx.xx active 1 -1 / CL
      ALPHA=0.1;
ESTIMATE 'Slope estimate' conc 1 / CL ALPHA=0.1;
RUN;
```

Here "ECGep" is the QTcN change from baseline, "active" is a dummy 0/1 variable indicating the active treatment (1=active, 0=placebo), "conc" is the corresponding plasma concentration value of the drug, and "xx.xx" is the given concentration value (i.e. the value of the geometric mean C_{max} of a given dose group). The class variable "time" is the time relative to the most recent infusion; here, measurements at time points at the end of infusion will not enter the model with the planned time, but only by means of the time points defined in Table 6.7: 3. The "TYPE=UN" option causes the two specified random coefficients to have a bivariate normal distribution. In case of convergence problems see Section 9.2 for possible improvements (option "TYPE=FA0(2)" may also be used as a potential solution, it requests a G matrix estimate that is constrained to be nonnegative definite). If the note "estimated G matrix is not positive definite" occurs in the SAS log file, the random slope "conc" might be removed from the "RANDOM" statement. When the plasma concentrations are not normally distributed, the exposure-response model can be applied to log(conc) instead of the raw concentration.

For visualization, the BI 655130 plasma concentration against the response will be plotted as well as the (fixed effect) regression line, its 90% confidence interval and the geometric mean of C_{max} for each dose. For each subject and each time point, subtract the mean value of all individual observed ΔQTc values from the placebo group for this time point from the individual observed ΔQTc value for this subject and time point. This results in estimates for "individual ΔΔQTc" values. These estimates should only be used for plotting purposes.

All of the above described graphical and statistical analyses will be also performed for QTcF, HR and QT in place of QTcN.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

For subjects with notable findings, the individual time courses of QTcN, QTcF, QT, HR, PR, and QRS of these subjects will be presented in figures.

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 infusions and time points) as well as by infusion and 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 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-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON

4 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON

5 *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON

6 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON

7 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version; IDEA for CON

8 *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version

9 *001-MCG-159:* "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON

10 *R17-0553:* Garnett C, Needleman K, Liu J, Brundage R, Wang Y; Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther 100 (2), 170 - 178 (2016)

11 *R10-2920:* Ring A: Statistical models for heart rate correction of the QT interval; Stat Med 29, 786 - 796 (2010)

9. ADDITIONAL SECTIONS

9.1 DETAILED DESCRIPTION OF ENDPOINTS FOR ECG

QT, PR, QRS and RR baseline and on-treatment measurements (see Table 6.7: 1) are included in the centralised ECG evaluation.

For each single ECG with centralised evaluation, measurements of QT, PR, QRS and preceding RR interval of four cardiac cycles will be determined and stored in the database as raw data. Their mean values will be used as the QT, PR, QRS, and RR interval values, respectively, for this ECG.

QTcF, HR and QTcB will be calculated based on the derivation rules as follows:

From the four cardiac cycles of a single ECG, the HR (measured in beats/min) will be calculated as

$$HR\ [beats/min] = \frac{60\ 000}{\overline{RR}}$$

where $\overline{RR}$ is the mean of the four RR intervals (measured in msec).

Similarly, the QT interval corrected for HR according to Fridericia's formula (QTcF) for a single ECG will be derived as

$$\text{QTcF [msec]} = \sqrt[3]{\frac{1000}{\overline{\text{RR}}}}\,\overline{\text{QT}}\,,$$

where $\overline{QT}$ is the mean of the four QT intervals and $\overline{RR}$ is the mean of the corresponding preceding RR intervals of the four cardiac cycles for this ECG.

Likewise, the HR-corrected QT interval according to Bazett's formula (QTcB) for a single ECG is given by

$$\text{QTcB [msec]} = \sqrt[2]{\frac{1000}{\overline{\text{RR}}}}\,\overline{\text{QT}}\,.$$

In addition, data dependent population heart rate correction QTcN will be derived for a given pair of QT and RR values as

$$\text{QTcN [msec]} = \left(\frac{1000}{RR}\right)^{slope} * QT[msec],$$

(RR and QT are given in msec). A common *slope* will be estimated for the whole population (all subjects in the TS) based on the random coefficient model described below. The RR and

QT intervals used for this slope estimation will be the arithmetic means of the four cardiac cycles from each single ECG on baseline and on placebo. If there is a missing baseline or placebo value, no imputed values will be used in the analysis described in the following:

A random coefficient model with covariate "log-transformed RR interval" is fit (natural log), which accounts for subject effects (Ring [R10-2920] (11)):

$$Y_{ik} = \mu_0 + s_{0k} + (\delta_1 + s_{1k})x_{ik} + \varepsilon_{ik} ,$$

where

Y_{ik}	log-transformed QT interval of the i^{th} ECG of subject k;
μ_0	the overall intercept;
s_{0k}	the random intercept associated with subject k;
δ_1	the regression effect of the covariate, i.e. the common slope associated with the relationship between the log-transformed QT and RR intervals;
s_{1k}	the random slope associated with subject k;
x_{ik}	log-transformed RR interval of the i^{th} ECG of subject k;
ε_{ik}	the random error associated with the i^{th} ECG of subject k.

The slope is then calculated as δ_1.

The following SAS code will be used to fit the model:

```
PROC MIXED DATA=xxxx CL METHOD=REML;
CLASS subject;
MODEL lnQT = lnRR / DDFM= KENWARDROGER ALPHA=0.05 CL;
RANDOM INT lnRR / TYPE=UN SUBJECT=subject;
ESTIMATE 'Population slope' lnRR 1 / ALPHA=0.05 CL;
RUN;
```

In case of triple ECGs at a time point, the respective ECG variable will be averaged over the triple ECG measurements at this time point (arithmetic mean). Note that in case of missing values the averaging is simply done for the available values.

9.2 STEPS IN CASE OF CONVERGENCE PROBLEMS FOR REPEATED MEASURES MODEL IN ECG

In case of convergence problems one may try one (or more) of the following steps:

1.) Set `MAXITER=100` (or even higher for `PROC GLIMMIX)` and/or `MAXFUNC=200` (for `PROC GLIMMIX`, these options are available within the `NLOPTIONS s`tatement)
2.) Set `SINGULAR=1E-10` as option (for `PROC MIXED`: in the model statement)
3.) Use option `SCORING=4` in the final run to request a Fisher scoring algorithm to be used for the first 4 iterations
4.) Include the additional statement in the `PROC MIXED` call:
```
PERFORMANCE NOTHREAD;
```
5.) Perform an initial run including the statement
```
ODS OUTPUT COVPARMS=covstart;
```
followed by a final run using
```
PARMS / PARMSDATA=covstart;
```
In the special case with the note "Convergence criteria met but final hessian is not positive definite" try instead/in addition
```
PARMS / OLS;
```
to request ordinary least squares starting values.
6.) One may also use estimates from a simpler model (e.g. using `AR(1)`) as starting values for the run with `TYPE=UN` or `UNR`

In case an unstructured covariance matrix (i.e. TYPE=UN or UNR) does not work, also in conjunction with all steps from 1)-6) mentioned above, the following covariance structures will be chosen, in the pre-defined order:

- Toeplitz structure with heterogeneous variances (TOEPH) for the REPEATED effect
- heterogeneous first-order autoregressive structure (ARH(1)) for the REPEATED effect
- TOEPH for both the RANDOM and the REPEATED effect
- ARH(1) for both the RANDOM and the REPEATED effect, but with the additional random statement RANDOM INT / SUBJECT=subject;

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**07-SEP-17**	[redacted]	None	This is the final TSAP without any modification