TRIAL STATISTICAL ANALYSIS PLAN

c27412368-01

BI Trial No.:	1416-0001
Title:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food Including Protocol Amendment 1 [c20427822-07]
Investigational Product:	BI 730460
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	06 MAY 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Dataset
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
BWC	Bioavailability/Bioequivalence, Within-Subject Design, Time-Controlled
CARE	Clinical Analysis and Reporting Environment
CDR	Clinical Data Repository
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DB	Dose Proportionality, Between-Subject Design
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
ECG	Electrocardiogram
ECGPCS	ECG Pharmacokinetic Concentration Set
eCRF	Electronic Case Report Form
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart rate

Term	Definition / description
ICH	International Conference On Harmonisation
ISF	Investigators Site File
iPD	Important Protocol Deviation
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
mRNA	Messenger Ribonucleic Acid
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK analysis set
POC	Percent of Control
PR	Pulse rate
PT	Preferred Term
Q1	1^{st} quartile
Q3	3^{rd} quartile
QD	Quaque die, once daily
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
S	Reference treatment
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SP	Sample Point
SRD	Single rising dose

Term	Definition / description
TMCP	Translational Medicine and Clinical Pharmacology
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
U	Test treatment
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary
XPKISTAT	Library of SAS® Macros for PK analysis

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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

Study data will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated Clinical Analysis and Reporting 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 adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the Clinical Trial Report (CTR) appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the TSAP are outlined in the CTP. The following changes compared to the protocol will be made:

According to the Reference Document 3 of the Boehringer Ingelheim (BI) Statistical Position Paper on Statistical Methods for PK (14), the 90% confidence intervals (CI) should be considered for the assessment of dose proportionality. Therefore, the 90% CI will be used instead of the 95% CI.

The trial was prematurely discontinued on 21 March 2019 after completion of dose group 6 (200 mg) of the SRD part, and without starting the originally-planned BA part of this trial. The TSAP will therefore only describe the analysis of the SRD part.

All subjects up to and including the 200 mg dose group have completed their follow-up period. The maximum exposure (C_{max}) observed in the SRD part following doses of 200 mg BI 730460 was 1,864 nM (gMean). Administration of the originally planned next 2-fold higher dose of 400 mg was not possible due to a higher predicted estimated C_{max} of 3,728 nM which is above the allowed exposure limit of 2,900 nM. Therefore, the SRD part was stopped as with the next planned dose group (400 mg) the pre-defined stopping rule was met. Due to the above mentioned exposure limitation, BI also decided to stop the BA part of trial 1416-0001.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 5.2.1 of the CTP:

Primary endpoint to assess safety and tolerability of BI 730460 is the number [N (%)] of subjects with drug-related adverse events.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 5.5.1.1 of the CTP:

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

It was planned that in total 84 volunteers participate in this study.
72 healthy male subjects will enter the SRD part, according to 9 sequential dose groups comprising 8 subjects per dose group (6 on active and 2 on placebo) and 12 healthy males will enter the BA part (one dose group, all on active).

For details of dosage and formulation see Tables 6.1: 1, and 6.1: 2 below.

Table 6.1: 1 Labels for treatments for use in the CTR (SRD part)

Dose group	Treatment		Short label
1-6	N*	Placebo film-coated tablet	Placebo
1	A	2mg BI 730460 film-coated tablet	BI 2mg
2	B	8mg BI 730460 film-coated tablet	BI 8mg
3	C	25mg BI 730460 film-coated tablet	BI 25mg
4	D	50mg BI 730460 film-coated tablet	BI 50mg
5	E	100mg BI 730460 film-coated tablet	BI 100mg
6	F	200mg BI 730460, film-coated tablet	BI 200mg
7	G**	400mg BI 730460 film-coated tablet	BI 400mg
8	H**	600mg BI 730460 film-coated tablet	BI 600mg
9	I**	800mg BI 730460 film-coated tablet	BI 800mg

*: The placebo group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated.
**: These dose groups were cancelled.

Dose escalation was stopped after the 200mg dose group, as the results of the preliminary PK analysis indicate that C_{max} for 400 mg (dose group 7) will very likely exceed the CTP stopping criterion. Therefore, all analyses will be performed for the first six dose groups only.

Table 6.1: 2 Labels for treatments for use in the CTR (BA part)

Treatment		Short label
S	50mg BI 730460 film-coated tablet, fasted	BI 50mg fast
U	50 mg BI 730460 film-coated tablet, fed	BI 50mg fed

The trial was stopped after the 200 mg dose group, skipping also the BA part.

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h on day of informed consent until administration time of study drug (BI or Placebo))
- **On treatment**
  - **BI/Placebo treatment** (separately for each treatment, ranging from the time of administration of BI 730460 or Placebo until 0:00h on the day after trial termination date (whatever occurs first))

Please note that all AEs reported between start of trial drug administration and the trial termination date will be considered on treatment (i.e. no follow-up period is considered in this trial).

Two types of AE displays will be provided in the report:

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis.
The following totals will be provided in addition:

- a total over all BI treated phases (**"BI Total"**)
- a total over all on treatment phases included in this analysis ("**Total on treatment**") (Section 15.3 only)

B) Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

- a total over all BI treated phases (**"BI Total"**)
- a total over all study phases ("**Total**")

Tables of vital signs, ECG and laboratory values will present results by the above mentioned on treatment phase.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewer`s guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

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

The iPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category /Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Incorrect intake of trial medication
	C5	Improper washout between treatments
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
E		**Missing data**
	E1	Certain violations of procedures used to measure secondary data
F		**Incorrect timing**[1]
	F1	Certain deviations from time schedule used to measure secondary data
G		**Other trial specific important deviations**
	G1	Appropriate fasting condition not met
	G2	Other protocol deviations affecting safety and rights

[1] Time deviations will only be flagged as iPD, when leading to exclusion of the entire subject from an analysis set

6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This is the full analysis set population in the sense of ICH-E9 (1). It is used for demographics, baseline characteristics, and safety analyses.
  The ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

Section 7.3.2 of the CTP: *Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol* deviation *relevant for the evaluation. Whether a protocol* deviation *is important will be decided no later than in the Report Planning Meeting.*

Reasons for exclusion of single pharmacokinetic parameters may be:

- *The subject experiences emesis at or before two times median tmax. Median tmax is to be determined for the test product excluding the subjects experiencing emesis.*
- *The subject experiences emesis at any time during the labelled dosing interval.*
- *Time deviations*
- *Use of restricted medications*

- PK analysis set (PKS):
  The PK analysis set (PKS) includes all subjects from the TS receiving BI 730460 who provide at least one secondary PK parameter that was not excluded according to the description above.
  It is used for assessment of dose proportionality and the descriptive analyses of PK parameters.

The descriptive analysis of PK concentrations will be based on the ADS ADPC.

- ECG Pharmacokinetic Concentration Set (ECGPCS):
  This subject set includes all subjects from the TS for whom at least one pair of a valid drug plasma concentration of BI 730460 and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses was provided. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid.
  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 DBLM/RPM before database lock.

Table 6.3: 1 Analysis sets for endpoints/data description

Endpoint/data description	Analysis set		
	TS	PKS	ECGPCS
Primary and further safety endpoints (incl. ECG)	X		
ECG endpoints and plasma concentrations used in exposure-response analysis			X
Secondary PK endpoints		X	
Demographic/baseline data	X		
Important protocol deviations	X		
Disposition	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

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

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

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on treatment QTc/QT intervals into "no new onset" / "new onset" categories, a missing value is obtained only in case that

(i) all on treatment values are missing and
(ii) the baseline value is less than or equal to 500 msec, or missing.

If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as 'no new onset'. If baseline is missing and the maximum on treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a 'new onset' in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as 'no new onset'. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

For placebo subjects, the missing plasma concentration values will be replaced by 0 for the exposure-response analyses. For subjects on active drug, missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of BI 730460 or Placebo.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK

Starting from 72 h post administration a deviation from the scheduled time for PK sampling of ±70 min is acceptable.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 6 h after trial drug administration and ± 30 min thereafter. Starting from 72 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests of ±70 min is acceptable.

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

Unscheduled measurements of laboratory data or vital signs will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation

of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

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

Table 6.7: 1 Time schedule of 12-lead ECG recordings (SRD part)

Visit	**Day**	**Planned time [hh:mm] (relative to drug administration)**	**Study phase**	**Central evaluation**
1	-21 to -1		Screening	NA
2	1	-1:30	Predose	first of three replicate ECG
		-1:15	Predose	first of three replicate ECG
		-1:00	Predose	first of three replicate ECG
		0:30	On treatment	first of three replicate ECG
		1:00		first of three replicate ECG
		2:00		first of three replicate ECG
		3:00		first of three replicate ECG
		4:00		first of three replicate ECG
		6:00		first of three replicate ECG
		8:00		first of three replicate ECG
		10:00		first of three replicate ECG
		12:00		first of three replicate ECG
	2	24:00		first of three replicate ECG
		34:00		first of three replicate ECG
	3	48:00		first of three replicate ECG
3	9 to 13		End of trial examination	NA

At Visits 1 and 3, single ECGs will be recorded.
At Visit 2, triple ECGs will be recorded (three single ECGs within 180 sec).
Prior to study drug administration, 3 triplicate ECGs (9 single ECGs) will be recorded. The vendor will analyse the first single ECG per triplicate for all on treatment timepoints.
The baseline value of an ECG variable is defined as the mean of the first triplicate ECG measurement at -01:30 prior to drug administration.

Section 5.2.4.1 of the CTP: *For the SRD part, central ECG lab evaluation will be performed post-study for the first of three replicate ECGs per time point on Days 1, 2 and 3. For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated. This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured*

semi-automatically. The remaining second and third replicate ECG will be stored for additional analysis if required, e.g. by authorities at a later time point.

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g. HR change from baseline and the plasma concentration measured at planned time 1:00 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded from the analysis will be decided no later than at the RPM. This critical time deviation depends on the PK properties. When plasma concentrations are expected to change only little around a given time point, the acceptable time deviation between ECG recording and PK blood sampling may be bigger.

7. PLANNED ANALYSIS

The placebo group will consist of all placebo treated subjects, regardless of the dose group in which they were treated.

Safety analysis (refer to Section 7.8) will be performed by and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by department Translational Medicine and Clin. Pharmacology (TMCP) and will be presented in Section 15.6 of the CTR.

Descriptive and inferential statistical analyses of PD endpoints (refer to Sections 7.6) will be performed by and will be presented in Section 15.7 of the CTR and in Appendix 16.1.13.6.

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Reporting of Clinical Trials and Project Summaries” [001-MCG-159] (6) with the exception of those generated for PK-calculations.

The individual values of all subjects will be listed, sorted by treatment group, subject number, and visit.
The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations, 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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th 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 (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) 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 will include parameters if they are not flagged for exclusion, that is APEXC is equal to “Included”.

Exclusion of PK 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

The data will be summarised by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 730460.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 Secondary endpoints

Assessment of dose proportionality – SRD part

Dose proportionality of the secondary PK endpoints $AUC_{0-\infty}$ and C_{max} in plasma of BI 730460 will be explored using the power model that describes the functional relationship between dose and PK endpoints based on the PKS. The basic model consists of a regression model applied to log-transformed data (log-transformation refers to using the natural logarithm). The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

The model is described by the following equation:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij} logarithm of the PK endpoint for subject j at dose level i; where i = 1, 2, …, 6, j = 1, 2, …, 6,

α intercept parameter;

β slope parameter;

X_i logarithm of dose i;

ε_{ij} random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

Section 7.1.3 of the CTP: *This equation can be fit as a linear regression model. Based on the estimate for slope parameter (β), a 2-sided 90% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.*

According to the Reference Document 3 of the Boehringer Ingelheim (BI) Statistical Position Paper on Statistical Methods for PK (14), the 90% confidence intervals (CI) should be considered for the assessment of dose proportionality. Therefore, the 90% CI will be used instead of the 95% CI.

This analysis will be accomplished by using the XPKISTAT macro (design DB), based on the PKS.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Graphical displays:

To support the analyses of dose proportionality, a regression plot will be performed, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality ($\beta=1$).

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by treatment group.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

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 and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [001-MCG-156] (9).

The standard AE analyses 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 an AE provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence)

For further details on summarization of AE data, please refer to [001-MCG-156] (9).

Section 5.2.2.1 of the CTP: *The following are considered as AESIs:*

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

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

The analysis of adverse events will be based on the concept of treatment emergent AEs.

Section 5.2.2.2 of the CTP: *The REP for BI 730460, the time interval when measurable drug levels or PD effects are still likely to be present after last administration, is not known for this first-in-human trial at this early stage of development. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment […].*

For more details see the TSAP ADS plan.

According to ICH E3 (10), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the RPM at the latest.

An overall summary of AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT), as well as by treatment, worst intensity, primary SOC and PT. Separate tables will be provided for subjects with other significant AEs according to ICH E3 (10), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.

The SOC and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (11).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM/DBLM at the latest).

Descriptive statistics of laboratory data will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (BP, PR).

Descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

7.8.4 ECG

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as AEs.

No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluations of ECG data will be based on the TS, except the exposure-response analyses, which are based on the ECGPCS set.

The following ECG analyses will only be performed:

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, 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.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.

The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their plasma concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression will be provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF). These figures will be generated for each subject (presented in Statistical Appendix of the CTR), as well as for means per active treatment (presented in the End-of-Text part of the CTR).

The relationship between BI 730460 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 730460 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of C_{max} for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et al. (12) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as continuous covariates, treatment and time as fixed categorical effects, and a random intercept and slope for each subject. For more details refer to Section 9.3.

For visualization, a scatterplot of the BI 730460 plasma concentration against the following individual QTcF values will be provided: For each subject on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this subject and time point. This results in estimates for "individual ΔΔQTcF" values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as and the geometric mean of C_{max} for each dose will additionally be displayed in the plot.

To check model assumptions, the conditional residuals will be plotted and presented in the Statistical Appendix of the CTR. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored in order to better characterise the PK-ECG relationship (e.g. effect compartment models, non-linear models, etc.).

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

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1 using all time points. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

7.8.5 Others

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
4.	*001-MCG-156_RD-01:* "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.
5.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6.	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
7.	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
8.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
9.	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
10.	*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
11.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
12.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn (2017) [R18-0143].
13.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med (2010) [R10-2920].
14.	BI Statistical Position Paper - Statistical Methods for PK - Reference Document 3: Regulatory recommendations for BA/BE trials and implementation instructions in clinical trial documents, version 1.0 (2017).

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	06-MAY-2019		None	This is the final TSAP without any modification

APPROVAL / SIGNATURE PAGE

Document Number: c27412368 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		09 May 2019 07:32 CEST
Approval-Medical Writer		09 May 2019 09:28 CEST
Author-Clinical Trial Leader		09 May 2019 09:59 CEST
Approval-Clinical Pharmacokinetics		09 May 2019 14:33 CEST
Approval-Project Statistician		09 May 2019 14:37 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**