TRIAL STATISTICAL ANALYSIS PLAN

c25683256-01

BI Trial No.:	1408-0002
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 705564 (double-blind, randomised, placebo-controlled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects Including Protocol Amendment 1, 2, 3 and 4 [c18130121-05]
Investigational Product:	BI 705564
Responsible trial statistician:	Phone: Fax:
Date of statistical analysis plan:	14 MAR 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
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BTK	Bruton's tyrosine kinase
BWU	Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled
CARE	Clinical Analysis and Reporting Environment
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
$C_{pre,t}$	Pre-dose concentration of the analyte in plasma immediately before administration of the next dose at time point t, trough level
C_{τ}	Plasma concentration at the end of the dosing interval
$C_{\tau,ss}$	Plasma concentration at the end of steady state
CRF	Case Report Form
CS	Compound symmetry
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation

Term	Definition / description
DB	Dose Proportionality, Between-Subject Design
DBLM	Database Lock Meeting
DG	Dose group
ECG	Electrocardiogram
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart rate
ICH	International Conference On Harmonisation
iPD	Important Protocol Deviation
LI	Linearity Index
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Mida	Midazolam
Min	Minimum
MMRM	Mixed model with repeated measurements
N	Number of non-missing observations
O*C	Oracle Clinical
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set
PT	Preferred Term
REML	Restricted maximum likelihood
QD	Quaque die, once daily
RAGe	Report Appendix Generator system
REP	Residual Effect Period

Term	Definition / description
RPM	Report Planning Meeting
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
TMCP	Translational Medicine and Clinical Pharmacology
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
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 trial database within the Oracle Clinical™ (O*C) system.

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 as planned in the CTP will be performed and are described in more detail in this TSAP. The following change compared to the protocol will be made:

The definition of study phases for the analyses of adverse events is contradictory in the CTP. As the residual effect period (REP) is not known at this early stage of development, the on treatment phase for each subject will be defined as time of first administration of BI / Placebo until 0:00h on the day after the subject's trial termination date. Therefore, no REP and no follow-up period will be considered.

According to the Reference Document 3 of the Boehringer Ingelheim (BI) Statistical Position Paper on Statistical Methods for PK (13), the 90% confidence intervals (CI) should be considered for all described PK analyses. Therefore, the 90% CI will be used instead of the 95% CI.

The ANOVA model for investigation of relative bioavailability will include effects accounting for the following sources of variation: 'subjects' and 'time point' and not 'subject' and 'treatment'.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 5.2.1 of the CTP:

Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with adverse reactions.

Please note, that adverse reactions are defined and analysed as drug-related AEs.

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:

BI 705564

After the first dose:

- *$AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

After the last dose:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

Midazolam (DGs 2 to 5)

After the first and last doses:

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

DGs 1 to 5

It is planned that in total 50 healthy male subjects participate in this study. There were to be 5 sequential dose groups comprising 10 subjects per group. Within each dose group, 8 subjects will receive the active drug and 2 will receive placebo.

Subjects will receive ascending doses of BI 705564 on Day 1 and then over 14 consecutive days from Day 4 to Day17: 10 mg (DG 1), 20 mg (DG 2), 40 mg (DG 3), 60 mg (DG 5) and 80 mg (DG 4).

Table 6.1: 1 Labels for treatments for use in the CTR

Dose group	Treatment		Short label
1-5	P/Q*	Placebo tablet on Day 1 and Days 4 to 17 (+ Midazolam, solution, 75µg, po, qd)	Placebo
1-5	P/Q/R	Placebo tablet (+ Midazolam, solution, 75µg, po, qd)	Placebo total
1	A	BI 705564, 10 mg tablet, qd on Day 1 and Days 4 to 17	BI 10mg
2	B	BI 705564, 2*10mg tablet, qd on Day 1 and Days 4 to 17 + Midazolam, solution, 75µg, po, qd on Day -1 and Day 17	BI 20mg
3	C	BI 705564, 4*10mg tablet, qd on Day 1 and Days 4 to 17 + Midazolam, solution, 75µg, po, qd on Day -1 and Day 17	BI 40mg
5	E	BI 705564, 6*10mg tablet, qd on Day 1 and Days 4 to 17 + Midazolam, solution, 75µg, po, qd on Day -1 and Day 17	BI 60mg
4	D	BI 705564, 8*10mg tablet, qd on Day 1 and Days 4 to 17 + Midazolam, solution, 75µg, po, qd on Day -1 and Day 17	BI 80mg

*: The ‘Placebo’ group in the safety evaluation will consist of all placebo treated subjects of DGs 1-5, regardless of the dose group in which they were treated.

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

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

Please note that all AEs reported between start of trial drug administration and the last per-protocol contact 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 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 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 in the O*C views, 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 from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, 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 minutes via an accompanying Excel spreadsheet (3). The following Table 6.2: 1 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
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
E		**Missing data**
	E1	Certain deviations from 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	Incorrect intake of meal before administration of treatment
	G2	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, as well as for the description of biomarkers and the PD endpoints

Section 7.3.2 of the CTP: *Plasma concentration data and parameters of a subject will be included in the statistical PK analyses, if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Blinded Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.*

Relevant protocol violations may be:

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

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

- *Subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *Missing samples/ concentration data at important phases of PK disposition curve.*

- PK parameter analysis set (PKS):
  The PK parameter analysis set (PKS) includes all subjects from the TS of DGs 1-5 receiving BI 705564 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, for the estimation of the linearity index and for the analysis of the attainment of steady state.

- PKS-Midazolam (PKS-Mida):
  The PKS-Midazolam (PKS-Mida) includes all subjects from the TS receiving BI 705564 / Placebo and Midazolam (DGs 2-5) who provide at least one secondary PK parameter for Midazolam that was not excluded according to the description above.
  It is used for investigation of relative bioavailability.

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

	Analysis set			
Class of endpoint	TS	PKS	PKS-Mida	ECGPCS
Primary and further safety endpoints (incl. ECG)	X			
Secondary PK endpoints (BI 705564)		X		
Secondary PK endpoints (Midazolam)			X	
Demographic/baseline endpoints	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).

For placebo subjects the missing plasma concentration values will be replaced by 0 for the exposure response analysis. 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 first administration of BI 705564 or Placebo (Day 1, -1:00).

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* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day -1 (in DGs 1 to 5) and Day 1 (in DG 8) are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

Starting from 72 h post administration, a deviation from the scheduled time for PK sampling of ± 30 min is acceptable.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 minutes for the first 4 h after trial drug administration and ± 30 minutes thereafter.

[…]

DGs 1 to5

BI 705564 will be administered on Day 1 and on Day 4 through to Day 17 at 0h (planned time).

Midazolam will be administered on Day -1 and on Day 17 at 0h.

The tolerance for drug administration on Days -1, 1 and 17 will be ± 1 min. On all other treatment days it will be ± 10 min.

7. PLANNED ANALYSIS

Section 7.3.4 of the CTP: *As the treatment duration in DG 8 is different from the treatment duration in DGs 1 to 5, all safety outputs for the placebo group will be displayed both, together and separately for DGs 1 to 5 and DG 8.*
The placebo group of DGs 1 to 5 will consist of all placebo treated subjects in DGs 1 to 5, 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 Sections 7.5.2 and 7.6) 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 the department of Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 of the CTR.

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 urinary excretion (not applicable for DG 8) 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 (refer to Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Refer to Section 7.8 for a description of the analysis of safety and tolerability of BI 705564.

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 of BI 705564 (DGs 1 to 5)

Dose proportionality of the PK endpoints $AUC_{\tau,1}$ and C_{max} in plasma after the first dose of BI 705564 and $AUC_{\tau,ss}$ and $C_{max,ss}$ in plasma after the last dose of BI 705564 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; j = 1, 2, …, 8, i = 1,…, 5,
- 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 7.3.2 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 PK endpoint and the log-transformed dose will be checked.*

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.

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

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 (β=1).

Linearity index (DGs 1 to 5)

Analysis of the linearity index (LI) will be based on the PKS.

Section 7.3.2 of the CTP: *Linearity with respect to multiple administration will be explored using the linearity index (LI) that will be computed as follows:*

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

In order to construct a confidence interval for LI, a statistical model using $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ will be set up: A linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random effect and 'AUC type' a fixed effect.

$Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, *where*

Y_{ij} *logarithm of the response (AUC after first dose, AUC after last dose) for subject j and AUC type i; where i=1 (after first dose* (day 1)*) or 2 (after last dose* (day 17 (DGs 1-5))*) and j=1,2,…,8*

μ *the overall mean*

τ_i *the AUC type* i (fixed effect)

s_j *the effect associated with subject j (random effect)*

e_{ij} *random error associated with subject j at AUC type i (assumed to be independent and identically normally distributed)*

The covariance matrix is chosen to be an unstructured matrix to allow for different variances for the two AUC types. In case the model does not converge (due to the unstructured covariance matrix), a compound symmetry structure can be chosen instead.

A pairwise comparison of both areas via the log transformed difference

$$\log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = \log(AUC_{\tau,ss}) - \log(AUC_{0-\infty})$$

will then be performed including calculation of a 2-sided 90% *CI. The back transformed point estimate then represents the estimate of LI. Perfect linearity with respect to multiple administrations holds true if this index equals unity.*

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable across dose levels, they can be analysed simultaneously. The corresponding model will then include the log transformed dose as (additional) covariate.

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

```
PROC MIXED DATA=indata;
CLASS AUCtype subject;
MODEL logkp = AUCtype / DDFM=KR;
REPEATED AUCtype / subject=subject TYPE=UN;
LSMEANS AUCtype / PDIFF CL ALPHA=0.1;
RUN;
```

Attainment of steady state (DGs 1 to 5)

Attainment of steady state will be explored by using the trough concentrations of BI 705564 between Days 4 and 18 and the concentrations taken directly at the end of the first and the last dosing interval for each dose level based on the PKS.

The following Table 7.5.2: 1 summarises the available pre-dose concentrations available for steady state assessment:

Table 7.5.2: 1 Available pre-dose concentrations for steady state assessment

Day	2	4	5	6	9	11	13	15	16
Planned time [h]	24	70:30	96	120	192	240	288	336	360
PK Parameter	C_{τ} / C_{24}	$C_{pre,2}$	$C_{pre,3}$	$C_{pre,4}$	$C_{pre,7}$	$C_{pre,9}$	$C_{pre,11}$	$C_{pre,13}$	$C_{pre,14}$

Day	17	18
Planned time [h]	383	408
PK Parameter	$C_{pre,15}$	$C_{\tau,ss}$ / $C_{24,ss}$

Individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profile will be plotted by dose group.

The attainment of steady state will be explored separately for each dose level by using a repeated measures linear model on the logarithmic scale including ‘time’ as a repeated effect and 'subject' as random effect,.

Section 7.3.2 of the CTP: *The calculation is based on a repeated measures linear model on the logarithmic scale.*

$Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, *where*

Y_{ij} *logarithm of the concentrations for subject j at time i, i=1, 2, … and j=1, 2,..., 8*

μ *the overall mean,*

τ_i *the effect associated with time point i (repeated effect),*

s_j *(random) effect of subject j, j=1, 2,..., 8*

e_{ij} *random error associated with subject j at time i (assumed to be independent and identically normally distributed).*

Dose can be included as an additional covariate, if there is evidence that the trough concentration profiles are comparable across dose levels.

The model will be used to explore the time to steady state by pairwise comparing concentrations pairwise from different time points: log-transformed differences between all subsequent time points ($log(C_{pre,i}/C_{pre,j}) = log(C_{pre,i}) - log(C_{pre,j})$, where $j>i$) will be compared and adjusted means (Least Squares Means) as well as 2-sided 90% CIs will be calculated. Thereafter, these quantities will be back-transformed by exponentiation to give the corresponding (adjusted) ratio and CI.

Comparisons which reveal CIs (for the adjusted ratio) not including 100% will be inspected to determine, if the differences between time points are resulting from not yet attaining steady-state.

As default, the structure of the covariance matrix will be unstructured (type=UN or UNR). In case an unstructured covariance matrix does not work, the following covariance structures will be chosen, in the pre-defined order: Toeplitz or AR1. A Compound Symmetry (CS) structure should not be considered, as this structure already postulates a steady-state. For the approximation of the degrees of freedom the Kenward and Roger method is recommended.

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

```
PROC MIXED DATA=indata;
CLASS subject time;
MODEL logkp = time / DDFM=KR;
REPEATED time / TYPE=UN SUBJECT=subject;
LSMEANS time / DIFF CL ALPHA=0.1;
RUN;
```

If there is evidence that the trough concentration profiles are comparable across dose levels, they may additionally be analysed simultaneously (e.g. if dose proportionality is given). Please refer to BI Statistical Position Paper - Statistical Methods for PK (14).

Investigation of relative bioavailability (Midazolam in DGs 2 to 5)

Relative bioavailability is to be determined on the basis of the secondary PK parameters (C_{max} and $AUC_{0\text{-}tz}$ after the first and last dose) of Midazolam based on the PKS-Mida. Those parameters will be log-transformed (natural logarithm) prior to fitting the model.

Section 7.3.3 of the CTP:

The statistical model used for the analysis of secondary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'subjects' and 'time point'. *The effect 'subjects' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:*

$$Y_{ij} = \mu + \tau_i + s_j + e_{ij}, \text{ where}$$

Y_{ij} = *logarithm of the endpoint for subject j (j=1, 2, …, 8) at Day -1 (first dose of midazolam, i=1) or at Day 17 (last dose of midazolam, i=2),*

μ *the overall mean,*

τ_i *the effect associated with time point i (Day -1 or Day 17)*

s_j *(random) effect of subject j, j=1, 2, …, 8, and*

e_{ij} *random error associated with the subject j at time i (assumed to be independent and identically normally distributed).*

The effect of BI 705564 on midazolam will be estimated by the ratios of geometric means (with the last dose of midazolam as the test and the first dose of midazolam as the reference) and their two-sided 90% confidence intervals (CIs) for C_{max} and $AUC_{0\text{-}tz}$. CIs will be calculated based on the residual error from ANOVA. These quantities will then be back transformed to the original scale to provide the point estimate and 90% CIs for each secondary endpoint.

This model will be evaluated separately for each dose group and, separately, for the placebo group.

The analysis will be accomplished by using the XPKISTAT macro, based on PKS-Mida (design BWU).

As a sensitivity analysis, a joint model for all doses will be investigated, including ‘dose’ as an additional factor. The corresponding ANCOVA model will include the logarithm of the dose as a covariate by using the XPKISTAT macro, including CLASSFIX=dose.

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 Case Report Form (CRF) 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* Adverse Events of Special Interest (*AESIs*)*:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters
  1. *an elevation of* Aspartate Aminotransferase (*AST*) *and/ or* Alanine Aminotransferase (*ALT*) ≥*3-fold* Upper Limit of Normal (*ULN*) *combined with an elevation of total bilirubin* ≥*2-fold ULN measured in the same blood sample, and/or*
  2. *aminotransferase (ALT, and/ or AST) elevations ≥10 fold ULN*

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

Section 5.2.2.2 of the CTP: *The* Residual Effect Period (*REP*) *for BI 705564, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known 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/DBLM at 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). 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 highlighted 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).

Bleeding times as well as, fold changes (value/baseline) and percent changes from baseline will be listed and descriptive statistics over time will be performed.
Individual time courses of bleeding times will be provided. The distribution of bleeding times, as well as the respective fold changes (value/baseline) and percent changes from baseline will be presented by treatment at each time point using boxplots.
For dose groups 1 to 3 (up to 40mg) bleeding time was only measured for 10 min. Therefore bleeding times over 600 sec may not be captured.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate).
Descriptive statistics over time will be performed for oral body temperature.
Body weight at screening and post examination will be listed only.

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 evaluations of ECG data will be based on the TS,

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.	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).
14.	BI Statistical Position Paper - Statistical Methods for PK, 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	14-MAR-2019		None	This is the final TSAP without any modification