TRIAL STATISTICAL ANALYSIS PLAN

c26150818-01

BI Trial No.:	1407-0002
Title:	Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers.
Investigational Product:	BI 730357
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	12 OCT 2018 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
λ_z	Terminal rate constant in plasma
ADS	Analysis Dataset
$Ae_{t1\text{-}t2}$	Amount of analyte that is eliminated in urine from the time interval t_1 to t_2
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}tz}$	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
$AUC_{t1\text{-}t2}$	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
$AUC_{\tau,1}$	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
BMI	Body Mass Index
BWU	Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled
$C_{max(,ss)}$	Maximum measured concentration of the analyte in plasma (at steady state)
$C_{pre,N}$	Predose concentration of the analyte in plasma immediately before administration of the Nth dose and after N-1 doses were administered
CI	Confidence Interval
$CL_{R,\ t1\text{-}t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2
CL/F	Apparent clearance of the analyte in the plasma after extravascular administration
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation

Term	Definition / description
DBLM	Database Lock Meeting
ECG	Electrocardiogram
fe_{t1-t2}	Fraction of given drug excreted unchanged in urine from time point t_1 to t_2
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
IL-17A	Interleukin 17A
iPD	Important Protocol Deviation
LI	Linearity Index
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
MRD	Multiple Rising Dose
mRNA	Messenger Ribonucleic Acid
MRT_{po}	Mean residence time of the analyte in the body after oral administration
PD	Pharmacodynamic(s)
PDS	PD Parameter Analysis Set
PK	Pharmacokinetic(s)
PKS	PK Parameter Analysis Set
POC	Percent of Control
PT	Preferred Term
PTF	Peak-Trough Fluctuation
QD	Quaque die, once daily
$R_{A, AUC}$	Accumulation ratio based on AUC_τ
$R_{A, Cmax}$	Accumulation Ratio based on $C_{max,ss}$
RAGe	Report Appendix Generator system
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RPM	Report Planning Meeting
SAS®	Statistical Analysis System

Term	Definition / description
SD	Standard Deviation
SOC	System Organ Class
SP	Sample Point
$t_{1/2}$	Terminal half-life of the analyte in plasma
$t_{max(,ss)}$	Time from dosing to maximum measured concentration of the analyte in plasma (at steady state)
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WHO-DD	World Health Organization- Drug Dictionary
XPKISTAT	SAS® Macro for analysis of PK data

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 RAVE EDC system.

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

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).

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.

In addition, dose proportionality will not only be assessed for fasted dose groups as described in the CTP but also separately for fed dose groups.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

Safety: Number of subjects with drug-related AEs, measured by the percentage of patients with drug related AEs within 7 days of treatment, which covers more than the residual effect period defined by 5 half-lifes of the study drug.

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 2.1.3 of the CTP:

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)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The study was performed as a double-blind, randomised, placebo-controlled, MRD trial with 7 dose groups. It was planned to assign 12 healthy volunteers in each dose group, 9 to be randomised to BI 730357, and 3 to be randomised to Placebo.

Table 6.1: 1 Dose Groups

Dose Group	1	2	3	4	5	7	8
Daily dose (mg)	25	50	100	200	50	200	400
Status	fasted	fasted	fasted	fasted	fed	fed	fed
Treatment duration (days)	14	14	14	28	14	28	28
Number of subjects	12	12	12	12	12	12	12
Subjects receiving placebo	3	3	3	3	3	3	3
Subjects receiving active drug	9	9	9	9	9	9	9

For details of dosage and formulation see Table 6.1: 2.

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)
- **On treatment**
  - Including residual effect period (REP); i.e. ranging from the time of first administration of BI 730357/Placebo until 7 days after the last administration of BI 730357/Placebo)
- **Follow-Up** (ranging from end of on-treatment phase until end of follow-up)

Table 6.1: 2 Treatments and labels used in the analysis

Treatment as received[2,3]		**Short label**
H	BI 730357, tablet, 25 mg, qd	BI 25mg
I	BI 730357, tablet, 50 mg, qd	BI 50mg
J	BI 730357, tablet, 2*50mg, qd	BI 100mg
K	BI 730357, tablet, 4*50mg, qd, std continental breakfast + 3 times Midazolam, 75µg, po, qd	BI 200mg fed
L	BI 730357, tablet, 8*50mg, qd, std continental breakfast + 3 times Midazolam, 75µg, po, qd	BI 400mg fed
M	BI 730357, tablet, 4*50mg, qd	BI 200mg
O	BI 730357, tablet, 50mg, qd, std continental breakfast	BI 50mg fed
Z	Placebo to match BI 730357 (DG 1-4)	Placebo fast
Y/Z[1]	Placebo to match BI 730357 (+ Midazolam) (DG 5,7,8)	Placebo fed
Y/Z[1]	Placebo to match BI 730357 (+ Midazolam)	Placebo total

[1]As Midazolam is only provided in a micro-dose with no therapeutic effect, groups Y and Z are combined to one Placebo group for all analyses.
[2]All analyses will be performed by treatment as received, i.e. if a subject did not receive the correct treatment, the subject will be counted towards the treatment group of the treatment that was received.
[3]Subjects who received a mixture of drugs due to administration errors will be analyzed as separate groups.

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 and follow-up will not be included in this analysis.

The following totals will be provided in addition (Section 15.3 only):

- a total over all on treatment phases involving BI treatment (“BI total on treatment”)
- a total over all on treatment phases included in this analysis ("Total on treatment")

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))
- Follow-up BI
- Follow-up Placebo

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

- a total over all study phases after BI treatment (“BI total”)
- a total over all study phases ("Total")

Tables of vital signs 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 Data Reviewers guide.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all randomised subjects.
Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the combined report planning and database lock meeting (RPM/DBLM), e.g. deviations in drug administration, in blood sampling etc. At this meeting, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation. A protocol deviation is considered an important protocol deviation (iPD) if it affects the rights or safety of the study subjects or if it can potentially influence the primary outcome measure(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. This last category of iPD forms the basis for the decision of whether a subject does or does not belong to an analysis set. Protocol deviations that do not influence the subject's rights and safety or the evaluability of the subjects for the main study objectives are not considered to be iPDs. These are only considered when checking the trial quality in general.

If any iPDs are identified, they are to be summarized into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet [BI-KMED-COPS-TMP-0001] (2). The following table contains the categories which are considered to be important protocol deviations in this trial. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM/DBLM.

Table 6.2: 1 Important protocol deviations

Category /Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria 1, 2, 3, 4, or 5 not met
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available / not done
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomization order not followed
	C3	Wrong dosage schedule
	C4	Non-compliance
	C5	Medication code broken inappropriately
D		**Concomitant medication**
	D1	Prohibited medication use
	D2	Mandatory medication not taken
E		**Missing data**
	E1	Certain deviations of procedures used to measure primary or secondary data
F		**Incorrect timing**[1]
	F1	Certain deviations of time schedule used to measure primary and secondary endpoints
G		**Other trial specific important violations**
	G1	PDs affecting safety and rights

[1] Time deviations will only be flagged as important PD, when leading to exclusion of the entire subject from an analysis set
Source: 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (3).

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 safety analyses.

- PK parameter analysis set (PKS):
  This subject set includes all subjects from the TS who provide at least one evaluable secondary PK endpoint that does not have an important deviation relevant for the evaluation of PK. Thus, a subject will be included in the PKS, even if he contributes only one PK endpoint value for one treatment period to the statistical assessment.

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

- PD parameter analysis set (PDS):
  This subject set includes all subjects from the TS who provide at least one evaluable secondary or further PD endpoint that does not have an important deviation relevant for the evaluation of PD. Thus, a subject will be included in the PDS, even if he contributes only one PD endpoint value for one treatment period to the statistical assessment.

Table 6.3: 1 Subject sets analysed

	Analysis set		
Class of endpoint	TS	PKS	PDS
Safety endpoints and primary endpoints	X		
PK endpoints		X	
PD endpoints			X
Demographic/baseline endpoints	X		
Important PVs	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 7.5.

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).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study day will be calculated relative to the date and time of the first dose of randomized treatment. The day prior to the start of randomized treatment will be 'Day -1' and the day of the start of randomized treatment will be 'Day 1'; therefore, 'Day 0' will not exist.

Baseline refers to the measurement recorded at randomization (Visit 2); if data at Visit 2 is missing, then data from Visit 1 will be considered baseline.

Time windows are defined in the CTP; the following time windows are planned:

- Screening: 1 to 28 days before drug administration

- Dose groups 1, 2, 3, and 5 treatment period: starts at first day of drug administration (day 1) and ends at last day of drug administration (day 14)

- Dose groups 4, 7, and 8 treatment period: starts at first day of drug administration (day 1) and ends at last day of drug administration (day 28)

- Dose groups 1, 2, 3, and 5 follow up period: starts at 1 day after last drug administration and ends at day 21

- Dose groups 4, 7, and 8 follow up period: starts at 1 day after last drug administration and ends at day 35

- Dose groups 1, 2, 3, and 5 end of study: Day 22 onwards

- Dose groups 4, 7, and 8 end of study: Day 36 onwards

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

7. PLANNED ANALYSIS

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 ClinPK at BI and will be presented in Section 15.6 of the CTR.

Inferential statistical analyses of PD endpoints (refer to Sections 7.5.2 and 7.6) will be performed by and will be presented in Section 15.7 of the CTR and in Appendix 16.1.13.6. Descriptive statistical analyses of PD endpoints will be performed by ClinPK and will be presented in the same sections.

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 analysis of PD parameters, as well as the tables and graphs, will follow the definitions of the BI standard procedure “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics” [001-MCS-36-472] (7).

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

In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places than the raw data. Minima and maxima are presented to the same number of decimal places as the raw data.

For analyte 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 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]).

If applicable, conversion from days to weeks, months and years will be as follows:

- weeks = days ÷ 7
- months = 12 × days ÷ 365.25
- years = days ÷ 365.25.

All p-values will be displayed to four decimal places (or "<.0001" if appropriate).

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" (8). PD parameters will be handled accordingly.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only standard descriptive statistics and summary tables are planned for this section of the report, based on the TS. The data will be summarised by treatment group and a "total" column will be included in the summary table. The following variables will be displayed: gender, ethnicity, race, age, height, weight, etc.

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 coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using 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

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

7.4 PRIMARY ENDPOINTS

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 730357.

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

Dose proportionality of the PK endpoints $AUC_{\tau,1}$ and C_{max} in plasma after the first dose of BI 730357 and $AUC_{\tau,ss}$ and $C_{max,ss}$ in plasma after the dose at day 14 of BI 730357 will be explored using the power model that describes the functional relationship between dose and PK endpoints. The basic model consists of a regression model applied to log-transformed data. The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

The model is described by the following equation:

Section 7.3.2 of the CTP:

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

where

- Y_{ij} *logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, ...,4, j = 1, 2, ..., 9,*
- 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).*

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% 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.

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.

Modelling will be performed twice: Once for all fasted dose groups (groups 1, 2, 3, and 4) and once for all fed dose groups (5, 7, 8).

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

Only the fasted dose groups will be used for assessment of linearity index.

Linearity with respect to multiple administration will be explored for BI 730357 using the linearity index (LI) that will be computed as follows:

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

Section 7.3.2 of the CTP: *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 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 14 for DG 4)*) and j=1,2,…,n*

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 95% 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=0.05;
RUN;
```

Attainment of steady state

Only the fasted dose groups will be used for assessment of attainment of steady state.

Attainment of steady state will be explored by using the trough concentrations of BI 730357 between days 2 and 14 or 28 respectively and the concentrations taken directly at the end of the first and the last dosing interval ($C_{\tau,1}$, $C_{\tau,14/28}$) for each dose level.

The following table summarises the available trough concentrations:

Table 7.5.2: 1 Available trough concentrations Dose Groups 1, 2, and 3

Day	2	3	7	10	11	12	13	14	15
Planned time [h]	23:30	47:30	143:30	215:30	239:30	263:30	287:30	311:30	335:30
PK Parameter	C_{τ}	$C_{pre,3}$	$C_{pre,7}$	$C_{pre,10}$	$C_{pre,11}$	$C_{pre,12}$	$C_{pre,13}$	$C_{pre,14}$	$C_{\tau,ss}$

Table 7.5.2: 2 Available trough concentrations Dose Group 4

Day	2	3	7	8	11	12	13	14	15
Planned time [h]	23:30	47:30	143:30	167:30	239:30	263:30	287:30	311:30	335:30
PK Parameter	C_{τ}	$C_{pre,3}$	$C_{pre,7}$	$C_{pre,8}$	$C_{pre,11}$	$C_{pre,12}$	$C_{pre,13}$	$C_{pre,14}$	$C_{pre,15}$
Day	16	17	21	24	28	29			
Planned time [h]	359:30	383:30	479:30	551:30	647:30	671:30			
PK Parameter	$C_{pre,16}$	$C_{pre,17}$	$C_{pre,21}$	$C_{pre,24}$	$C_{pre,28}$	$C_{\tau,ss}$			

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 by dose group by using a repeated measures linear model on the logarithmic scale including ‘time’ as a repeated effect and 'subject' as random effect.

CTP Section 7.3.2: *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, … I and j=1, 2,…, n*

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,…,n*

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 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 95% 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 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=0.05;
RUN;
```

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 and performed in accordance with BI standards. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyze continuous (quantitative) data.

The individual values of all subjects will be listed, sorted by treatment, subject number and visit.

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).

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT (10).

For analysis multiple AE occurrence data on the 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)
- 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).

The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between the date of the first administration of trial treatment till the date of the last administration of trial treatment + residual effect period will be assigned to the on-treatment period label with the trial treatment assigned on Day 1 of the first treatment cycle. All AEs occurring before the first administration of trial treatment will be assigned to 'screening' and all AEs occurring after the residual effect period will be assigned to 'follow-up'. For details on the treatment definition, see Section 6.1.

Adverse events of special interest (AESIs)

Section 5.1.6.1 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 and/ or ALT ≥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*

Other significant AE (according to ICH E3)

According to ICH E3 (11), 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 a Medical Quality Review Meeting.

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). This table will also be shown by RCTC grade (All, Grade 1, Grade 2 or higher). Separate tables by treatment and RCTC grade will be provided for subjects with other significant AEs according to ICH E3 (11), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events, for subjects with AESIs, for subject with AEs leading to treatment discontinuation, and for subjects with AEs leading to death.

The SOC and PTs will be sorted by frequency (within system organ class). 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] (12). Summary statistics will be based on normalized laboratory values. Both converted and normalized laboratory values will be listed.

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 clinically relevant will be highlighted in the data listings.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator’s comments on the CRF 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 will not be applied in this study.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). In the listing the difference from baseline will also be displayed.

Clinically relevant findings in vital signs will be reported as AEs.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as adverse events (when they occurred during treatment).

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.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
3.	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version, IDEA for CON.
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*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8.	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", 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.	Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 34:6. 1401-1414. 2007.
11.	*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
12.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	12-OCT-18		None	This is the final TSAP without any modification