TRIAL STATISTICAL ANALYSIS PLAN

Global ID:	228892_380931_1.0
BI Trial No.:	0352-2189
Title:	Transporter profiling study for P-glycoprotein 1 (P-gp), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), multidrug and toxin extrusion protein 2-K (MATE2-K), organic anion transporting polypeptide 1B1 (OATP1B1), organic anion transporting polypeptide 1B3 (OATP1B3) and breast cancer resistance protein (BCRP) in healthy subjects and in patients with stage 4 (F4) liver fibrosis / cirrhosis. (including Protocol Amendment No.1 [c38905284-02])
Investigational Product(s):	digoxin, furosemide, metformin, and rosuvastatin
Responsible trial statistician(s):	[redacted] Phone: +[redacted] Fax: +[redacted]
Date of statistical analysis plan:	17 MAR 2025
Version:	1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma from 0 to 24h
[redacted]	
BCRP	Breast Cancer Resistance Protein
BI	Boehringer Ingelheim
BMI	Body Mass Index
[redacted]	
BP	Blood Pressure
CARE	Clinical Analysis and Reporting Environment
CIs	Confidence Intervals
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	Coronavirus disease 2019
[redacted]	
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)

Term	Definition / description
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eDC	Electronic Data Capture
EDMS	Electronic Document Management System
EMA	European Medicines Agency
ES	Enrolled Set
FDA	The Food and Drug Administration
[redacted]	
F/U	Follow-up
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
iPD	Important Protocol Deviations
λ_z	Terminal rate constant in plasma
[redacted]	
MATE1	Multidrug and toxin extrusion protein 1
MATE2-K	Multidrug and toxin extrusion protein 2-K
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number of non-missing observations
[redacted]	
Nobs	Number of observations
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1

Term	Definition / description
OATP1B3	Organic anion transporting polypeptide 1B3
OCT2	Organic cation transporter 2
OPU	Operative Unit
P10	10th percentile
P90	90th percentile
P-gp	P-glycoprotein I
PK	Pharmacokinetics
PKS	PK parameter analysis set
PR	Pulse Rate
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
R	Reference
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RNA	Ribonucleic acid
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
$t_{1/2}$	Terminal half-life of the analyte in plasma
T	Test
[redacted]	
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	
WHO-DD	World Health Organization Drug Dictionary

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, and planning of sample size.

Study data as collected in the Case Report Form (eCRF) will be stored in a trial database within [redacted]. All study data also including external data will then be uploaded to the CDR data warehouse.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), 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 Clinical Trial Report (CTR) appendices).

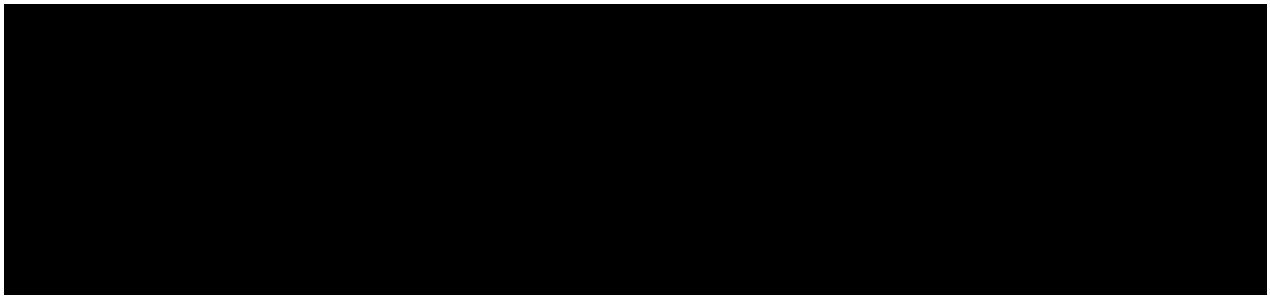
Pharmacokinetic (PK) parameters will be calculated using [redacted] software (version Phoenix 8.1.1, [redacted]).

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 changes compared to the CTP will be made:

According to the study design, the treatment groups incorrectly referred to in the CTP actually correspond to the study groups. Therefore, only the term “study group” is used in the TSAP and the citations from the CTP were corrected in the TSAP.

Smoking and drinking habits were not assessed in physical examinations as in CTP Section 5.2.5 indicated. So these will not be reported.



In Section 7.2.5 of the CTP, the analysis of laboratory data was stated twice, which could be misleading. Therefore, the citation from the CTP was corrected in the TSAP Section 7.8.2 so that values outside the reference range will be flagged and the laboratory values will be analysed descriptively by study group.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.2 of the CTP:
Primary endpoint(s) is to determine the following pharmacokinetic parameters for the different components following a single dose of the transporter cocktail containing digoxin (P-gp), furosemide (OAT1 and OAT3), metformin (OCT2, MATE1 and MATE2-K) and rosuvastatin (OATP1B1, OATP1B3 and BCRP).

- *AUC_{0-24} (area under the concentration time curve of the analyte in plasma over the time interval from 0 to 24 hours) for each component of the transporter cocktail: digoxin, furosemide, metformin, and rosuvastatin.*
- *C_{max} (maximum measured concentration of the analyte in plasma) for each component of the transporter cocktail: digoxin, furosemide, metformin, and rosuvastatin.*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

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

[redacted]

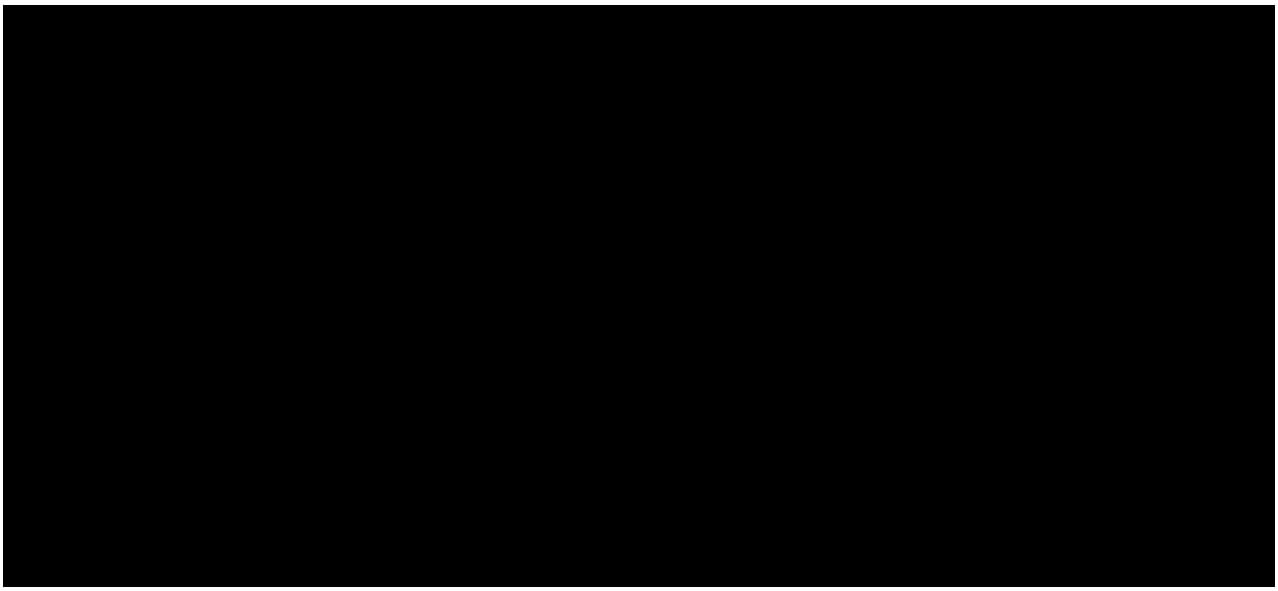
[redacted]

5.3.3 Safety endpoints

Safety endpoints will be assessed based on **Section 2.3.2 of the CTP:**

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

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered and selection of doses, refer to **Section 4 of the CTP**. For information of overall trial design, refer to **Section 3 of the CTP**.

The study will be performed as an open-label, single-dose, non-randomised trial. All subjects will receive the same single dose of the cocktail of drug transporter substrates, including 0.25 mg digoxin, 1 mg furosemide, 10 mg metformin hydrochloride, and 10 mg rosuvastatin.
In total, it was planned that 12 healthy subjects and 18 liver cirrhosis patients, of which 12 compensated F4 Child-Pugh A patients and 6 decompensated F4 Child-Pugh B patients, will enter the trial.

Section 1.2.5 of the CTP:
The Residual Effect Period (REP) of the cocktail is 10 days referring to digoxin, the drug with the longest half-life among the cocktail components […].

The following Table 6.1: 1 defines the three different phases, screening, on-treatment and follow-up phase, for the statistical analysis of AEs.

Table 6.1: 1 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of study cocktail
On treatment	**Cocktail**	Date/time of administration of study cocktail	Date/time of administration of study cocktail + residual effect period (10 days) or 12:00 a.m. on day after subject's trial termination date, whichever occurs first
Follow-up	**F/U**	Date/time of administration of study cocktail + residual effect period (10 days)	12:00 a.m. on day after subject's trial termination date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of laboratory data and vital signs.

AE summary tables will present results for the on-treatment phase, considering data between start of treatment and end of the REP, as well as AEs starting before cocktail intake and deteriorating under treatment, see **Section 7.2.5 of the CTP**.

In Section 9.4 and Appendix 10.6 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included.

Statistical analyses of data such as demography, medical history, concomitant medication, disposition, visit-based data (e.g. vital signs), PK parameters and [redacted] will be presented by study group.

The labels for the designation of the study groups will be used as displayed in Table 6.1: 2.

Table 6.1: 2 Labels defined by study group for tables/figures

Study group		Short label
1	Healthy subjects	Healthy
2	Compensated F4 Child-Pugh A liver cirrhosis patients	Child-Pugh A
3	Decompensated F4 Child-Pugh B liver cirrhosis patients	Child-Pugh B

More details on the technical implementation of these analyses are provided in the Analysis Data Set (ADS) Plan of this TSAP.

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 final RPM. At this meeting, all manual deviations identified at the sites by the Clinical Research Associates 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 (iPDs), and for the process of identification of these, refer to the Boehringer Ingelheim SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

The iPD categories are pre-specified in the DV domain sheet. The iPDs will be identified no later than in the RPM, and the iPD categories will be updated as needed.
If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) and in the decision log. Both documents will be stored within the Trial Master File in Electronic Document Management System.

The iPDs will be summarised and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable as no intercurrent events have been defined in this part of the trial according to **Section 7.2.1 of the CTP**.

6.4 SUBJECT SETS ANALYSED

The enrolled set (ES), treated set (TS), and pharmacokinetic parameter analysis set (PKS) will be used as defined in the **CTP, Section 7.2**:

- *Enrolled set (ES): This subject set includes all subjects having signed informed consent and who were screened for inclusion into the study. The enrolled set will be used for analyses of subject disposition.*
- *Treated set (TS): The treated set includes all subjects who signed informed consent and were treated with at least one dose of study drug. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Descriptive and model-based analyses of PK parameters will be based on the PKS.*

[redacted]

The following Table 6.4: 1 illustrates the different subject sets used for analyses.

Table 6.4: 1 Subject sets analysed

	Subject set			
Class of analysis	**Enrolled set**	**Treated set**	**PKS**	**[redacted]**
Primary endpoints			X	
Further PK endpoints			X	
[redacted]				X
Further safety endpoints		X		
Disposition	X			
iPDs		X		
Demographic & baseline		X		

Details on possible relevant protocol deviations and non-evaluability of plasma and urine concentrations are given in **CTP Section 7.2.**

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The imputation of missing values for safety parameters is not intended. One exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

Section 7.3.2 of the CTP:
PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

Missing data and outliers of PK data are handled according to BI standards (4) and (5).

If a subject is removed from or withdraws from the trial prior or after the administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be entered in the CRF and will be reported in the CTR.

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) or "ADYP" (PD parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) 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 APEX is equal to "Included".

Section 7.2 of the CTP:
Exclusion of a subject's data will be documented in the CTR. [...]

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) or "ADYC" (PD concentrations per time-point) contains column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) 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 λz) only; the value is included for all other analyses.

Further details are given in BI-KMED-TMCP-MAN-0014 "Noncompartmental PK/PD Analyses of Clinical Studies" (5) and BI-KMED-TMCP-MAN-0010: "Description of Analytical Transfer Files, PK/PD Data files and ADA files" (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last available value determined prior to administration of study cocktail will be defined as baseline.

Adherence to time windows will be checked at the final RPM. Time windows are defined in **Section 6.1 of the CTP**:
The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min.

Unscheduled measurements of laboratory data and vital signs data 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.

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by the [redacted] and will be presented in Sections 9.1 to 9.4 of the CTR and in Appendix 10.6 and 10.5.1.

Statistical model-based analysis of PK and [redacted] will be performed by BDS and will be presented in Section 9.5 of the CTR and in Appendix 10.5.3.

Descriptive data analysis of PK and [redacted] will be performed by the [redacted] and will be presented in Section 9.6 and 9.7 of the CTR and in Appendix 10.5.5 and 10.5.6.

The format of the listings and tables will follow the BI standards (7) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (8).

The individual values of all subjects will be listed, sorted by study group, subject number, and visit. The listings will be included in Appendix 10.6 of the CTR.

For End-Of-Text tables, the set of summary statistics for continuous variables is:

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

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	number of observations
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 to 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. The estimated values of inferential statistics analysis will be rounded to 2 decimal places.

Descriptive statistics of PK parameters and [redacted] will be calculated if N≥2 in each study group.

Data of a study group will be included in the regression model if N≥3 subjects contribute with data.

It should be noted that due to the exploratory nature of the analyses and due to the possibly relatively small number of subjects in a study group, the descriptive statistics or statistical results should be interpreted generally with caution. (When the number of subjects is low, data of single subjects has a higher impact on results.)

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective study group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. 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 brackets (e.g. (mg)).

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 study group and additionally in total for the Appendix 10.5.1.4:1.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant 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.

Only descriptive statistics are planned for this section of the report, based on the TS. The data will be summarised by study group.

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

7.3 TREATMENT COMPLIANCE

Section 4.5 of the CTP:

Compliance will be assured by administration of trial medication in the study centre under supervision of the investigating physician or a designee by the so-called four-eye principle (two-person rule). For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g., reconstitution), if correct dosage cannot be ensured otherwise. The measured plasma concentrations and urinary excretion of trial medication will provide additional confirmation of compliance.

Treatment compliance will not be analysed as a specific endpoint. Any deviation from complete intake will be addressed in the final RPM (see Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

7.4.1 Main analysis

The primary endpoints as specified in section 2.2 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472[sic]*). The analysis will be based on the PKS and will be descriptive in nature.*

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: '[study] *group', age, and BMI. All effects will be considered as fixed. The model is described by the following equation:*

$$y_{km} = \mu + \pi_k + age_m + BMI_m + e_{km},$$

where

- y_{km} *= logarithm of response measured on subject m* [from study group] *k,*
- μ *= the overall mean,*
- π_k *= the kth* [study] *group effect, i.e. degree of hepatic impairment, k=1 for healthy/normal (Group 1), 2 for Group 2* [Child-Pugh A] *or 3 for Group 3* [Child-Pugh B] *respectively,*
- age_m*= the age of subject m,*
- BMI_m*= the BMI of the subject m,*
- e_{km} *= the random error associated with the kth* [study] *group effect for subject m*
- *where* $e_{km} \sim N(0, \sigma_k^2)$ *i.i.d,*

Point estimates for the ratios of the geometric means (test [T]/reference [R]) for the primary endpoints (see section 2.2) and their two-sided 90 % confidence intervals (CIs) will be provided [where reference is healthy subjects and the test group are the individual patient groups].
For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means).

Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90 % CIs for each endpoint.

Note: 001-MCS-36-472 = BI-KMED-TMCP-HTG-0025 & BI-KMED-TMCP-MAN-0014 (4, 5; BI SOP was replaced).

All parameters are calculated and analysed descriptively by study group in addition to the model-based approach.

These analyses will be based on the PKS.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary objective analysis

This section is not applicable as no secondary endpoint has been specified in the protocol.

[redacted]

7.6.3 Safety endpoints

Safety endpoints and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

Since only a single dose is administered per subject, a listing will be sufficient to give account of the extent of exposure.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

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

The analyses of AEs will be descriptive in nature. For further details on summarisation of AE data, please refer to "Analysis and Presentation of AE data from clinical trials" (9) and "Handling of missing and incomplete AE Dates" (3).

Section 7.2.5 of the CTP:
Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e., all adverse events occurring between start of treatment and end of the REP [(10 days)]. *Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.*

For details on the treatment definition, see Section 6.1.

According to ICH E3 (10), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the CTR. These will be any non-serious adverse event that led to an action taken with study drug (e.g. dose reduced or interrupted).

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of adverse events of special interest (AESIs).

The following are considered as AESIs:

Section 5.2.6.1 of the CTP:
Hepatic injury
Patients with cirrhosis: Hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- *Patients with **normal** aminotransferases at baseline:*
  1. *ALT and/or AST ≥ 3xULN combined with a) or b) or c)*
     a) *Total bilirubin ≥ 2xULN at the same visit or within 30 days of each other*
     b) *INR ≥ 1.5xULN at the same visit or within 30 days of each other*
     c) *New-onset or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia (> 5 %)*

  OR
  2. *ALT and/or AST ≥ 5xULN*
- *Patients with **abnormal** ALT, AST, total bilirubin, or INR at baseline:*
  1. *ALT and/or AST ≥ 2x baseline or ≥ 300 U/L combined with a) or b) or c)*
     a) *Total bilirubin > 2x baseline*
     b) *INR > 1.2x baseline*
     c) *New-onset or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia (> 5 %)*

  OR
  2. *ALT and/or AST ≥ 3x baseline*

These lab findings constitute a hepatic injury alert. In such instances the testing should be repeated within 48 to 72 hours. If elevations persist, the patients need to be followed up according to the "DILI checklist" provided via eDC. Patients should be followed up until resolution of symptoms or signs in the above stated situations. Patients should also be referred to their hepatologist.
In case of new 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 these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described above should be followed.

For healthy volunteers no AESIs are defined.

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

The intensity (severity) and the causal relationship of AEs are considered according to **Section 5.2.6.1 of the CTP:**
Intensity (severity) of AEs
The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Causal relationship of AEs
Medical judgement should be used to determine the relationship between the adverse event and the trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

The frequency of subjects with AEs will be summarised by study group, primary System Organ Class (SOC), and preferred term (PT). Separate tables will be provided for subjects with serious AEs (SAEs), AESIs, drug-related AEs, drug-related SAEs and AE intensity.

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

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and PT. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and based on BI standards (11).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Section 7.2.5 of the CTP:
Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range [will be flagged]. [Study] *groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.*

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

Descriptive statistics of laboratory data including change from baseline (see Section 6.7) will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, the last measurement before drug administration will be used.

7.8.3 Vital signs

The analyses of vital signs (BP and PR) will be descriptive in nature.

Descriptive statistics of vital signs including change from baseline (see Section 6.7) will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, the last measurement before drug administration will be used.

Clinically relevant findings in vital signs will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Clinically relevant findings in ECG will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such. No separate listing or analysis of ECG data will be prepared.

7.8.5 Physical examination

Clinically relevant findings in physical examination will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such. No separate listing or analysis of physical examination data will be prepared.

7.9 OTHER ANALYSIS

[redacted]

7.9.2 Analyte concentration

The analyte concentrations will be descriptively analysed on the planned sampling times.

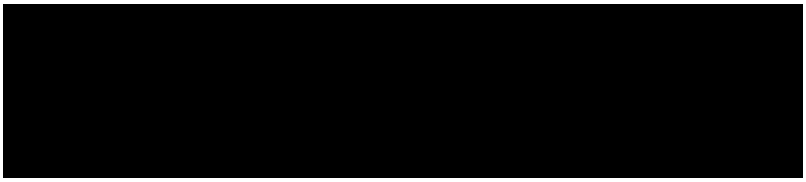
Section 7.2 of the CTP:
Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

9. 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-VQD-12045_40-413:* “Identify and Manage Important Protocol Deviations (iPD)”, current version, KMED.
3.	*BI-KMED-BDS-HTG-0035:* “Handling of Missing and Incomplete AE Dates”, current version, KMED.
4.	*BI-KMED-TMCP-HTG-0025:* “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version, KMED
5.	*BI-KMED-TMCP-MAN-0014:* “Noncompartmental PK/PD Analyses of Clinical Studies”, current version, KMED
6.	*BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files, PK/PD Data files and ADA files”, current version, KMED.
7.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, KMED
8.	*BI-KMED-TMCP-OTH-0003*: “Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses”, current version, KMED.
9.	*BI-KMED-BDS-HTG-0066:* “Analysis and Presentation of AE data from clinical trials”, current version, KMED.
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.	*BI-KMED-BDS-HTG-0042:* “Handling, Display and Analysis of Laboratory Data”, current version, KMED.



11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**17-MAR-25**	[redacted]	None	This is the final TSAP.