TRIAL STATISTICAL ANALYSIS PLAN

c35710967-01

BI Trial No.:	1411-0013
Title:	Pharmacokinetics and pharmacodynamic effects of different single oral doses of BI 474121 in healthy male subjects (Revised Protocol including Amendments 1-3 [c30700234-04])
Investigational Product(s):	BI 474121
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	02 JUL 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CSD	Company Standard Displays
CSF	Cerebrospinal fluid
cGMP	Cyclic guanosine monophosphate
$cGMP_{base}$	Baseline cGMP
$cGMP_{max}$	Maximum cGMP in a defined time window
$cGMP_{min}$	Minimum cGMP in a defined time window
CV	Arithmetic coefficient of variation
DG	Dose group
DILI	Drug induced liver injury
F/U	Follow Up
gCV	Geometric coefficient of variation
gMean	Geometric mean
λ_z	Terminal rate constant of the analyte in plasma
LLOQ	Lower limit of quantification
LLT	Lower level term
Max	Maximum

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
PfoS	Powder for oral solution
PDS	PD parameter analysis set
PDS-sens	PDS sensitivity analysis set
PKS	PK parameter analysis set
Q1	1st quartile
Q3	3rd quartile
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SD	Standard deviation
SOC	System organ class
T	Test treatment
t_{max}	Time of maximum measured concentration of the analyte in plasma
TS	Treated set
ULN	Upper limit of normal
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, planning of sample size, randomisation.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1 or higher, [redacted]).

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 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 changes compared to the clinical trial protocol will be made:

The definition of the treated set was slightly adapted. The treated set will not be based on "randomized" subjects but will include all entered subjects who were treated with one dose of study medication.

[redacted]

For the second primary endpoint, a statistical model only including fixed effects was defined in the protocol. The statistical model used for the primary analysis was changed to a mixed model in order to take the repeated measures within each subject into account. Treatment group specific effects of CSF vs. plasma will be evaluated by including an interaction term of treatment group and the PK matrix to the model. The originally defined model will be computed as a sensitivity analysis.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

This trial has two primary endpoints:

Section 2.1.2 of the CTP:

The following pharmacodynamic parameters will be determined

- *Maximum exposure-related change from baseline (calculated as ratio) of cGMP in CSF (see* CTP *Section 7.3.1)*

The following pharmacokinetic parameters will be determined for BI 474121:

- *C_{max} ratio of BI 474121 in CSF compared to plasma*

A precise definition of the first primary endpoint is provided in

Section 7.3.1 of the CTP:

Maximum measured exposure-related cGMP concentration in CSF ($cGMP_{max}$):
In subjects treated with BI 474121 this is the maximum cGMP value measured within 1 h prior and 4 h post BI 474121 C_{max} in CSF.
For subjects treated with placebo, this is the maximum cGMP value measured within 1 h prior to and 4 h after the median BI 474121 t_{max} in CSF of the BI 474121 treated subjects. That means, when comparing placebo and 20 mg (after Part 1), the median BI 474121 t_{max} in CSF of the subjects treated with 20 mg is used, and when comparing placebo and 40 mg (after Part 2), the median BI 474121 t_{max} in CSF of the subjects treated with 40 mg will be considered. For the final analysis, the median BI 474121 t_{max} in CSF for subjects treated with the highest investigated dose group will be used.
The t_{max} values of BI 474121 in CSF used to determine the time window for cGMP are based on planned times. In case one of the considered median BI 474121 t_{max} in CSF is not defined unequivocally the smallest planned time fulfilling the median properties will be used.

Additionally the minimum measured exposure-related cGMP concentration in CSF ($cGMP_{min}$) will be determined, using the same time interval around C_{max} of BI 474121 in CSF as used for $cGMP_{max}$.

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 2.1.2 of the CTP:

- *Maximum measured concentration (C_{max}) of BI 474121 in plasma*
- *Maximum measured concentration (C_{max}) of BI 474121 in CSF*
- *Time from dosing to maximum measured BI 474121 concentrations in plasma and CSF (t_{max})*
- *Maximum measured exposure-related cGMP concentration in CSF*

[redacted]

Safety and tolerability endpoints

Section 2.2.2.2 of the CTP: *Safety and tolerability of BI 474121 will be assessed based on:*

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

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups and selection of doses, please refer to CTP Section 4.

This trial in healthy male subjects consists of three trial parts with the same investigational product, BI 474121, administered in different single doses (A: 40mg, B: 20mg, C: 10mg, D: 2.5mg, see Table 6.1: 1). Preliminary analyses will be performed after each trial part. Escalation to the next part will depend on the results of these analyses. If all trial parts will be conducted, a total of 24 subjects will be included to the trial.

Part 1 will be conducted as a single-blind, randomized, placebo-controlled study with 10 subjects (n=6 **treatment B**, n=4 Placebo).

Part 2 will be an open-label, non-randomized study with 6 subjects on **treatment A**.

Part 3 will be performed as an open-label, randomized study with 8 subjects in two different dose groups (n=4 in each treatment **C and D**).

For details of dosage and formulation see Table 6.1: 1:

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		**Short label**
P	Placebo	Plc tab
D	BI 474121, 2.5mg, tablet, qd, oral	BI 2.5mg tab
C	BI 474121, 10mg, tablet, qd, oral	BI 10mg tab
B	BI 474121, 20mg, tablet, qd, oral	BI 20mg tab
A	BI 474121, 40mg, tablet, qd, oral	BI 40mg tab

Section 1.2.2 of the CTP:

The Residual Effect Period (REP) of BI 474121, when measurable drug levels and/or pharmacodynamic effects are still likely to be present, is not known for this trial. Conservatively, a minimum observation period of at least 5-fold estimated $t_{1/2}$ has been selected, and thus a REP of 7 days is assumed (…).

For statistical analysis of AEs, vital signs and laboratory parameters, the following analysis phases are defined for each subject:

Table 6.1: 2 Analysis phases

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of administration of study drug
On-treatment	**Plc tab** **BI 40mg tab** **BI 20mg tab** **BI 10mg tab** **BI 2.5mg tab**	Date/time of administration of study drug	Date/time of administration of study drug + 7 days (168h) or 0:00h (midnight) on the day after trial completion date, whatever occurs first
Follow-up	**F/U Plc tab** **F/U BI 40mg tab** **F/U BI 20mg tab** **F/U BI 10mg tab** **F/U BI 2.5mg tab**	Date/time of administration of study drug + 7 days (168h)	0:00h (midnight) on the day after trial completion date

The following AE displays will be provided in the report:

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

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

For Section 15.3:

- a total over all on treatment phases with BI **("BI Total"**)

and for Section 15.3. and 16.1.13.1.8:

- a total over all on treatment phases **("Total"**)

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, screening and follow-up periods will be included and no totals will be provided.

Tables of vital signs and laboratory values will present results by the above mentioned on-treatment phases.

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

In outputs for ClinicalTrials.gov and EudraCT all study parts will be combined.

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (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).

Section 7.3 of the CTP: *Important protocol deviation (IPD) categories will be specified in the iPD specification file prior to trial initiation, IPDs will be identified no later than in the Report Planning Meeting, 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 and the decision log. The iPD specification file (e.g. the DV domain specifications) will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

- *Treated set (TS):*
  The treated set includes all entered *subjects who were treated with one dose of study drug (i.e. verum or placebo). 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 or secondary 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'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment. Descriptive and model based analysis of PK parameters will be based on the PKS.
- *Pharmacodynamic parameter analysis set (PDS):*
  This set includes all evaluable subjects from the TS who provide at least one evaluable pre- and post-dose measure for a PD endpoint. Descriptive and model based analysis of the PD endpoints will be based on the PDS.

In addition to the analysis sets defined in the CTP, the following set of subjects will be used in the analysis:

[redacted]

Section 7.3 of the CTP:

Pharmacokinetics

The pharmacokinetic parameters listed in CTP *Section 2.1 and 2.2 for drug BI 474121 will be calculated according to the relevant BI internal procedures.*

Plasma and CSF concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the 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 deviations 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 and CSF concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The 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*

Plasma and CSF 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. Descriptive and inferential statistics of PK parameters will be based on the PKS.

The same criteria will be considered regarding PD concentrations and/or parameters for evaluability.

Table 6.3: 1 Subject sets analysed

	Subject analysis set			
Class of endpoint	TS	PKS	PDS	PDS-sens
Analyses of PK endpoints		X		
Analyses of PD endpoints			X	X
Disposition	X			
Demographic/baseline parameters	X			
Important protocol deviations	X			
Exposure	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 BI-KMED-BDS-HTG-0035) (3).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (4) and BI-KMED-TMCP-MAN-0014 (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is generally defined as the last measurement before administration of trial medication (BI 474121 or Placebo).

The baseline cGMP concentration ($cGMP_{base}$) is defined in **Section 7.3.1 of the CTP:**

The baseline cGMP value of a subject is defined as the arithmetic mean of all pre-dose measurements above LLOQ (lower limit of quantification) *obtained in that subject. In case all three values are BLQ* (below limit of quantification)*, the LLOQ of the bioanalytical assay will be used as baseline value.*

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 the end of trial examination are provided in the CTP *Flow Chart.*

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

The acceptable deviation from the scheduled time for vital signs, ECG, and sample collection for laboratory tests will be ± 30 min.

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

If not stated otherwise, the trial parts will be evaluated together. Outputs will be sorted by treatment group (Placebo, BI 2.5mg, BI 10mg, BI 20mg, BI 40mg).

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

Statistical model-based analysis of PK and PD endpoints will be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK endpoints and concentrations will be performed by the [redacted]) at [redacted] and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

Descriptive data analysis of PD/biomarker parameters will be performed by the [redacted] at [redacted] and will be presented in Section 15.7 of the CTR and Appendix 16.1.13.6.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (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 and non-PD 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 and PD 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 to the data format of the respective concentrations. The descriptive statistics of PK and PD 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 (%). 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 brackets (e.g. (mg)).

Exclusion of PK and PD parameters

The ADS “ADPP” (PK parameters) or “ADYP” (PD parameters) contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK or PD parameter and an analysis flag comment (APEXCO). All analyses based on the PKS and PDS, respectively, will include parameters if they are not flagged for exclusion, that is APEXC is equal to “Included”.

Exclusion of PK and PD concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) or “ADYC” (PD concentrations per time-point or per time-interval) contains column variables ACEXC and 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 *BI-KMED-TMCP-MAN-0014* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5) and *BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files" (8).

Interim analyses

No inferential statistical interim analysis is planned. Preliminary analyses of safety, PK and PD parameters were performed after trial part 1 and 2 (including C_{max} and AUC_{0-24} of BI 474121 in plasma and cGMP in CSF). The preliminary analyses after Part 1 and 2 were done to evaluate the proof-of-pharmacological-principal for BI 474121. Furthermore a preliminary analysis after Part 3 (PK and PD only) will be done to support dose finding for trial 1411-0003. In contrast to the final PK and PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times. All details about the preliminary analyses are described in a trial-specific logistics plan (9).

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 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.

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

7.4 PRIMARY ENDPOINTS

The final statistical analysis will include data from all trial parts.
Additionally to the model-based analysis of the primary endpoints as described below, the primary endpoints will be analysed using descriptive statistics.

7.4.1 Primary analysis of the primary endpoints

7.4.1.1 Analysis of first primary endpoint

Section 7.3.2 of the CTP:

Maximum exposure-related change from baseline of cGMP in CSF

The maximum exposure-related change from baseline in cGMP in CSF will be explored using an ANCOVA model, which can be described by the following equation:

$$y_{i,j} = \alpha\ ln(cGMP_{base,i}) + treatment_j + e_{i,j},$$

Where

$y_{i,j}$ = *natural logarithm of the ratio* $cGMP_{max,i}/cGMP_{base,i}$ *for subject i receiving treatment j*

α = *slope parameter for the baseline effect*

$cGMP_{base,i}$ = $cGMP_{base}$ *for subject i*

$treatment_j$ = *the* j^{th} *treatment effect, (placebo, 2.5mg, 10mg, 20 mg, 40mg)*

$e_{i,j}$ = *random error associated with* i^{th} *subject who received treatment j*

For the endpoint $cGMP_{max}/cGMP_{base,}$ *the difference between the expected means for ln(T) – ln(R) will be estimated by the difference in the corresponding least square means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator and interval estimates.*
Estimates will be computed for the different dose groups (T) versus placebo (R), respectively.

The analysis of the first primary endpoint will be performed on the PDS. The implementation for this analysis in SAS will be accomplished by using the MIXED procedure within the CSD macro %X_TLF_ANCOVA1:

```
PROC MIXED DATA=patdata CL METHOD=reml ORDER=data;
        CLASS treatment (REF='Plc tab');
        MODEL logpd = logbaseline treatment / SOLUTION;
        LSMEANS treatment / CL DIFF ALPHA=0.1;
RUN;
```

7.4.1.2 Analysis of second primary endpoint

C_{max} ratio of BI 474121 in CSF compared to plasma

The relationship between exposures of BI 474121 in CSF compared to plasma will be explored using a mixed effects model, which can be described by the following equation:

$$\ln(Cmax_{i,j,k}) = subject_i(treatment_j) + treatment_j + pkmatrix_k + e_{i,j,k}$$

where

$subject_i$	=	the i^{th} subject effect, a random effect nested within treatment group j
$treatment_j$	=	the j^{th} treatment effect (2.5mg, 10mg, 20 mg, 40mg)
$pkmatrix_k$	=	the k^{th} substance effect (CSF or plasma)
$e_{i,j,k}$	=	random error associated with i^{th} subject who received treatment j in substance k

The effect 'subject nested within treatment' will be considered random, while all other effects will be considered as fixed. The pharmacokinetic parameter C_{max} will be log transformed (natural logarithm) prior to fitting the model. The difference between the expected means for log(CSF)- log(plasma) will be estimated by the difference in the corresponding least square means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give an overall point estimator and interval estimates for the geometric mean of the ratio between exposure in CSF and exposure in plasma.

In further analyses, the mixed model (as outlined above) will be supplemented by an interaction term of treatment and PK matrix. This model will be used to derive estimates of exposure in CSF vs. plasma by treatment.

The analysis of the second primary endpoint will be performed on the PKS. The implementation for this analysis in SAS will be accomplished by using the PROC MIXED procedure:

(1) primary model:

```
PROC MIXED DATA=data METHOD=reml ORDER=data;
        CLASS treatment subject pkmatrix;
        MODEL logcmax = treatment pkmatrix;
        RANDOM subject(treatment) /S;
        LSMEANS pkmatrix / CL DIFF ALPHA=0.10;
        ODS  OUTPUT lsmeans=lsmeans diffs=diffs;
RUN;
```

(2) model for estimates by treatment group:

```
PROC MIXED DATA=data METHOD=reml ORDER=data;
        CLASS treatment subject pkmatrix;
        MODEL logcmax = treatment pkmatrix treatment*pkmatrix;
        RANDOM subject(treatment) /S;
        LSMEANS treatment*pkmatrix / SLICE=treatment CL DIFF ALPHA=0.10;
        ODS  OUTPUT slices=slices lsmeans=lsmeans diffs=diffs;
RUN;
```

[redacted]

7.5 SECONDARY ENDPOINTS

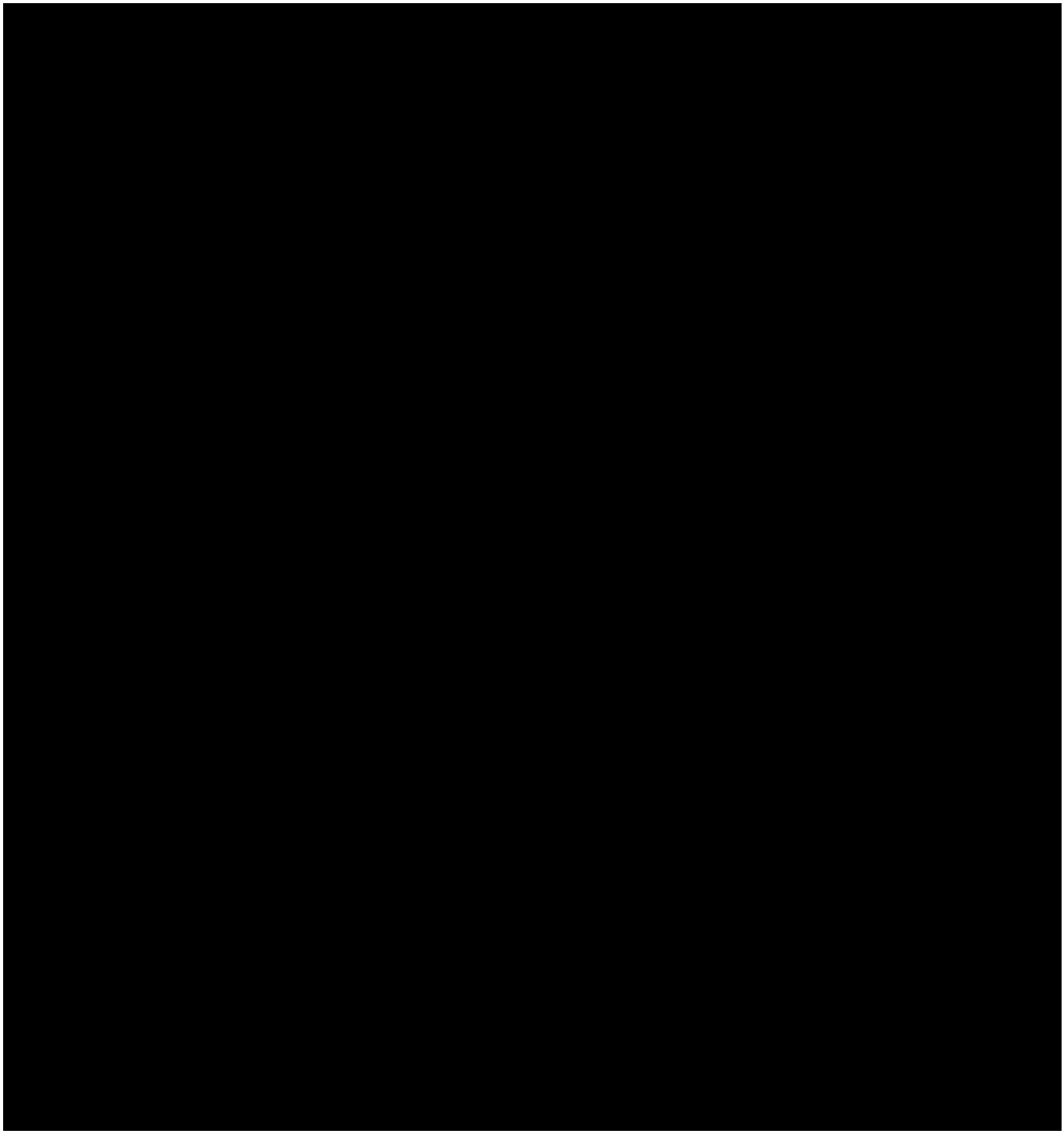
7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoints

The analysis of secondary endpoints will be performed as defined in the CTP, i.e. using descriptive statistics.

[redacted]



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.

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.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (10) and [BI-KMED-BDS-HTG-0066] (11) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', 'on-treatment' or 'follow-up' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.5.1.4 of the CTP: *The following are considered as AESIs:*

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

According to ICH E3 (12), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The system organ classes 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.
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 [BI-KMED-BDS-HTG-0042] (13).

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 possibly clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

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

7.8.3 Vital signs

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

For vital signs, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

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

7.8.4 ECG

ECG recordings were 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 AEs (when they occurred during treatment), and will be analysed as such.
No separate ECG listing will be provided.

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. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information was loaded into the trial database at trial initiation for all trial parts.

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.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
3.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
4.	*BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
8.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
9.	[redacted] Single rising dose snapshot analysis – Logistics plan for trial 1411-0013, version 4.0, BIRDS.
10.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
11.	BI-KMED-BDS-HTG-0066: "Analysis and Presentation of AE data from clinical trials", current version, KMED.
12.	*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.
13.	*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	**02-JUL-21**	[redacted]	None	This is the final TSAP