TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42155232-01**
BI Trial No.:	**1305-0025**
Title:	Pharmacokinetics, safety and tolerability of BI 1015550 following oral administration in male and female participants with different degrees of renal impairment (severe and moderate) as compared with individually matched male and female participants with normal renal function (an open-label, non-randomised, single dose, parallel, individual-matched design trial) Including Protocol Amendment 1 [c40079634-02]
Investigational Product:	BI 1015550
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	18 SEP 2023
Version:	1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
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
BI	Boehringer Ingelheim
BLQ	Below Limit of Quantification
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
C-SSRS	Columbia-Suicidal Severity Rating Scale
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EudraCT	European Clinical Trials Database
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
LLOQ	Lower limit of quantification

Term	Definition / description
MedDRA	Medical Dictionary For Regulatory Activities
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
RAGe	Report appendix generator
REP	Residual effect period
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SDL	Subject Data Listing
SIB	Suicidal Ideation and Behaviour
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range

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 revised Clinical Trial Protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the CTP and its 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 revised 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 as collected in the eCRF will be stored in a trial database within the RAVE EDC system. 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 CTR appendices).

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the revised CTP will be performed and are described in more detail in this TSAP.

After CTP finalisation a new analysis method was made available to differentiate between the chiral inversion of BI 1015550 (R-enantiomer, pharmacologically active) and the PD 1420 (S-enantiomer, pharmacologically inactive). It was decided that data from the chiral bioanalytical assay measuring R-BI 1015550 (R-enantiomer) is more relevant for further drug development than the previously available assay measuring BI 1015550 (measured with the non-chiral bioanalytical assay and consisting of both, the R- and S-enantiomer). To enable the comparison of in-vivo data between these two assays, all PK endpoints will be determined for R-BI 1015550 and BI 1015550 with the main focus on R-BI 1015550.

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints of R-BI 1015550 and BI 1015550:

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

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoints are PK endpoints of R-BI 1015550 and BI 1015550:

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

[redacted]

5.3.2 Safety parameters

Safety and tolerability of BI 1015550 will be assessed in participants with different degrees of renal impairment based on further safety parameters defined in **Section 2.2.2.3** of the **CTP:**

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *Assessment of suicidal ideation and behaviour (C-SSRS)*
- *12-lead ECG*
- *Vital signs (BP, pulse rate)*

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

For basic study information on treatments to be administered and assignment of impairment groups, cf. **Section 4** of the **CTP**.

The term 'impairment group' will be used to denote the 4 groups of interest: Sev, Mod, Control Sev and Control Mod, see Table 6.1: 1. The term 'impaired group' only refers to the severe and moderate impairment group without the control groups.

All participants will receive one single dose of 18 mg BI 1015550.

The participants with renal impairment will be assigned to the impairment groups according to their renal impairment based on their eGFR (moderate or severe). Participants with normal renal function will be matched individually to a participant* with impaired renal function by gender, race, age (within ±10 years) and weight (within ±15%) and assigned to the corresponding control groups as described in **CTP Section 3.1** and **4.1.3**.

Table 6.1: 1 Group labels used in analysis

Group	Details	Label
1	Severe renal impairment (eGFR at screening 15-29 mL/min/1.73 m^2)	Sev
2	Normal renal function individually matched to participants of Group 1 (eGFR at screening ≥90 mL/min/1.73 m^2) *	Control Sev
3	Moderate renal impairment (eGFR at screening 30-59 mL/min/1.73 m^2)	Mod
4	Normal renal function individually matched to Group 3 (eGFR at screening ≥90 mL/min/1.73 m^2) *	Control Mod

* Each participant with normal renal function may be matched to multiple participants with renal impairment across groups and can be matched to only 1 participant within a renal impaired group (moderate, severe).

For statistical analysis of AEs, the following analysis phases are defined for each participant.

Table 6.1: 2 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data, vital signs and C-SSRS

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	Screening	Date of informed consent	Date/time of administration of study drug
On-treatment	Control Mod, Mod, Control Sev or Sev	Date/time of administration of study drug	Date/time of administration of study drug [redacted]
Follow up	F/U Control Mod, F/U Mod F/U Control Sev or F/U Sev	Date/time of administration of study drug [redacted]	12:00 a.m. on day after last contact date

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

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

In AE tables in CTR Section 15.3 (but not for EudraCT and CT.gov AE tables), the following total will be provided in addition:

- "**Total Control**", defined as the total over all on-treatment phases for participants with normal renal function
- "**Total Impaired**", defined as the total over all on-treatment phases for renal impaired participant (moderate and severe)
- "**Total**", defined as the total over all on-treatment phases for all participants

Safety laboratory data and vital signs will be analysed based on impairment groups with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 2.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses, must be corrected in the clinical database or constitutes a PD.

Each protocol deviation must be assessed to determine whether it is an important PD (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2) and the DV domain template.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain specification. If the data show other iPDs, the definition in the DV domain specification will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. Which kind of iPDs could potentially lead to exclusion from which analysis set is specified in the DV domain specification. The decision on exclusion of participants from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM.

Non-important COVID-19 related PDs will only be listed.

6.3 INTERCURRENT EVENTS

Section is not applicable since no intercurrent events were defined in the **CTP**.

6.4 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in **CTP Section 7.2.1.1**.

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Disposition	X	
iPDs	X	
Demographic/baseline characteristics	X	
Treatment exposure	X	
Primary PK endpoints		X
Secondary PK endpoint		X
[redacted]		[redacted]
Safety parameters	X	

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP Section 7.3.1: "*It is not planned to impute missing values for safety parameters.*"

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).

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

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In all analyses (safety and PK analyses), baseline is defined as the last non-missing value prior to administration of study drug (baseline definition for safety analyses cf. **Section 7.2.5** of the **CTP)**.

Time windows are defined in **Section 6.1** of the **CTP**. Adherence to time windows will be checked at the Report Planning Meeting.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all participants will be listed. Listings will be sorted by impairment group, participant number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned impairment group (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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

For plasma and urine 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

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of plasma and urine 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 (%) relative to the respective impairment group. Percentages will be rounded to integer numbers. The category missing will be displayed only if there are actually missing values. Percentages will be based on all participants in the respective subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications and drug therapies will be coded according to the most recent version of the World Health Organisation – 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 CTR. These will be based on the TS.

CTP Section 7.2.5: "*Previous and concomitant therapies will be presented per* [impairment] *group without consideration of time intervals and treatment periods."*

A drug or non-drug therapy will be considered concomitant to a treatment, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

The diagnoses and drug as well as non-drug therapies will also be listed. Subjects without any concomitant disease or concomitant therapy will 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

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

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

7.4 PRIMARY OBJECTIVE ANALYSIS

The analysis of primary and secondary endpoints will be based on the PKS.
Participants in the PKS may not contribute data to every statistical analysis of PK endpoints, in case specific PK endpoints of this participant are missing or excluded for the following reasons.

Exclusion of PK parameters

The ADS ADPP 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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEX equal to "Included".

CTP Section 7.2.1.2: "*Plasma and urine concentration data and parameters of a participant will be included in the statistical 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 PK concentrations
The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or 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 only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5)

7.4.1 Main analysis

Relative bioavailability will be evaluated for the primary and secondary endpoints of R-BI 1015550, specified in Section 5.1 and Section 5.2.2.

CTP Section 7.2.2: *"The statistical model used for the analysis of the primary endpoints will be an 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 the effects accounting for the following sources of variation: 'degree of renal impairment' as a fixed effect as well as 'matched pair' as random effect.*

The model is described by the following equation:
$y_{ik} = \mu + s_i + \tau_k + e_{ik}$, *where*

y_{ik} = *logarithm of response measured for the degree of renal impairment k, matched pair i,*
μ = *the overall mean,*
s_i = *the effect associated with the* i^{th} *matched pair, i = 1, 2, ..., 8,*

τ_k = the effect associated with the k^{th} degree of renal impairment, k = 1 for normal renal function (control) and k=2, 3 for moderate, severe renal impaired respectively,
e_{ik} = the random error associated with the degree of renal impairment k for matched pair i

where $s_i \sim N(0, \sigma_B^2)$ i.i.d., $e_{ik} \sim N(0, \sigma_W^2)$ i.i.d. and s_i, e_{ik} are independent random variables (note that the indices 'B' and 'W' correspond to 'between' and 'within' matched pair variability, respectively).

The model described above will be fitted separately for the two renal impaired groups, i.e., one model for the participants with severe renal impairment and their matched controls and one model for the participants with moderate renal impairment and their matched controls.

For the evaluation of each primary endpoint, the difference between the expected mean for log response of renal impaired group k (k=2, 3) – log response of normal control group (k=1) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% CIs 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."

The SAS code is presented in Section 10.1.

All primary and secondary endpoints will also be analysed descriptively. The analysis of standard PK parameters is performed according to BI standards (4). Results of inferential statistical analysis will be used for decision making.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary objective has been specified in the **CTP**.

7.5.2 Secondary objective analysis

This section is not applicable as no secondary objective has been specified in the **CTP**.

7.7 EXTENT OF EXPOSURE

In this trial only single doses of the same trial treatment will be applied. Thus, for reporting treatment exposure, it is considered sufficient to summarize observed plasma and urine concentrations and additionally list dates and times of drug administration.

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.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of participants with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).
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 on the recorded time of AE onset, as defined in Table 6.1: 2.

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

CTP Section 5.2.6.1.4: "*The following are considered as AESIs:*

- *Potential severe DILI*
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

  o An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  o Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

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

- *Vasculitis events*
  In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels. The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning.

- *Serious infections, opportunistic or mycobacterium tuberculosis infections*
  These include Pneumocystis jirovecii, BK virus disease including polyomavirus associated nephropathy (PVAN), Cytomegalovirus (CMV), post-transplant lymphoproliferative disorder (Epstein–Barr virus (EBV)), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), Scedosporium/Pseudallescheria boydii, fusarium), legionellosis, Listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, Penicillium marneffei, Sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), Trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617]."

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

According to ICH E3 (8), 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). Since in this trial only one single tablet is administered, no action taken with study drug due to an AE is possible and therefore no other significant AE can occur.

The frequency of participants with AEs will be summarised by impairment group, primary SOC and preferred term. Separate tables will be provided for participants with

- AEs, which were considered by the investigator to be drug related
- SAEs
- AESIs
- AEs summarized by worst intensity.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all impairment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of participants with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by impairment group, primary SOC and preferred term. The frequency of participants 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 summarized.

For support of lay summaries, the frequency of participants with drug-related SAEs will be summarized by impairment group, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (9).

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory 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. Descriptive statistics will be calculated by planned time point

based on the worst value of the participant at that planned time point (or assigned to that planned time point).

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values (according to standard BI criteria defining possibly clinically significant abnormalities) will be highlighted in the listings. Possibly clinically significant laboratory values will be listed in Section 15.4.1. of the CTR.

In general, clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. With regard to laboratory abnormal values identified at the site it is the Investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not. Those will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment).

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

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

Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, for vital signs, descriptive statistics will be calculated by planned post-baseline time point based on the last value of the participant at that planned time point (or assigned to that planned time point). If the time of measurement is missing for a scheduled post-baseline measurement (e.g. for follow-up visits) the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed). If the time of measurement is missing for an unscheduled post-baseline measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.
In descriptive statistic of the Screening visit the planned time points will be used. However, if an unscheduled measurement on the same day as the screening visit exists then the unscheduled assessment will be used in descriptive statistics of Screening visit.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings in ECG will be reported as baseline conditions (at screening) or as AEs (after first 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 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Assessment of suicidal ideation and behaviour (SIB) based on C-SSRS

Suicidality monitoring will be performed as described in **Section 5.2.5.1** of the **CTP**. Results will be listed and findings will be reported as AEs as described in the **CTP Section 7.2.5**.

7.8.5.3 Body weight

Since body weight is only assessed at admission to trial and end of study, it will only be listed.

7.8.5.4 Matching pairs

Matching pairs of participants included in the moderate and severe renal function group will be listed with their matching criteria.

7.9 OTHER ANALYSIS

Not applicable

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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; KMED
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-TMCP-MAN -0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
5	*KM Asset BI-KMED-TCMP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; KMED
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*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
9	*KM Asset 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	**18-Sep-2023**	[redacted]	None	This is the final TSAP.