


TRIAL STATISTICAL ANALYSIS PLAN**c40045454-01**

| | |
|--|---|
| BI Trial No.: | 1305-0028 |
| Title: | Relative bioavailability comparison of BI 1015550 as the intended commercial formulation (iCF) versus trial formulation 2 and iCF with and without food following oral administration in healthy subjects (an open-label, randomised, single-dose, three-way crossover trial) (Clinical Trial Protocol [c37740081-01]) |
| Investigational Products: | BI 1015550 |
| Responsible trial statistician: | <div>[REDACTED]</div> <div>[REDACTED]</div> <div>Phone: [REDACTED]</div> <div>Fax: [REDACTED]</div> |
| Date of statistical analysis plan: | 14 OCT 2022 SIGNED |
| Version: | 1 |
| Page 1 of 27 | |
| <p align="center">Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.</p> | |

1. TABLE OF CONTENTS

| | |
|--|----|
| TITLE PAGE..... | 1 |
| 1. TABLE OF CONTENTS | 2 |
| LIST OF TABLES | 4 |
| 2. LIST OF ABBREVIATIONS..... | 5 |
| 3. INTRODUCTION | 7 |
| 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY | 8 |
| 5. ENDPOINTS..... | 9 |
| 5.1 PRIMARY ENDPOINT..... | 9 |
| 5.2 SECONDARY ENDPOINTS | 9 |
| 5.2.1 Key secondary endpoints | 9 |
| 5.2.2 Secondary endpoint..... | 9 |
| 5.3 FURTHER ENDPOINTS | 9 |
| 6. GENERAL ANALYSIS DEFINITIONS..... | 11 |
| 6.1 TREATMENTS | 11 |
| 6.2 IMPORTANT PROTOCOL DEVIATIONS..... | 12 |
| 6.3 SUBJECT SETS ANALYSED | 13 |
| 6.5 POOLING OF CENTRES..... | 14 |
| 6.6 HANDLING OF MISSING DATA AND OUTLIERS | 15 |
| 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS..... | 15 |
| 7. PLANNED ANALYSIS | 16 |
| 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS | 17 |
| 7.2 CONCOMITANT DISEASES AND MEDICATION..... | 17 |
| 7.3 TREATMENT COMPLIANCE | 18 |
| 7.4 PRIMARY ENDPOINTS | 18 |
| 7.4.1 Primary analysis of the primary endpoints | 18 |
| 7.5 SECONDARY ENDPOINTS | 20 |
| 7.5.1 Key secondary endpoints | 20 |
| 7.5.2 Secondary endpoint..... | 20 |
| 7.6 FURTHER ENDPOINTS | 20 |
| 7.7 EXTENT OF EXPOSURE | 20 |
| 7.8 SAFETY ANALYSIS | 20 |
| 7.8.1 Adverse Events | 21 |
| 7.8.2 Laboratory data..... | 22 |
| 7.8.3 Vital signs | 23 |
| 7.8.4 ECG | 23 |
| 7.8.5 Others | 23 |
| 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION | 24 |

| | | |
|--|----------------------------|-----------|
| 9. | REFERENCES | 25 |
|  | | |
| 11. | HISTORY TABLE | 27 |

LIST OF TABLES

| | | |
|--------------|--|----|
| Table 6.1: 1 | Treatments and labels used in the analysis | 11 |
| Table 6.3: 1 | Subject sets analysed | 14 |
| Table 11: 1 | History table | 27 |

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
<http://glossary>

| Term | Definition / description |
|---------------------|--|
| ALT | Alanine transaminase |
| 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-∞} | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| BMI | Body mass index |
| CI | Confidence interval |
| C _{max} | Maximum measured concentration of the analyte in plasma |
| CSD | Company Standard Displays |
| CV | Arithmetic coefficient of variation |
| F/U | Follow Up |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| iCF | Intended commercial formulation |
| Max | Maximum |
| Min | Minimum |
| N | Number non-missing observations |
| P10 | 10 th percentile |
| P90 | 90 th percentile |
| PKS | PK parameter analysis set |
| Q1 | 1 st quartile |
| Q3 | 3 rd quartile |
| RAGe | Report Appendix Generator system |
| REP | Residual Effect Period |
| RPM | Report Planning Meeting |
| SD | Standard deviation |
| SOC | System organ class |

| Term | Definition / description |
|------|--------------------------|
| T1 | Test treatment 1 |
| T2 | Test treatment 2 |
| TF2 | Trial formulation 2 |
| TS | Treated set |
| ULN | Upper Limit of Normal |

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). 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 trial 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 6.3 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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1015550:

- AUC_{0-t_z} (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 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 endpoint

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 1015550:

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

5.3 FURTHER ENDPOINTS

Pharmacokinetic (PK) endpoints

Other pharmacokinetic parameters measured for BI 1015550 are further study endpoints. For more details see CTP Section 2.2.2.1.

Safety and tolerability endpoints

Section 2.2.2.2 of the CTP: *Safety and tolerability of BI 1015550 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)*
- *Body weight*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The study will be performed as a randomised, open-label, single-dose, three-way crossover trial in healthy male and female subjects. A total of 24 subjects will be included to the study.

All subjects will receive single doses of each of the following three treatments: 18mg BI 1015550 of trial formulation 2 (TF2) administered in fasting state (**R**), and 18mg BI 1015550 of the intended commercial formulation (iCF) administered in fasting state (**T1**) and in fed state (**T2**). The subjects will be randomly allocated to the treatment sequences

- R/T1/T2,
- T1/T2/R or
- T2/R/T1.

There will be a washout period of at least 7 days between the treatments.

The objective of the trial is to compare the test treatment 1 (T1) to the reference treatment (R) and to compare test treatment 2 (T2) to test treatment 1 (T1).

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

Table 6.1: 1 Treatments and labels used in the analysis

| Treatment labels | | Short labels for analysis outputs | |
|------------------|--|-----------------------------------|---------------|
| D | BI 1015550, 3 film-coated tablets of 6 mg, TF2, fasted | R | TF2-fast (R) |
| E | BI 1015550, 1 film-coated tablet of 18mg, iCF, fasted | T1 | iCF-fast (T1) |
| F | BI 1015550, 1 film-coated tablet of 18mg, iCF, fed | T2 | iCF-fed (T2) |

Section 1.2.1 of CTP: *The Residual Effect Period (REP) of BI 1015550 is 7 days. This is the period after the last dose with measurable drug levels and / or pharmacodynamic effects still likely to be present.*

The following study phases will be defined for the analysis of adverse events (AEs):

- **Screening**
 - Ranging from 0:00h on day of informed consent until administration time of BI 1015550 in treatment period 1.
- **On treatment** (labelled “TF2-fast (R)”, “iCF-fast (T1)”, “iCF-fed (T2)”)
 - Ranging from the administration time of BI 1015550 until 7 days (168 h) thereafter OR until next administration of BI 1015550 in the next period, whatever occurs first.
- **Follow-up** (labelled “F/U TF2-fast (R)”, “F/U iCF-fast (T1)”, “F/U iCF-fed (T2)”)
 - Ranging from 7 days (168h) after administration of BI 1015550 until the next administration of BI 1015550 OR until 0:00h on the day after trial termination date, whatever occurs first.

Section 7.2.5 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and follow-up periods will not be included in this analysis. The following total will be provided in addition (Section 15.3 only):

- a total over all on treatment phases included in this analysis ("**Total**")

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Consistency check listings (for identification of deviations 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 7.2.1.1 of the CTP: *Important protocol deviation (iPD) categories will be suggested in the iPD specification file. 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 (DV domain specifications) and the decision log. Both documents will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3 SUBJECT SETS ANALYSED

Section 7.2.1.1 of the CTP:

- **Treated set (TS):** *The treated set includes all subjects who were treated with at least one dose of trial 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 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 for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

Section 7.2.1.2 of the CTP:

Plasma 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.

Important 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*
- *Incorrect intake of meal prior to drug administration in treatment periods under fed condition*
- *Use of restricted medications*

Plasma 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),*
- *A BI 1015550 predose concentration is $>5\%$ C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

Plasma concentration data and parameters of a subject which are 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.

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).

Table 6.3: 1 Subject sets analysed

| Class of endpoint | Subject set | |
|---------------------------------|-------------|-----|
| | TS | PKS |
| Analyses of PK endpoints | | X |
| Safety parameters | X | |
| Demographic/baseline parameters | X | |
| Important protocol deviations | X | |
| Disposition | 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 7.3.

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-HTG-0025 (4) and BI-KMED-TMCP-MAN-0014 (5)).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last measurement before administration of BI 1015550 in each treatment period.

Section 6.1 of the CTP: *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.*

Up to 48:00 h after drug administration (planned time), the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 60 min, if not stated otherwise in the CTP Flow Chart.

For planned blood sampling times, refer to the CTP Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

For logistical reasons, i.e. to provide more flexibility for ambulatory visits, a time window of ± 120 min will be allowed for all procedures beyond planned time of 48 hours after drug administration. Otherwise no time window is defined for PK sampling.

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

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 endpoints (refer to [Section 7.4](#) and [Section 7.5.2](#)) 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 department of Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (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 treatment sequence, subject number and visit. The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

For analyte concentrations 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.

Tabulations of frequencies for categorical data will include all possible categories available in the CRF and will display the number of observations in a category as well as the percentage

(%) relative to the respective treatment 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.

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) contains column variables ACEX and ACEXC indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXC). Exclusion of a concentration depends on the analysis flag comment ACEXC. For example, if ACEXC is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXC is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXC contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times.

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” (6).

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 sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics 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

Only descriptive statistics are planned for this section of the report.

It is not intended to list the compliance separately. Any deviation from complete intake will be addressed in the RPM (see [Section 6.2](#)) and described in the CTR.

7.4 PRIMARY ENDPOINTS

The relative bioavailability of BI 1015550 iCF compared to TF2 (T1 vs. R) and the effect of food on BI 1015550 iCF (T2 vs. T1) will be investigated on the basis of the primary PK endpoints AUC_{0-tz} and C_{max} (see [Section 5.1](#)).

7.4.1 Primary analysis of the primary endpoints

Section 7.2.2 of the CTP:

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: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j ,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, $i = 1, 2, 3$

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, $m = 1, 2, \dots, 8$

π_j = the j^{th} period effect, $j = 1, 2, 3$

τ_k = the k^{th} treatment effect, $k = 1, 2, 3$

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j .

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im} , e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means ($T1/R$ or $T2/T1$) for the primary endpoints (see [Section 5.1](#)) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for $\log(T1)-\log(R)$ and for $\log(T2)-\log(T1)$ 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.

The implementation for this analysis will be accomplished by using the CSD macros based on PKS. The following SAS code can be used:

```
PROC MIXED DATA=indata METHOD=REML;  
  CLASS subject treatment sequence period;  
  MODEL logpk = treatment sequence period / DDFM=KR;  
  RANDOM subject(sequence);  
  LSMEANS treatment / PDIF CL ALPHA=0.1;  
RUN;
```

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 Secondary endpoint

Section 7.2.3 of the CTP:

The secondary endpoint [...] $AUC_{0-\infty}$ will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.6 FURTHER ENDPOINTS

Pharmacokinetic (PK) endpoints

Section 7.2.4.1 of the CTP: *Further PK endpoints will be analysed descriptively.*

Safety and tolerability endpoints

Refer to [Section 7.8](#) for a description of the analysis of safety and tolerability.

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 administrations 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

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] (9) and [BI-KMED-BDS-HTG-0066] (10) 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 [Section 6.1](#).

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

Section 5.2.6.1.4 of the CTP: *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 subjects showing these lab abnormalities need to be followed up according to the ‘DILI checklist’ provided in the eDC. 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 Standardized MedDRA Query “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. A list of terms is provided in the ISF.
- Severe infections, serious infections, opportunistic or mycobacterium tuberculosis infections
The opportunistic infections include pneumocystis jirovecii, Human Polyoma-1 virus disease including polyomavirus-associated nephropathy, Cytomegalie Virus, post-transplant lymphoproliferative disorder (Epstein-Barr-Virus), 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), Hepatitis C progression.

According to ICH E3 (11), 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 AESI (including frequencies for the three different categories of AESI as defined above). In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary SOC and PT.

The system organ classes will be sorted 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]12 (12). 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.

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

For vital signs (blood pressure and pulse rate), descriptive statistics including change from baseline will be calculated by treatment group and by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point). In the listing the difference from baseline will also be displayed.

Additionally, descriptive statistics of the change from baseline in body weight at the end of study visit will be presented.

Clinically relevant findings 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.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as 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 (during the trial) 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 will be loaded into the trial database after completion of enrolment, i.e. the randomisation has been completed.

9. REFERENCES

| | |
|-----|--|
| 1. | <i>CPMP/ICH/363/96</i> : "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version. |
| 2. | <i>001-MCS-40-413</i> : "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON. |
| 3. | <i>BI-KMED-BDS-HTG-0035</i> : "Handling of Missing and Incomplete AE Dates", current version; KMED. |
| 4. | <i>BI-KMED-TMCP-HTG-0025</i> : "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED. |
| 5. | <i>BI-KMED-TMCP-MAN-0014</i> : "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED. |
| 6. | <i>BI-KMED-TMCP-MAN-0010</i> : "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED. |
| 7. | <i>BI-KMED-BDS-HTG-0045</i> : "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED. |
| 8. | <i>BI-KMED-TMCP-OTH-0003</i> : "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED. |
| 9. | <i>BI-KMED-BDS-HTG-0041</i> : "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED. |
| 10. | <i>BI-KMED-BDS-HTG-0066</i> : "Analysis and Presentation of AE data from clinical trials", current version, KMED. |
| 11. | <i>CPMP/ICH/137/95</i> : "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version. |
| 12. | <i>BI-KMED-BDS-HTG-0042</i> : "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 | 14-OCT-22 | | None | This is the final TSAP |