TRIAL STATISTICAL ANALYSIS PLAN

c31618226-01

BI Trial No.:	1386-0016
Title:	A phase I parallel group study in healthy subjects to evaluate the effect of multiple oral doses of BI 1467335 and phenelzine as positive control on blood pressure response to oral tyramine (double-blind, randomised, placebo-controlled design for BI 1467335 treatment groups, open label for phenelzine) Including revised protocol version 5 [c24752093-05]
Investigational Product:	BI 1467335
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	16 JUL 2020 SIGNED
Version:	1

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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
BI	Boehringer Ingelheim
BP	Blood pressure
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
IQRMP	Integrated quality and risk management plan
MedDRA	Medical Dictionary For Regulatory Activities
PD	Protocol deviation
[redacted]	
PPS	Per protocol set
PR	Pulse rate
RAGe	Report appendix generator
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
TS	Treated set
TSF	Tyramine sensitivity factor
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 CTP, and to include detailed procedures for executing the statistical analysis of the primary 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 CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data will be stored in a trial database within Medidata Rave system.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the revised CTP.

While the CTP lists both the ANOVA and the descriptive analyses of the primary endpoint as part of the primary analysis, this TSAP focusses on the ANOVA as primary analysis and declares the descriptive analyses as exploratory analyses.

Assessment of COVID-19 Impact

Due to the study interruption caused by the Covid-19 pandemic the decision was made to stop the study prematurely. This decision was based on the fact that the data from the 10 mg BI group was thought to be sufficient to adequately address the main study objective.

The study was permanently discontinued while the 15mg BI 1467335 group was still ongoing, due to lock down of the side. None of the subjects in the 15mg BI 1467335 group completed the tyramine challenge at visit 3. Therefore, TYR30 at steady state and the primary endpoint TSF are not available for the 15mg BI 1467335 group. As a consequence, the ratio of 15mg BI 1467335 (T2)/Placebo (R) (primary analysis of primary endpoint) can not be calculated. For safety evaluation all data will be used.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the tyramine sensitivity factor (TSF), ratio of TYR30 at baseline and steady state, as defined in CTP Section 2.1.2.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

Not applicable.

[redacted]

5.3.2 Safety parameters

Safety and tolerability of BI 1467335 and phenelzine will be assessed based on further safety parameters defined in Section 2.2.2.2 of the CTP:

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

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

CTP: *At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests (including drug screening and pregnancy test in females), and a physical examination.*

Body mass index will be calculated as weight [kg] / height $[m]^2$.

5.4.2 Treatment compliance and treatment exposure

Treatment compliance will not be analysed as a specific endpoint, cf. Section 4.3 of the CTP.

Treatment exposure is defined as the total dose and number of doses of BI 1467335, phenelzine and tyramine per subject.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

All subjects will start by undergoing a "baseline" tyramine challenge receiving escalating daily doses of 5-700 mg tyramine until baseline TYR30 is reached. Baseline TYR30 is the tyramine dose causing an increase of systolic BP (SBP) ≥ 30 mmHg for at least 3 consecutive measurements compared with baseline SBP (baseline SBP is defined in Section 6.6).

Each subject is then planned to be treated with multiple doses of 10 mg or 15 mg BI 1467335 or matching placebo up to 39 days or with phenelzine up to 19 days. Treatment is to be stopped once TYR30 at steady state is achieved. Therefore, starting on Day 29 for BI 1467335 and placebo arms and on Day 8 for phenelzine, the tyramine challenge is to be repeated until TYR30 at steady state is reached.

For statistical analyses of AEs the following separate analysis phases will be defined for each subject:

Table 6.1: 1 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of tyramine during Visit 2
On-treatment Tyramine screening challenge	**Tyr screening**	Date/time of first administration of tyramine during Visit 2	Date/time of first administration of BI 1467335, placebo or phenelzine respectively
On-treatment BI, Placebo or phenelzine	**Placebo, 10 mg BI, 15 mg BI** or **Phen,** respectively	Date/time of first administration of BI 1467335, placebo or phenelzine respectively	Date/time of first administration of tyramine during Visit 3 or 12:00 a.m. on day after last contact date whatever comes first
On-treatment BI + tyramine, Placebo + tyramine or phenelzine + tyramine	**Placebo + Tyr, 10 mg BI + Tyr, 15 mg BI + Tyr** or **Phen + Tyr** respectively	Date/time of first administration of tyramine during Visit 3	12:00 a.m. on day after last contact date

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 will present results for the on-treatment phase only.

In AE tables in CTR Section 15.3 (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- **"Total on-trt"**, defined as the total over all on-treatment phases
- **“Total BI + Tyr"**, defined as the total over all on-treatment phases involving BI + Tyr

- "**Total BI"**, defined as the total over all on-treatment phases involving BI

Vital signs and safety laboratory data will be analysed by treatment group (Placebo, Phen, 10 mg BI, 15 mg BI). Actual treatments displayed in addition will be based on the analysis phases of AEs (see Table 6.1: 1).

In summaries of disposition, demographics and baseline characteristics, a “Total” (across the treatment groups Placebo, 10 mg BI, 15 mg BI and Phen) will be presented additionally.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

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 the analyses or whether it must be corrected in the clinical database. 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).

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 integrated quality and risk management plan (IQRMP). If the data show other IPDs, the definition in the IQRMP will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. Table 6.2: 1 below specifies which kind of IPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects 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.

Table 6.2: 1 Handling of IPDs

IPD code	IPD Category & Brief Description	Excluded from which analysis set
A1	Inclusion criteria not met	PPS
A2	Exclusion criteria not met	PPS
B1	Informed consent not available/not done	TS, PKS
B2	Informed consent too late	None
C1	Non-compliance	PPS, PKS
C2	Incorrect intake of trial medication	PPS, PKS
C3	Incorrect trial medication taken	PPS, PKS
D1	Prohibited medication use	PPS
D2	Improper washout of prohibited concomitant medication	PPS
E1	Certain violations of procedures used to measure primary endpoint data	PPS
F1	Certain violations of time schedule used to measure primary endpoint data	PPS
G1	PDs affecting safety and rights of subjects	None

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in the CTP, Section 7.3.

Table 6.3: 1 Subject sets analyzed

	Subject set		
Class of endpoint	TS	[redacted]	PPS
Primary endpoint			X
[redacted]			
Safety parameters & treatment exposure	X		
Demographic/baseline endpoints	X		

[redacted]

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

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR.

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal reported in the CTR.

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

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last available value assessed prior to first BI 1467335, placebo or phenelzine administration.

"Baseline" SBP used for comparison of TYR30 is defined as follows: Consider all SBP values within 35 min before tyramine administration on each tyramine testing day. If the SBP of the last 3 of these measurements are within a range of 10 mmHg, the mean of these 3 SBP values will be defined as baseline. If they are not within a range of 10 mmHg, the mean of all SBP values within 35 min before first tyramine administration will be defined as baseline. Baseline SBP is calculated prior to each tyramine testing day.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

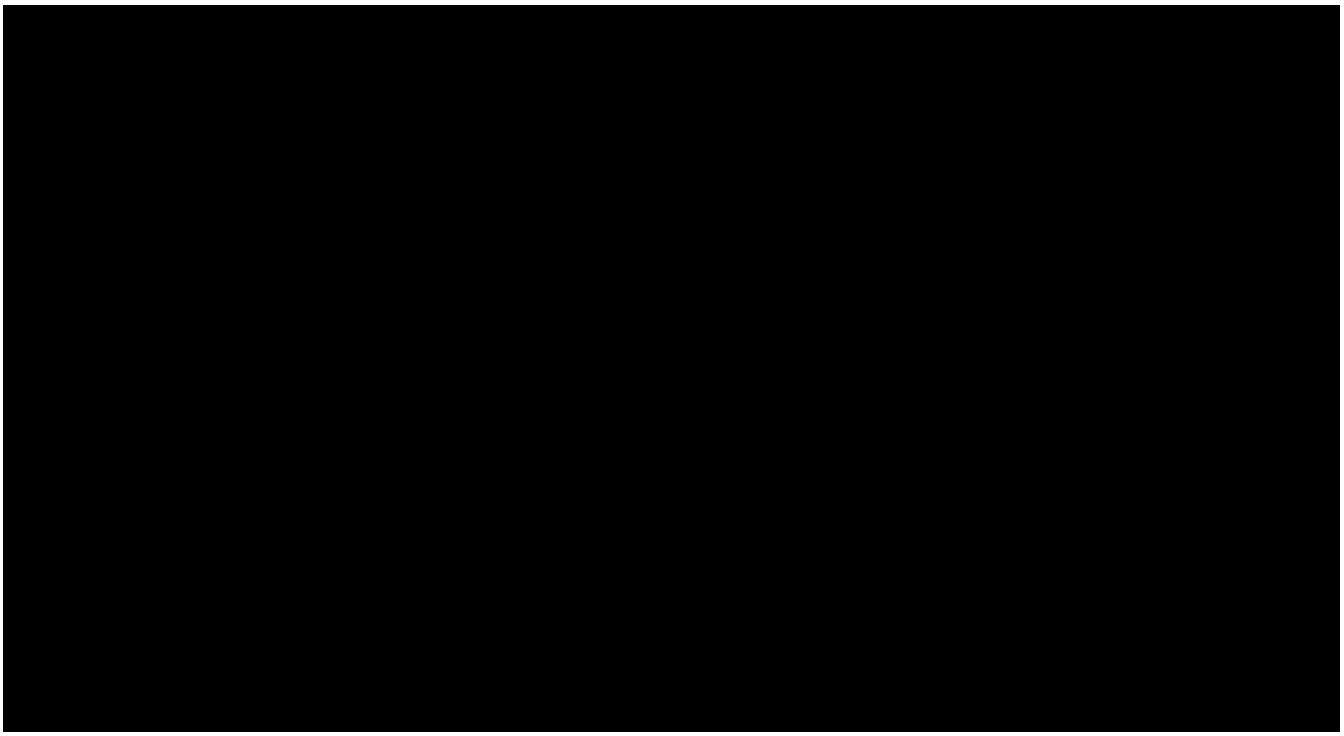
7. PLANNED ANALYSIS

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 subjects will be listed. Listings will be sorted by treatment group subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (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



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 treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects 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.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant, if it

- is ongoing at the time of first 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 relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analyzed 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.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoint

Primary analysis of the primary endpoint will be performed as defined in Sections 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP is an analysis of variance (ANOVA) model on the logarithmic scale including "treatment" as fixed effect. The model will include all three treatments at the same time, i.e., including data from treatments T1, C and R in the same analysis. The difference in TSF will be estimated by the ratios of the geometric means of

- 10 mg BI 1467335 (T1)/ Placebo (R)
- Phenelzine (C)/ Placebo (R)

of the primary endpoint.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

The primary endpoint will also be assessed descriptively. Summary statistics, by treatment, will be presented for TSF, TYR30 at baseline and TYR30 at steady state.

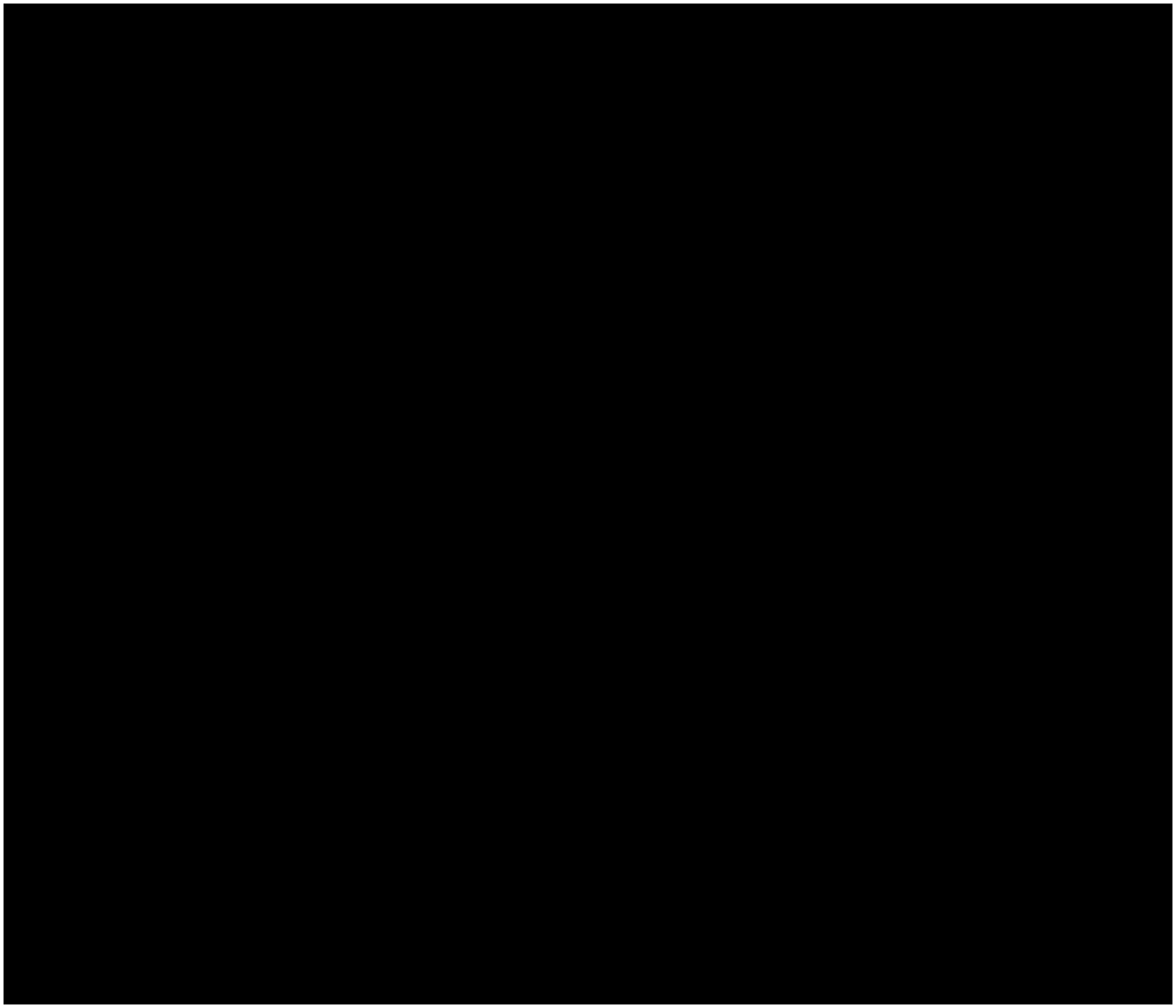
7.5 SECONDARY ENDPOINTS

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 endpoints

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



7.6.2 Safety parameters

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

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report.

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 subjects 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, as defined in Table 6.1: 1.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 (8) and for the class of AESIs.

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*

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

According to ICH E3 (8) AEs classified as "other significant" need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (8)). AEs will also be summarized by maximum intensity.

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

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

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

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, 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 "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 subject at that planned time point (or assigned to that planned time point).

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

Clinically relevant findings in laboratory 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 analyzed as such.

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.

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 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 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 analyzed as such.
Data from the BP monitoring will be listed. In addition, the maximum increase in SBP at TYR30 at screening and steady state will be analyzed descriptively. The maximum increase is defined as the highest change from the three SBP measurements used to attain TYR30, compared to the baseline SBP value used to calculate TYR30.

7.8.4 ECG

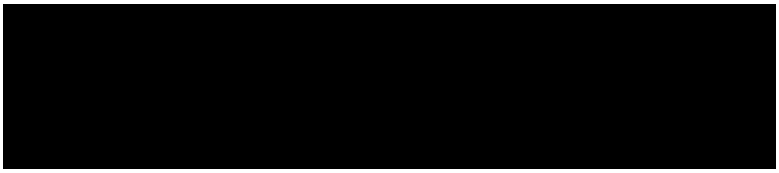
Relevant ECG findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis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

7.8.5 Others

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.

8. 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 Trialss, current version
2	*001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
[redacted]	
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0041:* "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:* "Display and Analysis of Laboratory Data", current version; KMED



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**16-JUL-2020**	[redacted]	None	This is the final TSAP