TRIAL STATISTICAL ANALYSIS PLAN

c31864115-01

BI Trial No.:	1405-0015
Title:	Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1323495 in healthy male subjects (open, single-dose, randomised, two-period crossover design in each trial part)
Investigational Product:	BI 1323495
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	26 OCT 2020 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
Website: glossary

Term	Definition / description
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
Cmax	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DILI	Drug induced liver injury
gCV	Geometric coefficient of variation
gMean	Geometric mean
LLT	Lower level term
IQRMP	Integrated Quality and Risk Management Plan
λz	Terminal rate constant of the analyte in plasma
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of non-missing observations
P10	10th percentile
P90	90th percentile
po	Orally
PKS	Pharmacokinetic parameter analysis set
Q1	1st quartile
Q3	3rd quartile

Term	Definition / description
qd	Once daily
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual effect period
SD	Standard deviation
SOC	System organ class
T	Test treatment
TS	Treated set
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP). In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

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

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

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).

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 ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for rosuvastatin (Part 1) and dabigatran (Part 2):

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

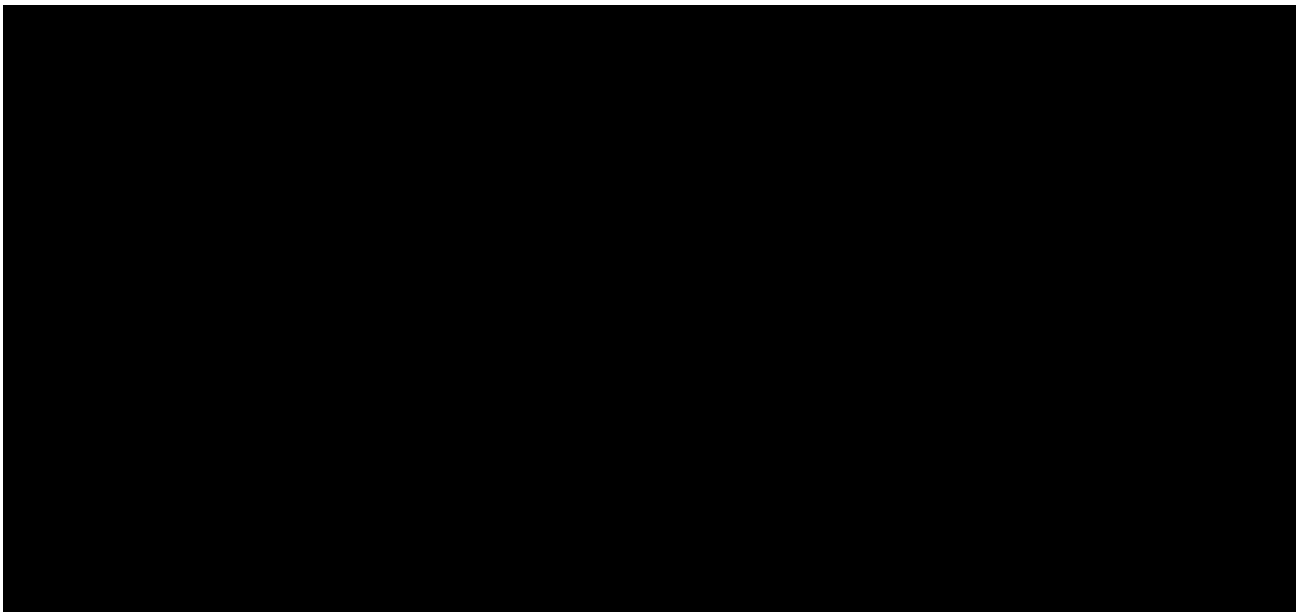
This section is not applicable as no key secondary endpoints have been defined in the CTP.

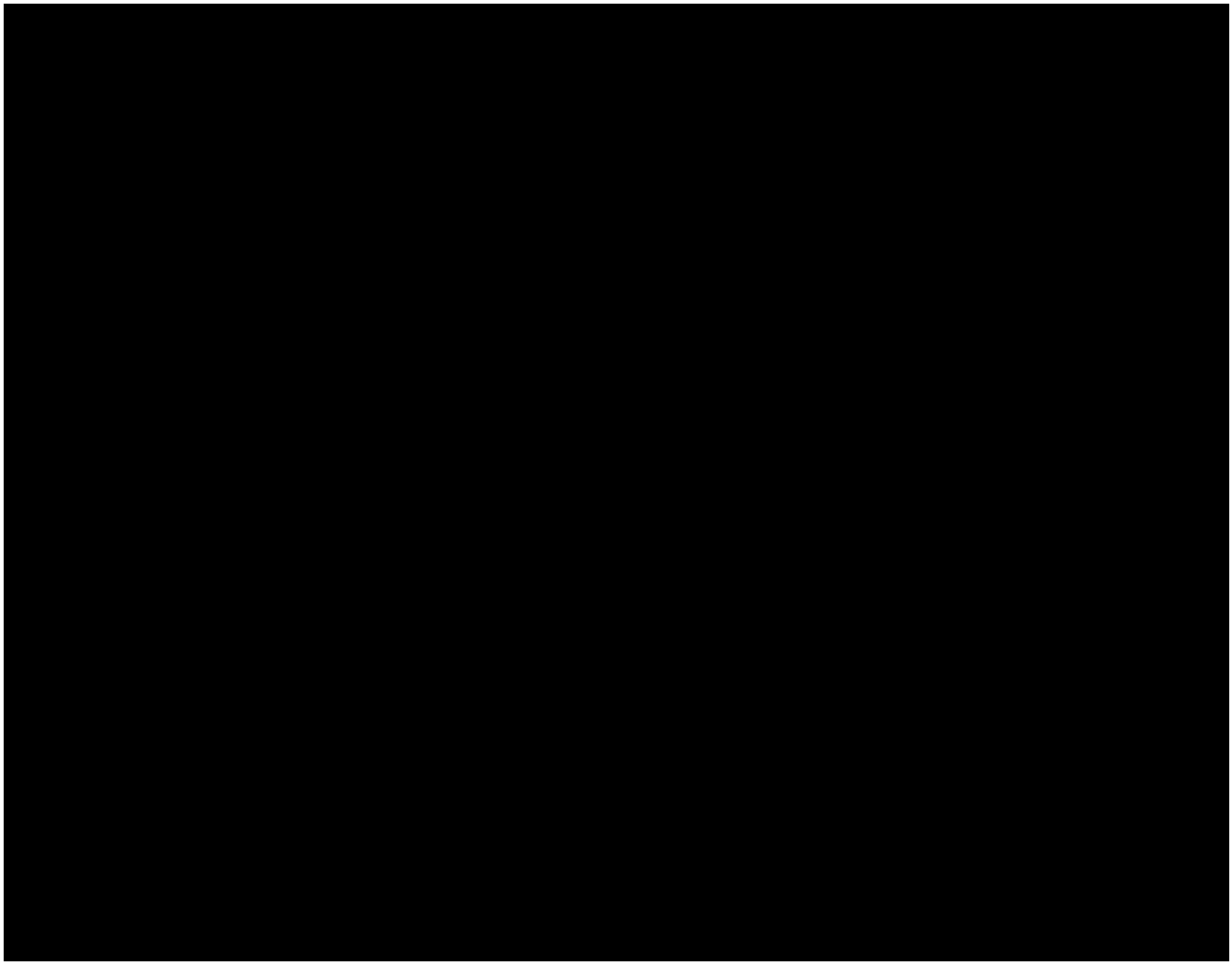
5.2.2 Secondary endpoint

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for rosuvastatin (Part 1) and dabigatran (Part 2):

- *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)*





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The study consists of 2 trial parts, Part 1 with rosuvastatin and Part 2 with dabigatran. It is planned that within each part of the study, 14 healthy male subjects will enter. Each part follows an open-label, randomized, two-period, two-way crossover design in order to compare the test (B, D) and reference (A, C) treatments as defined in Table 6.1: 1 below.

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
Part 1		
A	Rosuvastatin, 10 mg tablet, qd	Rosu
B	BI 1323495, 6*50 mg tab + Rosuvastatin, 10 mg tab, qd	BI+Rosu
Part 2		
C	Dabigatran etexilate, 75 mg capsule, qd	Dabi
D	BI 1323495, 6*50 mg tab + Dabigatran etex, 75 mg caps, qd	BI+Dabi

Section 1.2.4 of CTP:

The Residual Effect Period (REP) of BI 1323495, rosuvastatin, and dabigatran, i.e. the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present, will be defined as 7 days for each of the 3 products.

The following study phases in Part 1 and Part 2 will be defined for the analysis of adverse events (AEs):

- **Screening** (ranging from 0:00 h on day of informed consent until first administration of study medication in treatment period 1)
- **On treatment** (ranging from the time of administration of test or reference treatment until administration time of next study drug dose or until 0:00 h on day 7 after time of administration, whatever occurs first)

  → labelled **Rosu, BI+Rosu, Dabi, BI+Dabi**

- **Follow-up (F/U)** (ranging from 0:00 h on day 7 after the time of administration of test or reference treatment until administration time of next study drug dose or until 0:00 h on day after trial termination date, whatever occurs first)

  → labelled **F/U Rosu, F/U BI+Rosu, F/U Dabi, F/U BI+Dabi**

Section 7.3.4 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:

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

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

For Section 15.3:

- a total over all on treatment phases in study Part 1 (**"Total - Part 1"**)
- a total over all on treatment phases in study Part 2 (**"Total - Part 2"**)

For ClinicalTrials.gov and EudraCT 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, screening and follow-up periods will be included and no totals will be provided.

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

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Section 7.3 of the CTP: *Important protocol deviation (IPD) categories will be suggested in the IQRM plan, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.*

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).

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). An overview of the defined iPDs and if they could potentially lead to exclusion from defined analysis sets (see 6.3) is given in Table 6.2: 1. The decision on exclusion of subjects from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses. If the data show other iPDs, the definition in the IQRMP will be supplemented accordingly by the time of the Report Planning Meeting.
The iPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category/ Code		Description	Exclusion from
A		**Inclusion/Exclusion Criteria**	
	A1	Inclusion Criteria Not Met	PKS
	A2	Exclusion Criteria Violated	PKS
B		**Informed consent**	
	B1	Informed consent not available/not done	TS / PKS
	B2	Informed consent too late	none
C		**Trial medication and randomization**	
	C1	Incorrect trial medication taken	PKS
	C2	Randomisation not followed	PKS
	C3	Non-compliance	PKS
	C5	Incorrect intake of trial medication	PKS
	C6	Improper washout between treatments	PKS
D		**Concomitant medication**	
	D1	Prohibited medication use	PKS
E		**Missing data**	
	E1	Certain deviations from procedures used to measure primary or secondary data	PKS

F		**Incorrect timing**	
	F1	Certain deviations from time schedule used to measure primary or secondary data	PKS
G		**Other trial specific important deviations**	
	G1	Incorrect intake of meal	PKS

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

- *Treated set (**TS**): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (**PKS**): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary 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.*

The two trial parts will be analysed separately, if not stated otherwise. Therefore, the two analysis sets will be split into TS/PKS of the Rosuvastatin part and TS/PKS of the Dabigatran part.
The primary and secondary analysis will be performed in the PKS. The PKS will also be used for the descriptive analyses of PD/biomarker parameters.

Section 7.3 of the CTP:

Pharmacokinetics

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.

Relevant protocol deviations may be

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*

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 tmax of the respective treatment (Median tmax is to be determined excluding the subjects experiencing emesis)*
- *A predose concentration is >5% Cmax value of that subject in the respective treatment period*
- *Missing samples/concentration data at important phases of PK disposition curve*

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Analyses of PK endpoints		X
Analyses of PD/biomarker endpoints		X
Safety parameters	X	
Demographic/baseline parameters	X	
Important protocol deviations	X	
Disposition	X	
Exposure	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

Handling of missing data and outliers will be performed as described in the CTP, Section 7.5.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (4).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before trial medication administration in each treatment period.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, the end of trial examination, and measurements and assessments scheduled to occur 'before' trial medication administrations are provided in the CTP Flow Chart.*

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for the assessment of safety (e.g. vital signs, ECG, laboratory tests) will be ± 60 min.

For planned blood sampling times, refer to the 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.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

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

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

7. PLANNED ANALYSIS

If not stated otherwise, the trial parts will be evaluated separately.

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.

Inferential statistical analyses of PK endpoints (refer to Section 7.4 and Section 7.5.2) will also 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 [redacted] as of the department [redacted] at [redacted] and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

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

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (7).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate).
The listings will be included in Appendix 16.2 of the CTR.

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

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

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

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

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

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK and PD parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%). Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK and PD parameters

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

Exclusion of PK and PD concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) or “ADYC” (PD concentrations per time-point or per time-interval) contains column variables ACEXC and ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (3).

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

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

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

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

The primary endpoints for Part 1 (rosuvastatin) and Part 2 (dabigatran) are $AUC_{0-\infty}$ and C_{max} (see Section 5.1). The primary analysis of these endpoints will be performed using an analysis of variance model for relative bioavailability of rosuvastatin or dabigatran, respectively.

7.4.1 Primary analysis of the primary endpoints

Section 7.3.1 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 logtransformed (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:*

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *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,*
- s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..,* n_i
- π_j = *the* j^{th} *period effect, j=1,2,*
- τ_k = *the* k^{th} *treatment effect, k = 1, 2,*
- 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 (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

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;
        CLASS subject treatment sequence period;
        MODEL logkp = treatment sequence period / DDFM=KR;
        RANDOM subject(sequence);
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
        ESTIMATE 'T-R' treatment -1 1;
RUN;
```

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

Section 7.3.1 of the CTP: *The same statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects.*
In addition to the model based approach all parameters will be calculated and analysed descriptively.

The sensitivity analysis with fixed effects will be performed by fitting the model described above, but using all effects as fixed. This analysis will be done using PROC GLM The following SAS code can be used:

```
PROC GLM DATA=indata;
        CLASS subject treatment sequence period;
        MODEL logkp = treatment sequence period subject;
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
RUN;
```

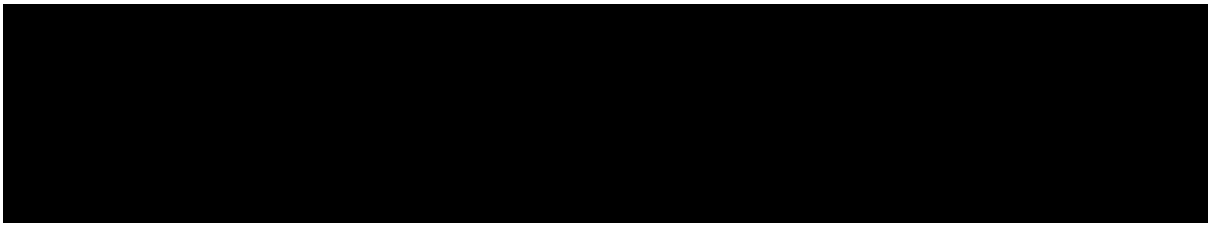
7.5 SECONDARY ENDPOINTS

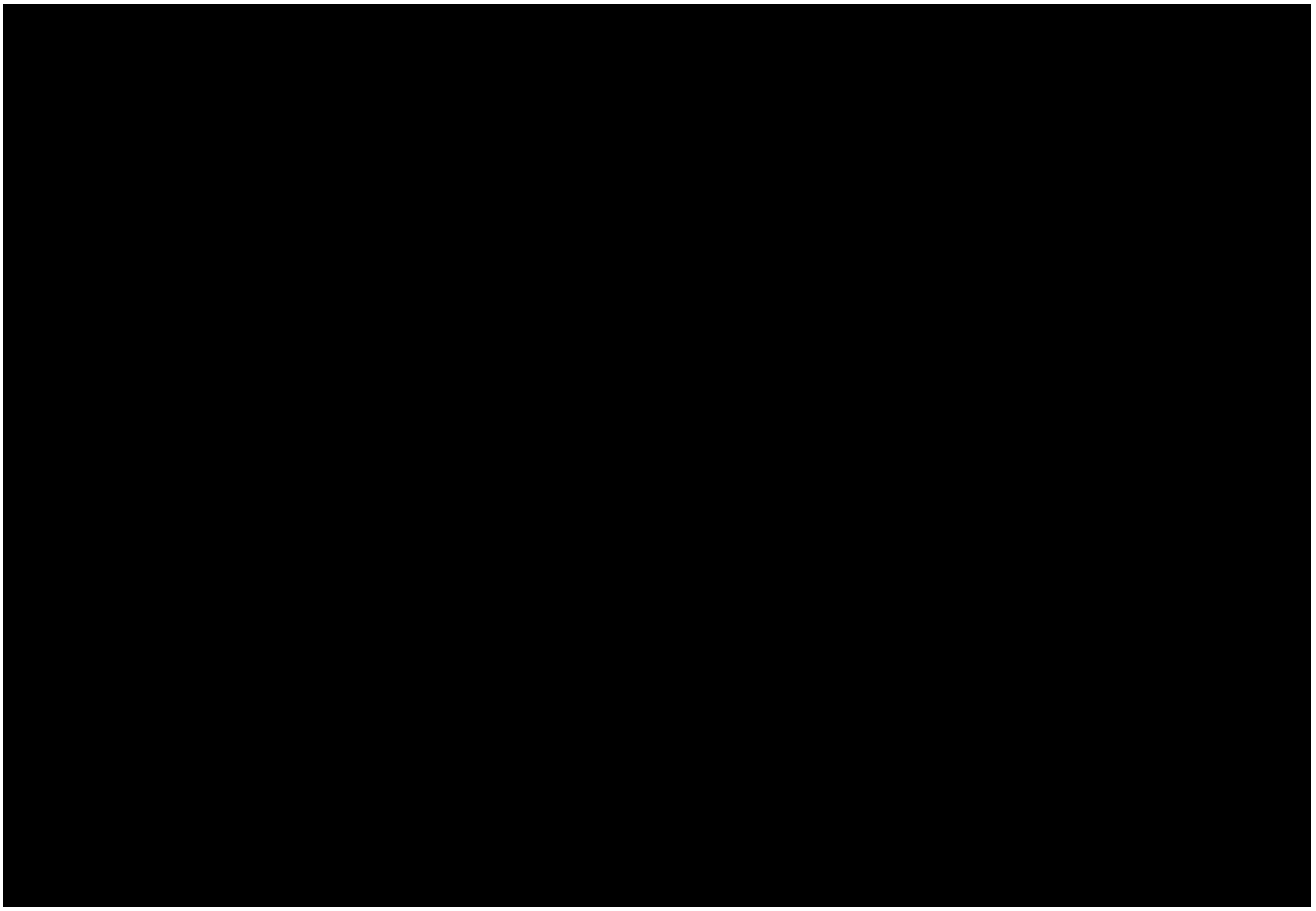
7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoint

The secondary PK parameter $AUC_{0\text{-}tz}$ for rosuvastatin (part 1) and dabigatran (part 2) will be assessed statistically using the same methods as described for the primary endpoints.





7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

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

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (8) and [BI-KMED-BDS-HTG-0066] (11). All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

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

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

Section 5.2.6.1.4 of the CTP: *The following are considered as AESIs:*

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

  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 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.

According to ICH E3 (9), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented.

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

summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).
The SOCs and 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] (10).

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 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.

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

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' (if they pre-exist prior to trial inclusion) or will be reported as AEs (if they occurred on treatment), and will be analysed as such.

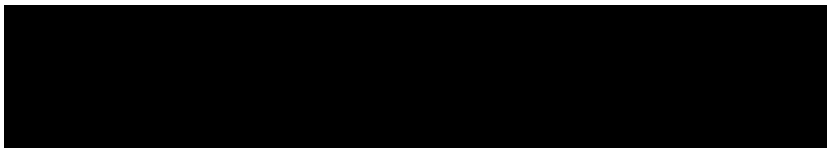
No separate ECG listing will be provided.

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 (if they occurred on treatment) and will be summarised 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 Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
3.	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
4.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	001-MCS-36-472_RD-01: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
9.	*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.
10.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
11.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**26-OCT-2020**	[redacted]	None	This is the final TSAP