TRIAL STATISTICAL ANALYSIS PLAN

c32989625-02

BI Trial No.:	0135-0340
Title:	Bioequivalence of alteplase derived from two different manufacturing processes following intravenous administration in healthy male volunteers Final Protocol (Revised Protocol (based on global amendment 1) (c30603221-02))
Investigational Product(s):	alteplase (TPA-05, 50 mg/vial and TPA-02, 50 mg/vial)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax:
	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	19 APR 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, Distribution, Metabolism and Excretion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
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
BI	Boehringer Ingelheim
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Council for Harmonisation
PKS	Pharmacokinetic parameter analysis set
RAGe	Report appendix generator
SD	Standard Deviation
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
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 and secondary variables and other data.

This TSAP assumes familiarity with the CTP and its amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 'Statistical Methods and Determination of Sample Size'. Therefore, TSAP readers may consult the revised CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data will be stored in a trial database within the RAVE EDC system.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4 or higher, 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).

The trial is kept on-hold. Clinical activities will only re-start after a new benefit-risk assessment has been approved by authorities.

Part A of this trial has been terminated after 12 subjects due to procoagulant effects that interfered also with alteplase analytics. The PK-data could not be used for hypothesis testing and hence the data was only analysed descriptively.

After implementation of measures to mitigate the risk of thromboembolic complications and to avoid methodological problems with alteplase analyticsPart B will be performed following a 2-stage design.

The establishment of bioequivalence will be only based on data of Part B (stage 1 and 2).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

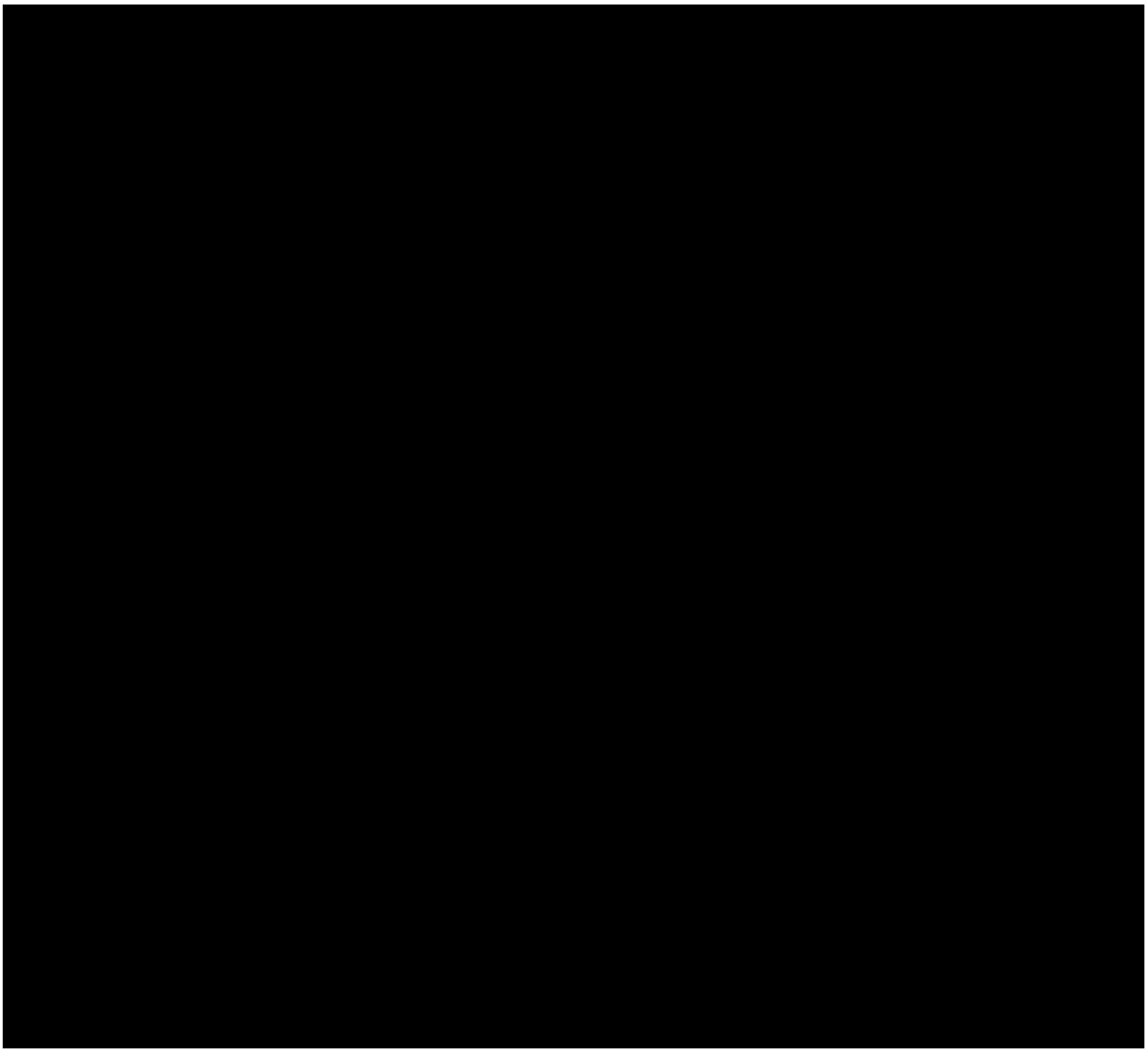
The following pharmacokinetic parameters will be determined for TPA-02 and TPA-05:

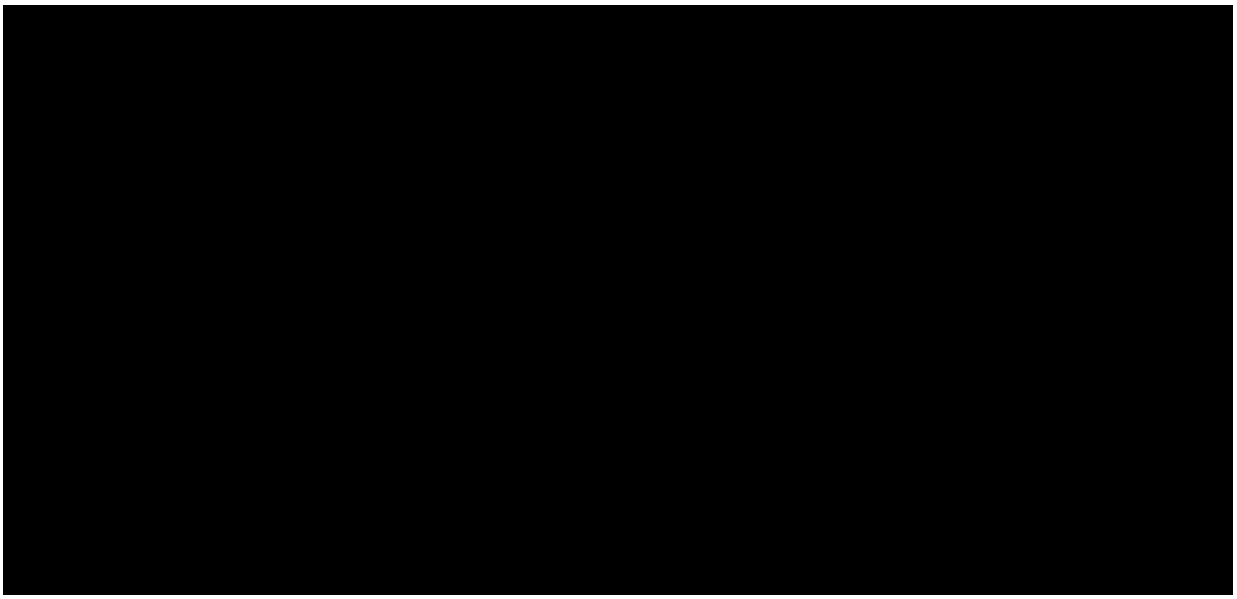
- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINTS

The following pharmacokinetic parameter will be determined for TPA-02 and TPA-05:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*(AUC0-inf_pred and supportive AUC0-inf_obs)





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 receive the 2 treatments (TPA-02 and TPA-05) in randomised order at 2 consecutive days. The specific alteplase dose to be administered to a given subject will be calculated based on the body weight measured at screening examination. Prior to the first administration of trial medication, subjects will be assigned to treatment sequences T-R or R-T.

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

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of TPA-02/ TPA-05
On-treatment	**TPA-02** **0.2 mg/kg body weight**	Date/time of first administration of TPA-02	Date/time of first administration of TPA-05 or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
On-treatment	**TPA-05** **0.2 mg/kg body weight**	Date/time of first administration of TPA-05	Date/time of first administration of TPA-02 or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier

Analysis phases for statistical analysis of AEs are defined for each subject as described in the table above.

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase and screening phase.

In CTR Section 15 AE tables (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 involving BI

Safety laboratory data and vital signs will be analysed by treatment (TPA-02 or TPA-05).

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 for the final analysis. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (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).

For the interim analysis a meeting to discuss deviations related to PK will be conducted and the decisions will be documented in a decision log.

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).

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 Report Planning Meeting, 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 Report Planning Meeting.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
A1	Inclusion Criteria violated	PKS
A2	Exclusion Criteria violated	PKS
B1	Informed consent not available/not done	TS, PKS
B2	Informed consent too late	None
C1	Incorrect trial medication intake	PKS
C2	Randomisation not followed	PKS
C3	Non-compliance	PKS
C4	Medication code broken inappropriately	PKS
C5	Incorrect intake of trial medication	PKS
C6	Improper washout between treatments	PKS
D1	Prohibited medication use	PKS
D2	Mandatory medication not taken	PKS
D3	Improper washout of concomitant medication	PKS
E1	Certain violations of procedures used to measure primary or secondary data	PKS
F1	Certain violations of time schedule used to measure primary or secondary data	PKS
G1	Incorrect intake of meal	PKS

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in the **Section 7.3 of the CTP**:

Part A:

- *Treated set - part A (TS-A): 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 - part A (PKS-A): This set includes all subjects in the treated set - part A (TS-A) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol violation 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.

Part B (stage I and II):

- *Treated set - part B (TS-B): 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 - part B(PKS-B): This set includes all subjects in the treated set - part B (TS-B) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol violation 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.*

Table 6.3: 1 Subject sets analysed

Part A:

	Subject set	
Class of endpoint	TS-A	PKS-A
Disposition	X	
IPDs	X	
Primary endpoints		X
Secondary endpoints		X
Further PK endpoints		X
Safety parameters	X	
Demographic/baseline conditions	X	
Exposure	X	

Part B:

	Subject set	
Class of endpoint	TS-B	PKS-B
Disposition	X	
IPDs	X	
Primary endpoints		X
Secondary endpoints		X
Further PK endpoints		X
Safety parameters	X	
Demographic/baseline conditions	X	
Exposure	X	

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because the trial is 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 Section 7.5.1: *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).

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

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters, the last non-missing value determined prior to first dosing of the trial medication of the respective treatment period will be defined as baseline.

For plasma concentrations:
Individual endogenous TPA will be determined for each period as a mean of two measurements at baseline. Individual baseline levels will then be subtracted from all concentration measurements in that treatment period. In case the resulting concentration value is negative, it will be set to zero.

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 analyses for endpoint apply for both study parts Part A and Part B. However, since the data of Part A could not be used for a formal statistical assessment all analyses in Part A are only considered to be descriptive.

The data from Part A will be analyses separately and will not contribute to the bioequivalence assessment.

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

The individual values of all subjects will be listed. Listings will be sorted by treatment group/sequence, 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

For plasma concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated:

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

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

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

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the

respective 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.

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included" (see protocol Section 7.3).

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or 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 only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

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

7.1 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 ENDPOINT

7.4.1 Primary analysis of the primary endpoint

The statistical model used for the analysis of the primary endpoints for each stage of the trial will be an analysis of variance (ANOVA) model on the logarithmic scale as described in the CTP, section 7.3.1.

Each stage will be analyzed separately based on data from only this stage, see CTP Section 7.2.

Stage 1 analysis

After stage 1, an assessment for bioequivalence will be performed. Data of stage one will be analyzed with the statistical model described in the **CTP, section 7.3.1.**

CTP section 7.3.1 *Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided confidence intervals (CIs) will be provided. At stage 1, the* $(1 - 2\alpha_1)*100\%$ *confidence interval for the gMean ratio will be calculated.*

The alpha spent for the first stage is fixed to 0.03585 (one-sided), see **CTP section 7.2.**

The analysis of stage 1 data will be implemented using SAS PROC MIXED:

```
PROC MIXED DATA=pks_stage1;
  CLASS subject treatment(ref=="TPA-02") sequence period;
  MODEL logkp = treatment sequence period subject / DDFM=KR;
  LSMEANS treatment / PDIFF CL ALPHA=0.0717;
RUN;
```

Bioequivalence is concluded, if the corresponding (adjusted) confidence intervals for the comparison of the primary and secondary (same model, see CTP section 7.5.2) endpoints are within the pre-specified boundaries 80.00% to 125.00% (original scale).

1 A) If bioequivalence is shown, the trial will be closed after stage 1.

1 B) If bioequivalence is not shown for all primary and secondary endpoints after stage 1, then a decision regarding continuation of the trial will be made by the Principal Investigator, the Trial Statistician, and the Clinical Trial Lead or their respective designees.

As stated in the CTP, for all endpoints not meeting the bioequivalence criterion, the following calculations will be performed.

The power of the TOST procedure based on the first stage data will be calculated (using the planned treatment effect, the observed variability and the adjusted alpha level for stage 1). If this power is greater or equal to 0.9, the trial is recommended to stop for futility, cf. (11) Note that this futility rule is considered nonbinding.

The SSR will be based on the conditional power as described in (11), i.e. it will use the conditional error rates as well as the estimated conditional target power for the second stage. For the SSR it is planned to use the observed variability (gCV) and the observed geometric mean ratio (GMR) from the (unblinded) stage 1 data. Note that a specific power adjustment due to multiple endpoints will not be done and the sample size recalculation, if required, will be based on observed results from primary and secondary PK parameters. The calculation will be performed for each parameter and the highest sample size will be used. Note that the minimum sample size for stage 2 is set to 4, as done and recommended in (11). Moreover, for this study a maximum overall sample size of 60 will be considered.

This step may be implemented using function `interim.tsd.in` from the R package Power2Stage:

```
interim.tsd.in(weight = 0.8, max.comb.test = FALSE, targetpower =
0.9,
               GMR1 = GMR1, CV1 = CV1, n1 = n1, ,
               GMR = 1.09, usePE = TRUE, max.n = 60, fCrit = "No")
```

For GMR1 and CV1 it is planned to use the observed results from stage 1, i.e. the gMean ratio and gCV as derived from the above proc mixed call. Similarly, df1 and SEM1 are the degrees of freedom and standard error of the difference of LSmeans, respectively, and are to be taken (on the log-scale) from the same proc mixed call. n1 is the number of subjects in the PKS from stage 1,
Note that the weight of 0.8 may be adjusted as described in the CTP Section 7.2.

If applicable, Stage 2 analysis

Step 2 A)
Data of stage two will be analyzed with the same statistical model described in the **CTP, section 7.3.1** using in principle the same SAS dummy code as described above in Section

7.4.1 of the TSAP**.** Note again that the input data for the proc mixed call will be PKS data from stage 2 only.

```
PROC MIXED DATA=pks_stage2;
  CLASS subject treatment(ref=="TPA-02") sequence period;
  MODEL logkp = treatment sequence period subject / DDFM=KR;
  LSMEANS treatment / PDIFF CL ALPHA=2*alpha2;
RUN;
```

where alpha2 is planned to be 0.03585 and may be adjusted based in accordance with the weight.

Step 2 B)
Study success will then be determined based on the standard inverse normal combination test.

CTP section 7.2 *If the study continues to the second stage, let p_{2j} denote the two p-values of the second stage, j = 1, 2. Note that p_{2j} are obtained using only the data from stage 2. BE is concluded (i.e. the null hypothesis is rejected) after the second stage if the combination of the p-values p_{1j} and p_{2j} (j=1, 2) is greater than the critical boundary c_2 for the final assessment, cf.* (10) *and* (11)*:*

$$\sqrt{w}\Phi^{-1}(1-p_{1j}) + \sqrt{1-w}\Phi^{-1}(1-p_{2j}) \geq c_2,$$

where j = 1, 2 and j again refers to the j-th hypothesis of the TOST procedure and ***Φ*** *refers to the cumulative distribution function of the standard normal distribution.*

Note that α_2 and the critical value c_2, will possibly adapted according the user-defined alpha spending function as described in the **CTP, section 7.2.**

CTP section 7.3.1. *If the study continues to stage 2, the repeated confidence interval corresponding to the test decision will be calculated, in conjunction with the median unbiased point estimate as estimate for the final adjusted geometric mean ratio.* For details see (12).

Bioequivalence is concluded, if the corresponding (repeated) confidence intervals for the comparison of the primary and secondary endpoints (that did not show bioequivalence in the first stage) are within the pre-specified boundaries 80.00% to 125.00% (original scale).

This step B) may be implemented using function `final.tsd.in` from the R package Power2Stage:

```
final.tsd.in(weight = 0.8, max.comb.test = FALSE,
             GMR1 = GMR1, CV1 = CV1, n1 = n1,
             GMR2 = GMR2, CV2 = CV2, n2 = n2)
```

where GMR1, CV1, n1 are the same values as described above and GMR2, CV2, n2are the corresponding values obtained from stage 2 data only, i.e. from the proc mixed call in Step 2 A).

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

The analysis of secondary endpoints will be based on the PKS.

The secondary endpoints will be assessed statistically using the same methods as described for the primary analysis of the primary endpoints.

[redacted]

[redacted]

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 Adverses Events

AEs will be coded with the most recent version of MedDRA. The Residual Effect Period (REP) of alteplase is 24 hours (i.e. 23.5h after end of infusion) in this trial, see CTP Section 1.2.3.

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 or on-treatment 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 Section 5.2.6.1.4: *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 typically intended for 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 mean 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 absolute values and change from baseline from laboratory parameters over time (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.

Individual line plots as well as plots on aggregated data presenting median with Q1 and Q3 as error bars will be provided for plasminogen and α2-antiplasmin.

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 absolute values and change from baseline from vital signs over time (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.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (from first study drug administration onwards) if judged clinically relevant by the investigator.

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 or neurological 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 Trials, 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
4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
5	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
10	Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 55, 1286 – 1290 (1999). [R14-1197]
11	Maurer W, Jones B, Chen Y. Controlling the type 1 error rate in two-stage sequential designs when testing for average bioequivalence. Stat Med. 2018; 37(10): 1587--1607. [R19-3175]
12	Wassmer G, Brannath W. Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. Springer 2016. doi: 10.1007/9783319325620. [R20-2316]

9. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	14-AUG-2020	[redacted]	None	This is the final TSAP