Trial Statistical Analysis Plan

c13465372-02

BI Trial No.:	135.331
Title:	An open label, multicenter, single-arm trial to assess safety and efficacy of alteplase (rt-PA) in Chinese patients with acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4.5 hours after stroke onset Including Protocol Amendment 02 <135.331>-protocol-amendment-x [include c08776773]
Investigational Product(s):	Actilyse®, Alteplase (rt-PA)
Responsible trial statistician(s):	Phone:
Date of statistical analysis plan:	23 Aug 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BP	Blood Pressure
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
CRF	Case Report File
CT	Computer Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EoT	End-of-Text
EX	Exclusion Criteria
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
sICH	symptomatic Intracranial Haemorrhage
IN	Inclusion Criteria
IPV	Important Protocol Violation
LOCF	Last Observation Carried Forward
IV	Intravenous
MAC	Meta-Analytic-Combined
Max	Maximum
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minimum
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
N	Number of Patients
NIHSS	National Institute of Health Stroke Scale
PN	Preferred Name

Term	Definition / description
PR	Pulse Rate
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
REP	Residual Effect Period
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
sICH	symptomatic Intracranial Haemorrhage
SOC	System Organ Class
TCM	Trial Clinical Monitor
ToC	Table of Contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
WHO-DD	World Health Organization's Drug Dictionary
WLOCF	Worst and Last Observation Carried Forward

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), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in Section 7 of the CTP [2] "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.

This TSAP is also used as the interim TSAP. The interim analysis will be performed when 60 patients enter and complete the study. The safety and efficacy will be evaluated on the first 60 patients who complete the study.

SAS® Version 9.2 versions will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analyses from the statistical methods described in the CTP.

5. ENDPOINT(S)

Please refer to Section 5.1 in CTP [2].

5.1 PRIMARY ENDPOINT(S)

The primary efficacy endpoint is the percentage of patients with mRS 0-1 (favourable outcome) at Visit 5 (i.e., Day 90) after stroke onset by face-to-face interview with patient. A patient is considered to be a mRS 0-1 responder (response value set to 1) if he/she obtained a response of 0 or 1 on the modified Rankin scale otherwise the response value will be set to 0.

The primary safety endpoint is the percentage of patients with symptomatic intracranial haemorrhage (sICH) centrally evaluated by DMC consultants according to ECASS III definition within the whole study period. ECASSIII definition is any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration (defined by an increase in the National Institute of Health Stroke Scale (NIHSS) score of 4 or more points), or that led to death and that was identified as the predominant cause of the neurological deterioration.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 (Other) Secondary endpoint(s)

The percentage of global outcome responder at Visit 5 (i.e. Day 90) if he/she obtains the following results at Visit 5 (i.e. Day 90) (for all of the 4 endpoints)

mRS score of 0 to 1
Barthel Indext score$\geqslant$95
NIHSS score of 0 to 1
Glasgow Outcome Scale score of 1

The secondary safety endpoints are:

- Patient's survival at Visit 5 (censoring at day 90)
- Frequency of deaths related to stroke or of neurological causes
- Frequency and severity of adverse events
- Incidence of cerebral herniation and symptomatic edema

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is a single dose study. The treatment periods are defined as below:

- Screening: from the time of signing informed consent to the start time of bolus treatment administration

- On-treatment: through the drug treatment administration and residual effect period (REP, is defined as 7 days after finishing the drug medication)

- Post-treatment: after end of the REP to the Visit 5 (i.e. Day 90)

- Post-study: after Visit 5 (i.e. Day90)

Adverse events (AEs) in on-treatment period will be summarized as primary interest. The frequency of all AEs collected from signing informed consent until to Visit 5 (i.e. Day 90) will also be summarized.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol analysis will be performed for this study; however patients with potential important protocol violations (IPVs) will be documented. The following list of potential IPVs will be used; note that this is a working list and may not be finalised until the final Blinded Report Planning Meeting (BRPM) prior to database lock. Inclusion criteria/exclusion criteria numbers refer to the definition given in the protocol or case report file (CRF).

Table 6.2: 1 Important protocol violations

Category / Code		Description	Comment/Example	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion Criteria Not Met		
	A1.1*	Age is greater than 80 or lower than 18	Inclusion criterion IN1 not met	None
	A1.2	Women pregnant, nursing or with childbearing potential do not use highly effective methods of birth control	Inclusion criterion IN2 not met Exclusion criterion EX17 met	None
	A1.3	Diagnosis of ischemic stroke without a measureable neurological deficit	Inclusion criterion IN4 not met	None
	A1.4.1*	Thrombolytic therapy initiated within 3 hours of stroke onset.	Inclusion criterion IN5 not met or Exclusion criterion EX1 met	None
	A1.4.2*	Thrombolytic therapy initiated beyond 4.5 hours of stroke onset.	Inclusion criterion IN5 not met or Exclusion criterion EX1 met	None
	A2	Exclusion Criteria Met		
	A2.1*	The time of symptom onset is unknown	Exclusion criterion EX1 met	None
	A2.2	Evidence of intracranial haemorrhage on the CT/MRI-scan or symptoms suggestive of subarachnoid haemorrhage, even if the CT/MRI-scan is normal	Exclusion criterion EX2 met	None
	A2.3	Patients who must or wish to continue the intake of restricted medications (see protocol section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial	Exclusion criterion EX3 met	None
	A2.4	Acute bleeding diathesis (detailed items can be found in CRF)	Exclusion criterion EX4 met	None
	A2.5	Bacterial endocarditis, pericarditis, acute pancreatitis, or severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis	Exclusion criterion EX5, EX6 or EX7 met	None
	A2.6	Significant trauma or major surgery (according to the investigator's assessment) in past 3 months	Exclusion criterion EX8 met	None
	A2.7	Severe stroke as assessed clinically (e.g. NIHSS>25) and/ or imaging demonstrates multi-lobar infarction (hypodensity >1/3 cerebral hemisphere)	Exclusion criterion EX9 met	None
	A2.8	Symptoms rapidly improved significantly before start of study drug	Exclusion criterion EX10 met	None
	A2.9	Severe uncontrolled arterial hypertension	Exclusion criterion EX11 met	None
	A2.10*	Serious abnormal blood glucose	Exclusion criterion EX12 met	None
	A2.11*	Any history of prior stroke in previous 3 months, or any history of prior stroke with concomitant diabetes	Exclusion criterion EX13 met	None
	A2.12	Seizure at stroke onset	Exclusion criterion EX14 met	None

	A2.13	Known hypersensitivity to active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients	Exclusion criterion EX15 met	None
	A2.14	Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s)	Exclusion criterion EX16 met	None
B		**Informed consent**		
	B1	Informed consent not available /not done	e.g. date of informed consent missing No signature on ICF Detected automatically/manually	All
	B2	Informed consent too late	e.g. date of informed consent for the study not obtained prior to any study related procedure	None
C		**Non compliance**		
	C1	Patients not treated as label instructed	e.g. bolus date missing	None
D		**Concomitant medication**		
	D1	Prohibited medication use	Concomitant medications for prohibited medication use. Refer to Section 4.2.2 of the CTP.	None
E		**Trial specific**		
	E1	Non-stroke patient	e.g. Lyme disease	None

* IPVs will be identified programmatically; others will be manually recorded.

6.3 PATIENT SETS ANALYSED

The treated set (TS) includes all enrolled patients who received alteplase (rt-PA) treatment at any dose. The full analysis set (FAS) is the same as TS since all treated patients will be evaluated.
All safety and efficacy analysis will be performed on the TS.

6.5 POOLING OF CENTRES

Not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

According to CTP, all efforts should be made to collect complete CRF information referring to all patients with drug administration. No missing values regarding vital status and intracranial bleeds are expected.

The missing values related to efficacy outcome parameters will be imputed according to the rules described below and listed in Table 6.6:1.

Baseline imputation

In case of missing data for baseline NIHSS, the baseline NIHSS will be imputed to the best possible score (0).

Post baseline imputations

WLOCF: Worst and last observation carried forward

- any missing data that it is not due to death will be replaced by the last observation carried forward (LOCF) i.e., either Visit 4, Visit 3, Visit 2, Visit 1C, Visit 1B.

- if the missing data is due to death, the data will be replaced by the worst score: the highest possible score (42) for the NIHSS, the score of 6 (i.e. Dead) for the modified Rankin scale, the score of 5 (i.e. Dead) for the Glasgow outcome, the lowest score (0) for the Barthel index.

- if the patient status (i.e. alive yes/no) is missing, the data will be replaced by the worst score excluding death: the highest possible score (42) for the NIHSS, the score of 5 for the modified Rankin scale, the score of 4 for the Glasgow outcome, the lowest possible score (0) for the Barthel index.

When all post baseline measurements are missing, the imputation across visits will depend on survival status (dead/missing/alive, alive will be handled the same as missing in this scenario) as per definition above. These imputations will be used for the derived endpoints (e.g. dichotomized endpoint) as defined in Section 5.

For multi items scales (NIHSS, Barthel index): Imputation will be performed in two steps:

1.) Individual items will be imputed following the LOCF or worst score
2.) Total score is calculated

When all post baseline measurements are missing, the individual values for post baseline measurements will stay missing and the imputation across visits will depend on survival status (dead/missing/alive, alive will be handled the same as missing in this scenario) as per definition above.

In case of NIHSS missing at baseline and at all post baseline time points, then the individual values for post baseline measurements will stay missing and the total NIHSS score for all post baseline data will be imputed depending on survival status (dead/missing/alive, alive will be handled the same as missing in this scenario).

Barthel index is present only at Visit 4 and Visit 5. In case of missing items for the Barthel index at Visit 4, the worst value will be imputed for these items.

Furthermore, in cases where one of more individual items is missing, the total score must be set to missing for the observed case type of analysis.

Table 6.6:1 Handling of missing data

Endpoint	Baseline value	Baseline imputation value	Post-baseline value at visit	Patient dead/alive at visit	Post baseline imputation value at visit
modified Rankin scale			Available	Alive	NA
			Missing	Alive	LOCF or worst excluding death (5) if missing at Visit 4
			Missing	Dead	Worst (6)
			Missing	Missing	Worst excluding death (5)
Barthel Index			Available	Alive	NA
			Missing	Alive	LOCF or worst if missing at Visit 4
			Missing	Dead	Worst (0)
			Missing	Missing	Worst (0)
Glasgow outcome			Available	Alive	NA
			Missing	Alive	Worst excluding death (4)
			Missing	Dead	Worst (5)
			Missing	Missing	Worst excluding death (4)
NIHSS total score	Available or missing	If missing impute best value (0)	Available	Alive	NA
	Available or missing	If missing impute best value (0)	Missing	Alive	LOCF or worst (42) if all post-baseline were missing
	Available or missing	If missing impute best value (0)	Missing	Dead	Worst (42)
	Available or missing	If missing impute best value (0)	Missing	Missing	Worst (42)

NIHSS Total score:

The total score of the NIHSS is the sum of the **15** individual item scores: level of consciousness (1), LOC questions (2), LOC commands (3), best gaze (4), visual (5), facial paresis (6), motor arm right (7), motor arm left (8), motor leg right (9), motor leg left (10), limb ataxia (11), sensory (12), best language (13), dysarthria (14), extension and inattention (15).

For the calculation of the total score:

The scores of '9' on motor (7-10) indicating amputation or joint fusion on motor arm right or left, motor leg right or left will be replaced by (4) for post baseline value and by best case (0) at baseline.

A score of '9' on dysarthria (14) will be replaced by the worst case value (2) for post baseline value and by best case (0) at baseline.

This rule is to be applied for observed cases and WLOCF.

The censoring rules for time to death (survival time, [day]) at Day 90 and censoring flag will be calculated as following manner:

- **for a dead patient:**
  death=yes
  censoring flag=0
  survival time=date of death – date of start bolus +1

  if survival time >90 (patient alive at Visit5)
  then death=no, censoring flag=1, survival time=90

- **for patient alive at Visit 5:**
  death=no
  censoring flag=1
  survival time= date of last contact – date of start bolus +1
  if survival time>90 then survival time=90

- **for a lost to follow up patient:**
  death = no
  censoring flag=1
  if « last date patient known to be alive » is known
  then survival time= last date patient known to be alive – date of start bolus +1
  if « last date patient known to be alive » is unknown
  then survival time= date of last contact – date of start bolus +1
  if survival time>90 then survival time=90

Date of last contact is the maximum of {date of last measurement or visit, date of trial completion, last available date from AE and last available date from CM}.

The censoring rules for time to death (survival time, [day]) overall study and censoring flag will be calculated as following manner:

All deaths are taken into account whatever their time of occurrence, and even if they occurred after the 97 days (90 days +7).

- **for a dead patient:**
  death=yes
  censoring flag=0
  survival time=date of death – date of start bolus +1

- **for patient alive at Visit 5:**
  death=no
  censoring flag=1
  survival time= date of last contact – date of start bolus +1

- **for a lost to follow up patient:**
  death = no
  censoring flag=1
  if « last date patient known to be alive » is known
  then survival time= last date patient known to be alive – date of start bolus +1
  if « last date patient known to be alive » is unknown
  then survival time= date of last contact – date of start bolus +1

Date of last contact is the maximum of {date of last measurement or visit, date of trial completion, last available date from AE and last available date from CM}.

The length of stay in hospital will be calculated as follows:

The length of stay in hospital is expressed in days and is equal to the date of discharge date and time is approximated to 23h O'clock for the end of day minus the date and time of the start of bolus. Because the date in SAS are expressed in seconds, the results will be divided by 86400 (24*60*60) in order to obtain a results expressed in number of days. The exact time of day of when the discharge time occurred is fixed at 23H59 PM for all patients (exact time not recorded in CRF).

Example: Start of bolus: 23/01/03 12H00 and date of discharge: 30/01/03

The length of stay in hospital will be: date of discharge (30/01/03, 23H59) - date of bolus (23/01/03, 12H00) / 86400 = 7.5 days.

Missing or incomplete AE onset dates are imputed according to BI standards [27, 27].

Missing or incomplete concomitant therapy onset dates are also imputed referring to AE standards. The end dates of missing or incomplete AE and concomitant therapy will be not imputed.

Trial completion is defined as the patients who are treated and completed Day 90 visit (i.e Visit 5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The table below presents the visit structure according to the study flowchart depending on the time window scheduled in the CTP.

Table 6.7: 1 Visit structure

Period	Baseline	Trial drug admin.	On-treatment & Post-treatment					
Visit number per protocol	V1A		V1B#	V1C#	V2	V3	V4	V5
Planned study window	-4.5-0 hour	←x→ 60 mins	1 hour ± 15 mins	2 hrs ± 30 mins	24 hrs ± 2hr	7 days ± 3 day	30 days ± 3 days	90 days ± 7 days
Study Day	← D0 →				D1	D7	D30	D90
Visit description*	Baseline		Day0 (1H)	Day0 (2 H)	Day1	Day7	Day30	Day90

*label to be used in tables.
'Baseline' is defined as from enrolled in this study to the start time of bolus treatment administration.
'Study Day' is calculated from the date & time of starting bolus treatment administration.
date & time is calculated from the date & time of starting infusion treatment administration.

Start of treatment:

The start of treatment (used for survival start time, length of stay in hospital, treatment at onset for adverse event) will be the **start of bolus treatment administration**; end of treatment is the end of infusion/drug/treatment administration.

Baseline value:

The baseline value will be the value recorded at V1A (last available value before the start of bolus treatment).

Change from baseline:

The change from baseline for any efficacy or safety endpoints (Vital signs) will be calculated as: value after baseline – value at baseline (V1A).

All efficacy analyses will be based on 'nominal visits' (CRF raw data visit) which will be labelled as indicated in the 'Visit description' row in tables, listings and graphs.

7. PLANNED ANALYSIS

Unless otherwise specified, the following general conventions for End-of-Text (EoT) [5] tables should be used regarding all descriptive statistical analysis and result presentations.

The set of summary statistics: N / Mean / SD / Min / Median / Max are for continuous data with one more decimal place compared to the original data in the subject data listing. For tables that are provided for endpoints with some extreme data, Q1 and Q3 would be preferred to Min and Max.

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 (%) (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. All the confidence interval calculations for proportions will use the Wilson score method.

The visit will be analysed as calculated visit and should be named ‘Baseline’, ‘Day0(1H)’, ‘Day0(2H)’, ‘Day1’, ‘Day7’, ‘Day30’ and ‘Day90’ as described in Section 6.7. The units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mmHg]), unless the variable does not have a unit (e.g. scores). And the imputation rules for missing data will be applied as in Section 6.6.

An independent data monitoring committee (DMC) will oversee the trial conduct, monitor safety data monthly, and review the interim analysis results when 60 patients complete the study. As for details please refer to DMC SAP. [6]

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics of concomitant therapy (medication and other treatment) are planned for this section of the report based on TS.

Concomitant therapy will be coded according to the WHO-DD (current version at the time of analysis), sorted by the ATC3 class and the preferred name (PN). PNs that belong to different ATC3 classes will be shown under all applicable ATC3 classes.

All concomitant therapies after the start of bolus until Visit 5 will be summarized. Antithrombotic therapies (e.g, aspirin, heparin, etc.) within 24 hours after the start of bolus will be summarized separately.

Concomitant therapy without end date will be considered as ongoing.

7.3 TREATMENT COMPLIANCE

Not applicable.

7.4 PRIMARY ENDPOINT(S)

Primary analysis

The primary efficacy endpoint is the percentage of mRS 0-1 (favourable outcome) responder at Visit 5 after stroke onset by face-to-face interview with patient. The proportion of patients with mRS 0-1 will be presented with corresponding 95% confidence intervals (CIs). The imputation rules described in Section 6.6 will be applied for the primary analysis. The observed case analysis, that is the proportion of patients with mRS 0-1 observed at Visit 5, will be performed as sensitivity analysis.

The null hypothesis of $p \leq 40\%$ versus the alternative hypothesis of $p > 40\%$ will be tested using a one sample t-test at two-sided significance level of 0.05. The horizontal stacked bar graphs of each level in the ordinal mRS will be presented.

The primary safety endpoint is the proportion of patients with symptomatic intracranial haemorrhage (sICH) evaluated by DMC consultants within whole study period. The proportion of patients with sICH will also be presented along with corresponding 95% CIs.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable.

7.5.2 (Other) Secondary endpoint(s)

The secondary efficacy endpoint is the percentage of global outcome at Visit 5. A global outcome responder is defined as patient with outcomes at Visit 5 of a score of 0 or 1 on the mRS, a score of 95 or higher on the Barthel Index, a score of 0 or 1 on the NIHSS, and a

score of 1 on the Glasgow Outcome Scale. The proportion of global outcome responders will be displayed along with corresponding 95% CIs. Each item of the composite criteria global outcome responder (refer to Section 5.2.2) will be evaluated separately as well. Its observed result will also be summarized. The imputation rules described in Section 6.6 will be applied for the primary analysis.

The secondary safety endpoints are:

- Patient's survival at Day 90 (censoring at 90 days)

The cumulative probability (Kaplan-Meier estimate) of death from bolus treatment administration to Day 90 will be analysed and plotted by a Kaplan-Meier survival with the median survival along with 95% confidence interval, using Greenwood's standard error estimate. The Kaplan-Meier estimates will also be analysed over the observation period of 90 days.

- Frequency of deaths related to stroke or of neurological causes will be analysed descriptively.

- Incidence of cerebral herniation and symptomatic edema will be analyzed descriptively.

- Frequency and severity of adverse events refer to Section 7.8.1.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS).

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, and outcome).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to the guidance [3, 4].

The primary interest analysis of AEs will be based on the concept of treatment emergent (on-treatment period) AEs, i.e. AEs which occurred through the single dose treatment phase and throughout the REP (i.e. exactly day 7). AEs stopped before the start of bolus treatment administration will be assigned to ‘screening’ and AEs occurring after the end of REP to Visit 5 will be assigned to ‘post-treatment’. The frequency of all AEs collected after Visit 5 until the end of the study (i.e. Visit5) defined as ‘post study’ will also be summarized. For details on the treatment definition, see Section 6.1.

According to ICH E3 [7], AEs classified as ‘other significant’ needs to be reported and will include those non-serious and non-significant AEs with

(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by primary system organ class (SOC) and preferred term (PT) of MedDRA (using the version that is current at the time of analysis). Frequency tables will be created for the following AEs:

- All AEs
- Serious AEs
- Drug−related AEs
- AEs leading to treatment discontinuation
- AEs leading to death
- Other significant AEs (according to ICH E3) [7]
- AEs with incidence in preferred term greater than 2%

The system organ classes will be sorted alphabetically, and preferred terms will be sorted by descending frequency within system organ class.

The above tables will be repeated within the on-treatment period and the overall period from Inform consent to Visit 5.

7.8.2 Laboratory data

Laboratory data will not be analysed. Any clinical significant abnormalities in laboratory will be reported as AEs.

7.8.3 Vital signs

Blood pressure (BP, systolic and diastolic) and pulse rate (PR) are measured at baseline (prior to administration of trial medication i.e. Visit 1A). Further BP/PR monitoring take place in the following order: every 30 minutes for 6 hours, then hourly until 24 hours after IV rt-PA treatment, thereafter on Visit 2, Visit 3, Visit 4, and Visit 5 (seated and rested for a minimum of 5 minutes).

Descriptive tables of the following variables will be presented in the time points of Visit 1A, Visit 1B: 0.5H, Visit 1C: 1h,4h, 6h,12h, Visit 2, Visit 3, Visit 4, and Visit 5.

- Systolic blood pressure [N(%)]: ≤185 mmHG, and >185 mmHG

- Diastolic blood pressure [N(%)]:≤110 mmHG, and >110 mmHG

- Pulse rate [beats/min]

In addition, descriptive tables of blood pressure will be presented over all measured time points. Figures of blood pressure will be presented over specified time points.

7.8.4 ECG

ECG data will not be analysed. Any clinically significant relevant changes in the ECG will be reported as AEs.

7.8.5 Others

Not applicable.

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	"*Clinical Trial Protocol (CTP) of Boehringer Ingelheim Trial 135.331*", current version, BIRDS.
3	001-MCG-156: "*Handling and summarization of adverse event data for clinical trial reports and integrated summaries*", version 8.0; IDEA for CON.
4	001-MCG-156_RD-01: "*Handling of missing and incomplete AE dates*", version 3.0; IDEA for CON.
5	001-MCG-159_RD-03: "*Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)* ", current version; IDEA for CON.
6	"*DMC SAP of Boehringer Ingelheim Trial 135.331*", current version.
7	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. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**10-Jan-17**		None	This is the initial TSAP without any modification.
Final	**23-Aug-17**		None	This is the final TSAP without any modification.