TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42514142-02**
BI Trial No.:	**1123-0040**
Title:	A phase III multi-centre, prospective, randomised, open label, blinded endpoint (PROBE), active-controlled parallel group trial to assess efficacy and safety of tenecteplase versus alteplase in Chinese patients with acute ischaemic stroke within 4.5 hours after stroke onset
Investigational Product(s):	Metalyse®, tenecteplase
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	6 SEP 2023 REVISED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AIS	Acute ischaemic stroke
AME	Average Marginal Effects
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BMI	Body Mass Index
CI	Confidence interval
CM	Concomitant medication
CTP	Clinical trial protocol
DBL	Database lock
DBP	Diastolic blood pressure
ECASS	European Cooperative Acute Stroke Study
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EOS	End of Study
EOT	End of Text
eCRF	Electronic case report form
ES	Enrolled set
FAS	Full analysis set
FCS	Fully Conditional Specification
H	Hour(s)
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
iPD	Important Protocol deviations
iv	Intravenous
LOCF	Last observation carried forward
MAR	Missing at random
MedDRA	Medical Dictionary for Drug Regulatory Activities
min	Minute(s)
m	Month(s)

Term	Definition / description
MI	Multiple imputation
MMRM	Mixed model repeated measures
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OC	Observed Case
PPS	Per-protocol set
PROBE	Prospective, randomised, open label, blinded endpoint
REML	Restricted Maximum Likelihood
RS	Randomised Set
REP	Residual effect period
PN	Preferred Name
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
sICH	Symptomatic intracerebral haemorrhage
SITS-MOST	Safety Implementation of Thrombolysis in Stroke: Monitoring Study
SS	Safety set
SOC	System organ class
TSAP	Trial statistical analysis plan
TMF	Trial Mater Files

3. INTRODUCTION

As per International Council on Harmonisation (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 "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.

The statistical analyses will be performed using SAS® Version 9.4.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (version 4.0) will be performed as planned with the following adaptations.

[redacted]

5. ENDPOINTS(S)

A description of the assessments as the basis of the endpoint determinations, is provided in Section 5.1 in CTP. Of particular importance, low values on the mRS, Glasgow Outcome Score and NIHSS represent a favorable status of the patient, whilst a low value on the Barthel Index represents a non-favourable status of the patient.

An overview of efficacy endpoints is listed in Table 5: 1, and an overview of safety endpoints is listed in Table 5: 2.

Table 5: 1 Overview of Efficacy endpoints

Endpoints		**Timepoint**				
Score [integer]	**Efficacy Endpoint**	**2h**	**24h**	**D8**	**D30**	**D90**
mRS [0--6] where 6 represents death	0-1[1]				[redacted]	Primary
	0-2[1]				[redacted]	Secondary
	Ordinal[3]					Secondary
Barthel Index [0--100] where 100 represents independent	≥ 95[1]				[redacted]	Secondary
	[redacted]					[redacted]
[redacted]	[redacted]					[redacted]
NIHSS [0--42] where 0 represents normal	Absolute or change from baseline[2]	[redacted]	[redacted]	[redacted]	[redacted]	Secondary
	[redacted]				[redacted]	
	[redacted]			[redacted]		
	Major neurological improvement [0, or Δ ≥ 4][1]		Secondary			

1: Binary endpoint
2: Continuous endpoint
3: Ordinal endpoint

Table 5: 2 Overview of Safety endpoints

Safety Endpoint	D90	Treatment emergent
sICH per ECASS III definition[1]		Secondary[2]
90-day mortality	Secondary[2]	
mRS:5-6	Secondary[2]	
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

1: Adjudicated by EAC
2: Binary endpoint
3: Time to event endpoint

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of this study is a mRS score of 0 or 1 at day 90.

5.2 SECONDARY ENDPOINT(S)

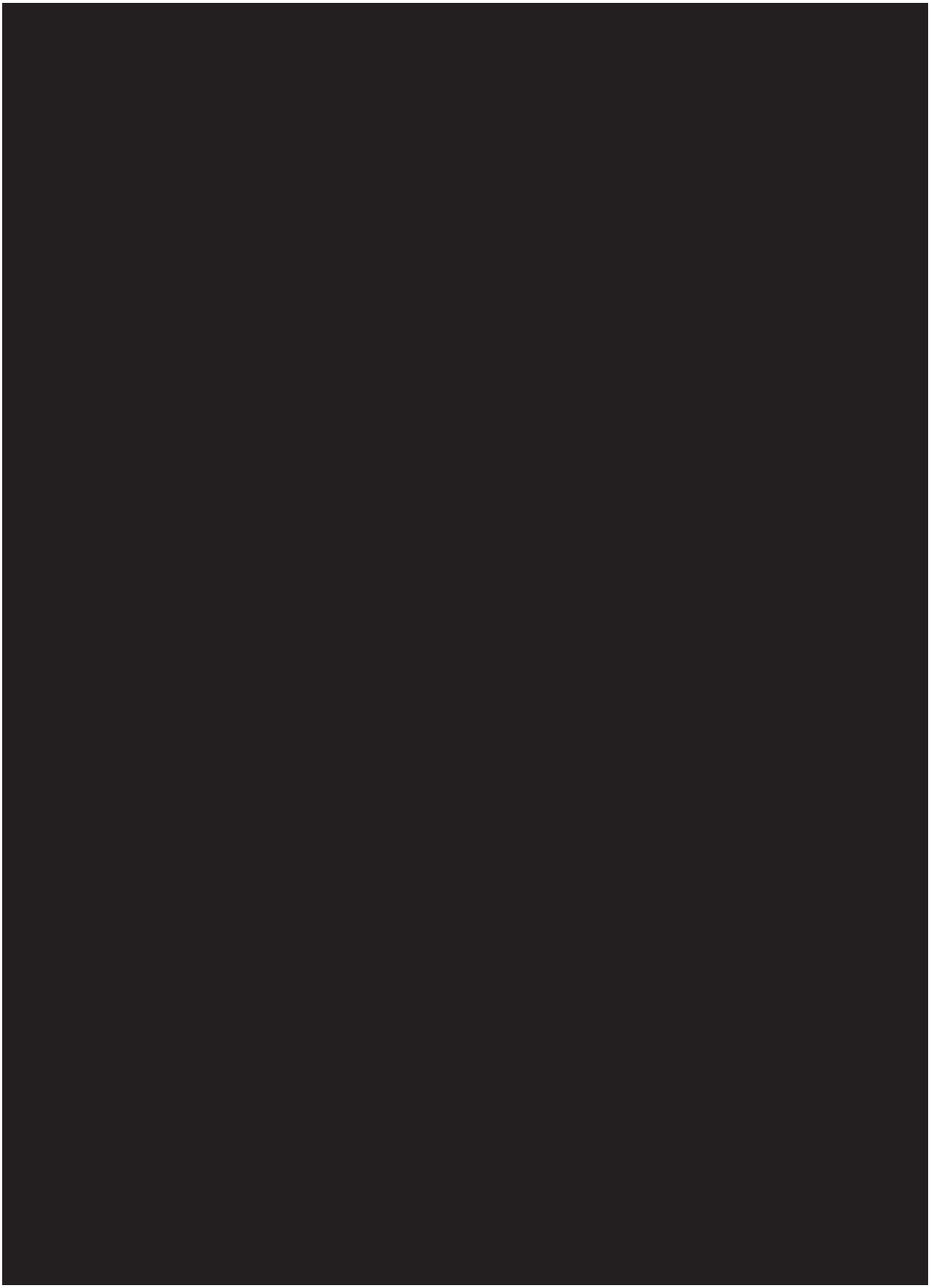
5.2.1 Key secondary endpoint(s)

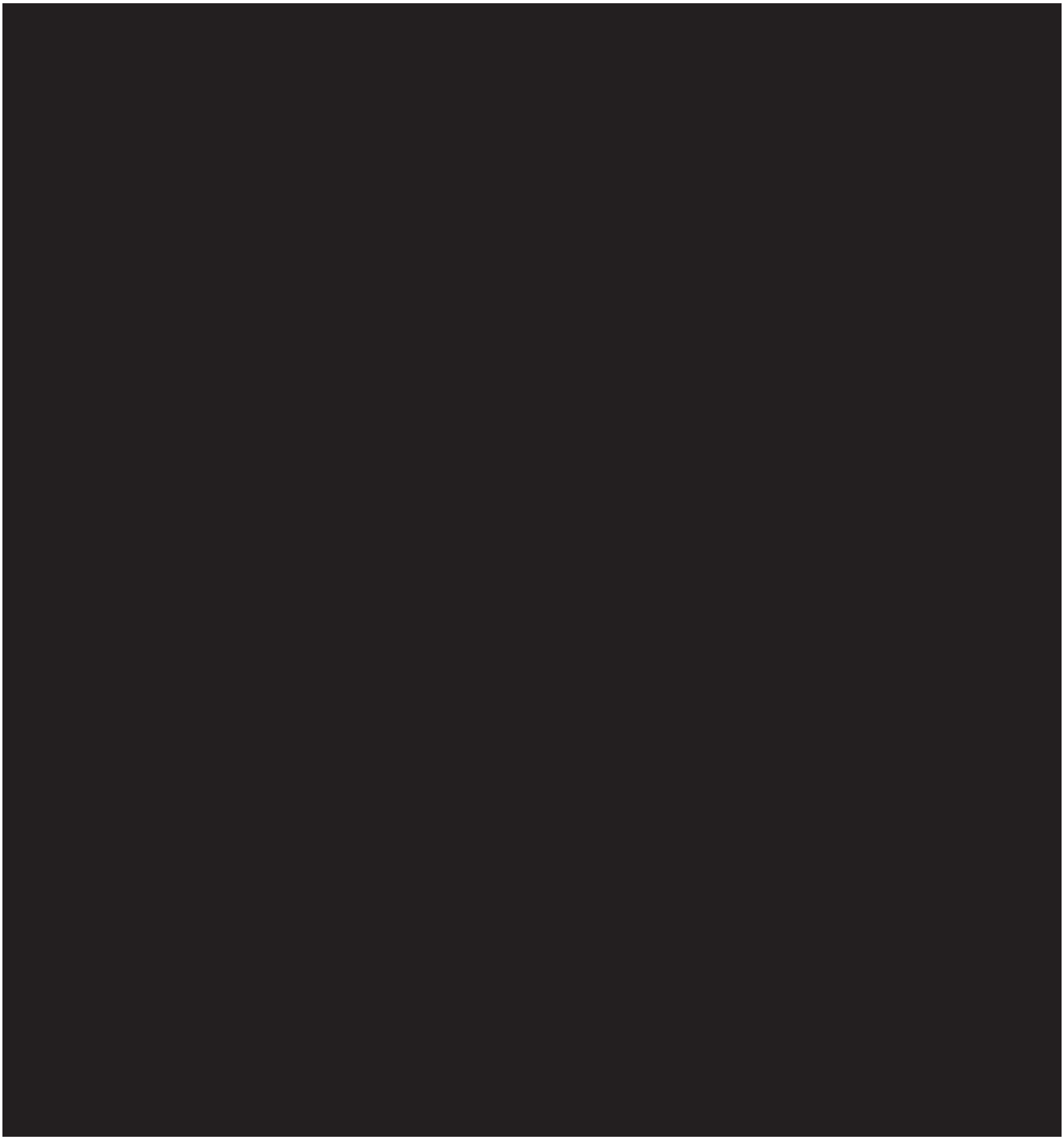
Not applicable since there are no key secondary endpoints specified in CTP.

5.2.2 Secondary endpoint(s)

The secondary efficacy and safety endpoints are described in Section 2.1.3 in CTP.

[redacted]





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, refer to CTP Section 4. There will be four treatment study phases in this trial: screening, on-treatment, post-treatment and post-study. For detailed information, see Table 6.1: 1.

Table 6.1: 1 Treatment regimens / study intervals

Label	Interval	Start date	Start time
Screening	Screening	Date of informed consent	Time of informed consent
On-treatment	On-treatment	Date of start bolus administration of study medication	Time of start bolus administration of study medication
Post-treatment	Post-treatment	Date of end administration of study medication +7 +1	00:00
Post-study	Post-study	Trial completion date +1	00:00

The purpose of the definitions above is to describe all the different study/treatment intervals, to which a patient can be assigned during the course of the trial. Note that the term “treatment regimen” can also cover time periods with no active treatment.

In general, for safety analyses, data up to 7 days (Residual effect period, REP) after the end of study drug administration will be considered as on-treatment for Adverse events (AE), which will be summarized as primary interest. The frequency of all AEs collected from signing informed consent until study completion will also be summarized.

6.2 IMPORTANT PROTOCOL DEVIATIONS

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]".

Handling of iPDs in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). Not all iPDs will lead exclusion from the Per-Protocol set (PPS). Deviations that lead to exclusion from analysis populations are indicated in Table 6.2:1.

Table 6.2: 1 Important protocol deviations

IPD Code	IPD Category & brief description	Example/Comment	Exclude from which analysis set
A	Eligibility criteria not met		
A1	Inclusion criteria not met		
A 1.01	Age <18 years old	Inclusion criterion #1 not met	None
A 1.02	No diagnosis of ischemic stroke with a measurable neurological deficit on NIHSS (0<NIHSS≤25; if NIHSS<4, patients have to be with at least a measurable deficit on motor power (upper or lower limbs ≥ 1))	Inclusion criterion #2 not met	PPS
A 1.03	Stroke symptoms present for less than 30 minutes or with significant improvement prior to randomisation	Inclusion criterion #3 not met	PPS
A 1.04	Thrombolytic therapy cannot be initiated within 4.5 h of acute ischaemic stroke (AIS) onset	Inclusion criterion #4 not met	PPS
A 1.05	Modified Rankin Scale (mRS) > 1 prior to the stroke	Inclusion criterion #5 not met	PPS
A2	Exclusion criteria met		
A 2.01	Evidence of intracranial haemorrhage (ICH) or symptoms suggestive of subarachnoid haemorrhage	Exclusion criterion #1 met	PPS
A 2.02	Patients who must or are expected to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	Exclusion criterion #2 met	None
A 2.03	Acute bleeding diathesis	Exclusion criterion #3 met	None
A 2.04	Bacterial endocarditis, or pericarditis at screening	Exclusion criterion #4 met	None
A 2.05	Acute pancreatitis at screening	Exclusion criterion #5 met	None

IPD Code	IPD Category & brief description	Example/Comment	Exclude from which analysis set
A 2.06	Significant trauma or major surgery (according to the investigator's assessment) in the past 3 months	Exclusion criterion #6 met	None
A 2.07	Imaging demonstrates multi-lobar infarction (hypodensity >1/3 cerebral hemisphere)	Exclusion criterion #7 met	PPS
A 2.08	Severe uncontrolled arterial hypertension, e.g. systolic blood pressure (BP) >185 mmHg or diastolic BP >110 mmHg	Exclusion criterion #8 met	None
A 2.09	Blood glucose <50 mg/dL(2.8 mmol/L) at screening	Exclusion criterion #9 met	PPS
A 2.10	Seizure at stroke onset	Exclusion criterion #10 met	None
A 2.11	Known hypersensitivity to active substance alteplase or tenecteplase, gentamicin or to any of the excipients	Exclusion criterion #11 met	None
B	Informed Consent		
B1	Informed consent not available/not done	Inclusion criterion #6 not met	All
B2	Informed consent too late, i.e., after randomization	Date of informed consent not obtained prior to any study related procedure.	None
C	Trial medication and randomisation		
C1.01	Incorrect medication received by patients	Wrong medication taken, i.e. Electronic case report form (eCRF) kit number does not match kit number assigned by interactive response technology (IRT) [Needs unblinding to determine if kit is same medication as assigned or not – so, will be finally judged after database lock(DBL)]	PPS

IPD Code	IPD Category & brief description	Example/Comment	Exclude from which analysis set
C2.01	Non-compliance with study drug intake not due to AE	Administration dose less than planned dose 67% or over planned dose 10%	PPS
C3.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IRT	FAS, PPS
D	Concomitant medication (CM)		
D2.01	Use of prohibited therapy	Review of eCRF for prohibited medication	None
E	Critical study procedure/assessment		
E1	Improper unblinded primary endpoint assessment		PPS

6.3 INTERCURRENT EVENTS

The expected intercurrent events (ICE) of interest in this trial are listed in Table 6.3:1 together with handling strategy.

Table 6.3: 1 Intercurrent events (ICE) and handling strategy

ICE	Handling strategy	Comments
Perform thrombectomy	Treatment policy (Include all available data)	This event reflects the clinical practice and will be included in efficacy evaluation
Death	Will not be considered as ICE for primary objective	Death event is included in mRS variable (death is equivalent to score 6)
	Composite strategy for secondary and further functional score related objective	Missing data due to death will be replaced to corresponding worst score

6.4 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial.

Enrolled Set (ES)
This subject set includes all patients who signed informed consent. It will be used for analysis of disposition.

Randomised Set (RS)
This subject set includes all randomised patients, whether treated or not.

Safety Set (SS)
This subject set includes all patients who are randomised and received any dose of treatment. It will be the basis for safety analysis. The assignment of patients to treatment groups will be based on the initial actual study medication administration in the treatment period.

Full Analysis Set (FAS)
This subject set includes all randomised patients received any dose of treatment. The assignment of patients to treatment groups will be based on the planned randomised study medication at the time of randomisation. It will be the basis for efficacy analysis according to the intention-to-treat principle.

Per-Protocol Set (PPS)
This subject set includes all patients in the FAS who adhered to the CTP without any iPDs relevant for efficacy which lead to exclusion from the PPS. A protocol deviation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint, which will be assessed on a case-by-case basis. This set will be used for sensitivity analysis for the primary efficacy endpoint.

The summary of which data sets will be used for which class of endpoints is illustrated in Table 6.4: 1.

Table 6.4: 1 Subject sets analysed

	Subject sets			
Class of endpoint	**ES**	**SS**	**FAS**	**PPS**
Disposition	X			
Demographic/baseline variables			X	X
Primary endpoints			Primary analysis [redacted]	[redacted]
Subgroup analysis			X	
Secondary and further efficacy endpoints			X	
Safety endpoints & treatment exposure		X	X	

The number of patients with available data for an endpoint may differ.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The functional outcome parameters missing due to death will be replaced by the worst scores, i.e. 6 for mRS; 42 for NIHSS; 0 for Barthel Index score; 5 for Glasgow Outcome Scale. This is the first step for all functional outcome parameters related analysis by default.

Every effort will be made to collect complete data at all visits. However, functional outcome parameters of surviving patients missing values might occur. The below approaches will be used to handle of these missing values.

The summary of missing data handling approaches for each endpoint is displayed in Table 6.6: 1. More details for the handling approaches are mentioned in Section 6.6.1 and 6.6.2.

Table 6.6: 1 Summary of missing data handling approaches for each endpoint

Class of endpoint	**Full analysis set (FAS)**	**Per-protocol set (PPS)**	**Safety set (SS)**
Primary endpoint	Primary analysis: Multiple imputation (MI)		
Secondary endpoint	Binary: MI for mRS related, OC for others; Continuous: Mixed model for repeated measures (MMRM)*		Binary: OC

* Missing data will be handled implicitly by MMRM under the assumption of missing at random (MAR).

6.6.1 Efficacy data

Based on the different reasons for patients' data missing for different endpoints, various approaches will be used to assess the impact of missing data on the efficacy endpoint of this trial. Imputation approaches to be applied are described below.

Missing data imputations will be performed using all available data observed up to the respective analysis date.

6.6.1.1 Binary efficacy endpoints

MI approach-primary imputation approach

This approach will be used for endpoints: Dichotomized endpoints for mRS score (0-1, 0-2, 5-6) at day 90 and mRS score (0-1, 0-2) at day 30.

Use data observed at day30 and day 90, impute mRS as ordinal variables with values 0, 1, 2, 3, 4, 5 and 6. The imputation will be done using OC data as the input dataset and will follow the steps outlined below:

Step 1: Multiple imputation of missing data: The SAS procedure PROC MI with the Fully Conditional Specification (FCS) method will be used. Logistic regression method is used to impute missing values by using the ordering of the class level in each variable.

The variables mRS_day30 and mRS_day90 represent the mRS score in Visit 5 and Visit 6. These two variables are treated as ordinal variable from 0 (best) to 6 (worst). For each mRS imputed at specific visit, the mRS at the other visit are used as covariates together with the treatment and other continuous factors (NIHSS score at baseline, age and time to administration). Example SAS code is as follows:

```
PROC MI DATA= data_input seed= 112340 nimpute=1000 out=mi_fcs;
    CLASS mRS_day30 mRS_day90 trt;
    FCS logistic (mRS_day30  mRS_day90 /details);
    VAR mRS_day30 mRS_day90 trt factors;
RUN;
```

Note that the seed 112340 will be used throughout. The imputation process will be conducted 1000 times to produce 1000 complete datasets.

Step 2: Analysis of completed datasets: For each imputed complete dataset, the statistical analysis specified in Section 7.4.1 will be performed to produce risk ratio. This will then result in 1000 sets of results, from the analysis on each of the 1000 completed datasets.

The 1000 completed datasets will be saved and directly used for other analysis which also uses MI approach and is based on the same analysis set.

Step 3: Combine results:

For the response rate of each arm, the point estimate will be calculated as the mean of each response rate from each imputation and the 95% confidence interval (CI) for each arm calculation will implement the MIWilson approach [3]. Algorithms to calculate 95% CI for each arm are provided in Section 10.1.

For the risk ratio, Rubin's rules will be applied on the log-transformed estimates to get the final combined estimate of RR and CI in log scale, which will then be back-transformed to the original scale. Example SAS code is as follows:

```
PROC MIANALYZE DATA=Estimates (where=(label="beta"));
    ODS OUTPUT PARAMETERESTIMATES=mian_lgrr_t;
    MODELEFFECTS LBETAESTIMATE;
```

```
    STDERR STDERR;
RUN;
DATA mian_lgrr_bt;
    SET mian_lgrr_t;
    Estimate_back = EXP(ESTIMATE);
    LCL_back=EXP(LCLMEAN);
    UCL_back=EXP(UCLMEAN);
RUN;
```

For risk difference in the supplementary analysis for primary endpoint, the distributions are approximately normal, so Rubin's rules will be implemented directly using PROC MIANALYZE.

[redacted]

Observed case (OC) approach: include all collected data with no imputation performed on the missing data except that the missing data due to death will be replaced as the worst value 6.

This approach will be used for endpoints below:

mRS score 0-1 at day 90;

Major neurological improvement at 24 h (NIHSS score of 0 or improvement of at least

4 points compared with baseline);

Barthel Index score ≥95 at day 90;

Barthel Index score ≥85 at day 90;

[redacted]

[redacted]

[redacted]

[redacted]

6.6.1.2 Continuous efficacy endpoints

1) For continuous endpoint "Change from baseline of NIHSS score at day 90", missing data will be handled implicitly by the statistical model MMRM under the assumption of MAR;

2) For continuous endpoint "NIHSS score at [redacted] 24 h, [redacted]", missing data handling approach will be OC approach.

6.6.2 Safety data

Missing or incomplete AE onset dates and time are imputed according to BI standards [4].

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 not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of any randomised treatments.

Table 6.7: 1 presents the visit structure according to the study flowchart depending on the time window scheduled in the CTP. Table 6.7: 2 presents the extended time windows around the planned visit dates.

Table 6.7: 1 Visit structure

Period	**Baseline**	**Randomisation and drug administration**	**On-treatment & Post-treatment**					
Visit number per protocol	V1	V2a	V2b	V2c	V3	V4	V5	V6/End of study (EOS)
Planned study window	none	none	1 hour ± 15	2 hrs ± 30 mins	24 hrs ± 2hr	7 days ± 2 d	30 days - 2d or +7 d	90 days ± 7 d

[redacted]	[redacted]	[redacted]	[redacted]				
			[redacted]				
Study Day	← D1 →			D2	D8	D30	D90
Visit description *	Baseline	1H	2 H	24 H	Day 8	Day3 0	Day90

*Label to be used in tables.

[redacted]

7. PLANNED ANALYSIS

Disposition of the patient population participating in the trial will be analysed by treatment groups and presented as a frequency distribution. The number of patients participating in the study will also be analysed by treatment group and presented as a frequency distribution.

A frequency of patients with iPDs will be presented by treatment group. The frequency of patients with trial specific COVID-19 related PD categories will be presented by treatment group. The frequency of patients in different analysis sets will also be presented by treatment group.

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 / standard deviation (SD) / Min / Median / Max are for continuous data, with one more decimal place compared to the original data for Mean, SD, Median; with same decimal place compared to the original data for Min and Max. 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 missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section. The demographic and baseline characteristics listed in Section 5.4.1 will be presented by treatment groups based on FAS and PPS, respectively.

A summary of the number of patients in each randomisation stratum per treatment group will also be shown based upon the information from the IRT provider. However, all other analyses will use the actual information collected via the CRF to derive the actual stratification category. Summary of patients allocated to the wrong stratum will be shown as well.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics of concomitant disease and therapy (medication and non-drug therapy) by treatment group are planned based on RS.

Concomitant disease (i.e. baseline conditions) will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA). All concomitant disease will be summarised by treatment, System Organ Class (SOC) and Preferred Term (PT).

Concomitant therapy will be coded according to the World Health Organisation – Drug Dictionary (current version at the time of analysis), sorted by the Anatomical-Therapeutic-Chemical classification level 3(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 that started on or before study drug bolus administration and is stopped after end of infusion and therapies with new onset after treatment start until Visit 6 (EOS) will be summarized by treatment groups.

Concomitant non-drug therapy will be coded according to the most recent version of MedDRA and will be summarised by treatment, SOC and PT.

7.3 TREATMENT COMPLIANCE

Descriptive statistics are planned for this section of the report. The number and percentage of patients with overall compliance will be reported on SS. Treatment administration including planned dose, actual dose and reason for administration altered or stopped prematurely will be listed by each patient.

7.4 PRIMARY OBJECTIVE ANALYSIS

The primary endpoint in this trial is mRS score of 0 or 1 at day 90. An overview table of analysis approach for primary endpoint is listed in Table 7.4: 1.

7.4.1 Main analysis

Comparisons between treatment groups regarding the binary endpoint mRS 0-1 at day 90 will be performed on FAS using Log-binomial regression model with subsequent transformation for the estimated parameters to risk ratio including the respective CI. The difference in log (proportion of mRS0-1 at day90) between tenecteplase and alteplase will be estimated with 95% CI adjusting for continuous covariates (NIHSS at baseline, age and time to drug administration). The estimate and CI will be exponentiated to return to the ratio scale. The statistical model will be described as follows:

(M1) Log (E{proportion of mRS0-1 at day90}) = treatment + NIHSS at baseline + age + time to drug administration.

The analysis will be related to the defined primary estimand and performed on FAS. All data collected after performing thrombectomy will be used for the analysis. Patients will be assigned to treatment groups as randomised. Multiple imputation method mentioned in Section 6.6 will be used to handle the missing data of primary endpoint.

Example SAS code for Log-binomial regresson model is as follows:

```
proc genmod data = indata descending;
class trtVar (ref = 'trtref' param=ref);
model resp = trtVar &covar. / dist = binomial link = log;
estimate 'beta' trtVar 1 /exp;
run;
```

If the Log-binomial model fails to converge and thus the model fails to provide valid risk ratio estimate, then the modified Poisson regression model will be adopted to provide the risk ratio estimate and confidence interval.

Example SAS code for Modified Poisson regression model is as follows:

```
proc genmod data = indata descending;
class usubjid trtVar (ref = 'trtref' param=ref);
model resp = trtVar &covar. / dist = poisson link = log;
repeated subject = usubjid / type = unstr;
estimate 'beta' trtVar 1 /exp;
run;
```

Distribution of mRS at day 90 before dichotomization for primary analysis will be plotted using Grotta bars.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

Not applicable as no key secondary endpoints have been specified in CTP.

7.5.2 Secondary objective analysis

Secondary endpoints will be analysed in an exploratory manner.

7.5.2.1 Responder analysis

The responder analysis includes the analysis of secondary efficacy endpoints of major neurological improvement at 24 h (NIHSS score of 0 or improvement of at least 4 points compared with baseline), mRS score of 0-2 at day 90 and Barthel Index score ≥ 95 at day 90.

The responder analysis will be performed on FAS by determining the percentage of patients that fulfill responder criteria. The corresponding imputation approach for each endpoint mentioned in Section 6.6 will be used to handle the missing data. The analysis will consist of a tabulation by treatment of the percentage of responders along with 95% confidence intervals. Same Log-binomial regression model used for primary analysis of primary endpoint with categorical treatment and continuous NIHSS at baseline, age and time to drug administration since onset of stroke symptoms will be fitted on the corresponding binary response variable to calculate the estimate of the risk ratio of treatment to active control group. Estimate of risk ratio and 95% confidence intervals will be presented along with the p-values for the comparison.

If the Log-binomial model fails to converge and thus the model fails to provide valid risk ratio estimate, then the modified Poisson regression model will be adopted.

7.5.2.2 Change from baseline of NIHSS score at day 90

A restricted maximum likelihood (REML) based MMRM approach will be used to compare the change from baseline in NIHSS score at day 90. The analysis will be based on FAS. If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the MAR assumption.

The statistical model will be:

Change in NIHSS score from baseline = overall mean + treatment + visit + baseline NIHSS + age + time to drug administration since onset of stroke symptoms + treatment by visit interaction + baseline NIHSS by visit interaction + random error.

For each patient, the error terms from all visits represent the within-patient variability and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors.

7.5.2.3 Distribution of mRS at day 90

Distribution of mRS at day 90 will be summarised. Comparisons between treatment groups

regarding the ordinal variable mRS at day90 will be performed using the ordinal logistic regression model including continuous covariates NIHSS at baseline, age and time to drug administration since onset of stroke symptoms. If the proportional-odds assumptions are not met, alternative assumption-free ordinal analysis [7, 8, 9] on the mRS score will be used. Grotta bars will be presented as well.

A forest plot showing odds ratio of a good stroke outcome, for each alternative definition of 'good' outcome (mRS 0; 0-1; 0-2; 0-3; 0-4; 0-5) will also be presented.

7.5.2.4 Symptomatic Intracerebral Haemorrhage (sICH) per European Cooperative Acute Stroke Study (ECASS) Ⅲ definition

Number of patients with sICH occurred during on-treatment period per ECASS Ⅲ definition will be tabulated in frequency tables by treatment groups based on SS. Comparisons between treatment groups regarding the binary endpoint variable will be performed using Suissa-Shuster test. The unadjusted risk ratio together with 95% confidence interval will be used to quantify the treatment effect for the following pair-wise comparisons of interest: tenecteplase vs alteplase. No imputation is planned for the analysis. Wilson method [10] will be used to provide confidence intervals for single proportions. Chan and Zhang [11] method will be used to provide confidence interval for unadjusted risk ratio.

Number of patients with investigator reported Intracranial Haemorrhage(ICH) events identified by MedDRA PTs during on-treatment period will be tabulated in frequency tables by treatment groups based on SS. The MedDRA PTs are shown in Section 10.2. Comparisons between treatment groups regarding the binary endpoint variable will be performed using Suissa-Shuster test.

Number of patients with ICH events by cerebral imaging as well as the haemorrhage clarification (HI1, HI2, PH1 and PH2) during on-treatment period will be tabulated in frequency tables by treatment groups based on SS. Comparisons between treatment groups regarding the binary endpoint variable patients with Intracranial hemorrhage clarification PH2 by CT image will be performed using Suissa-Shuster test.

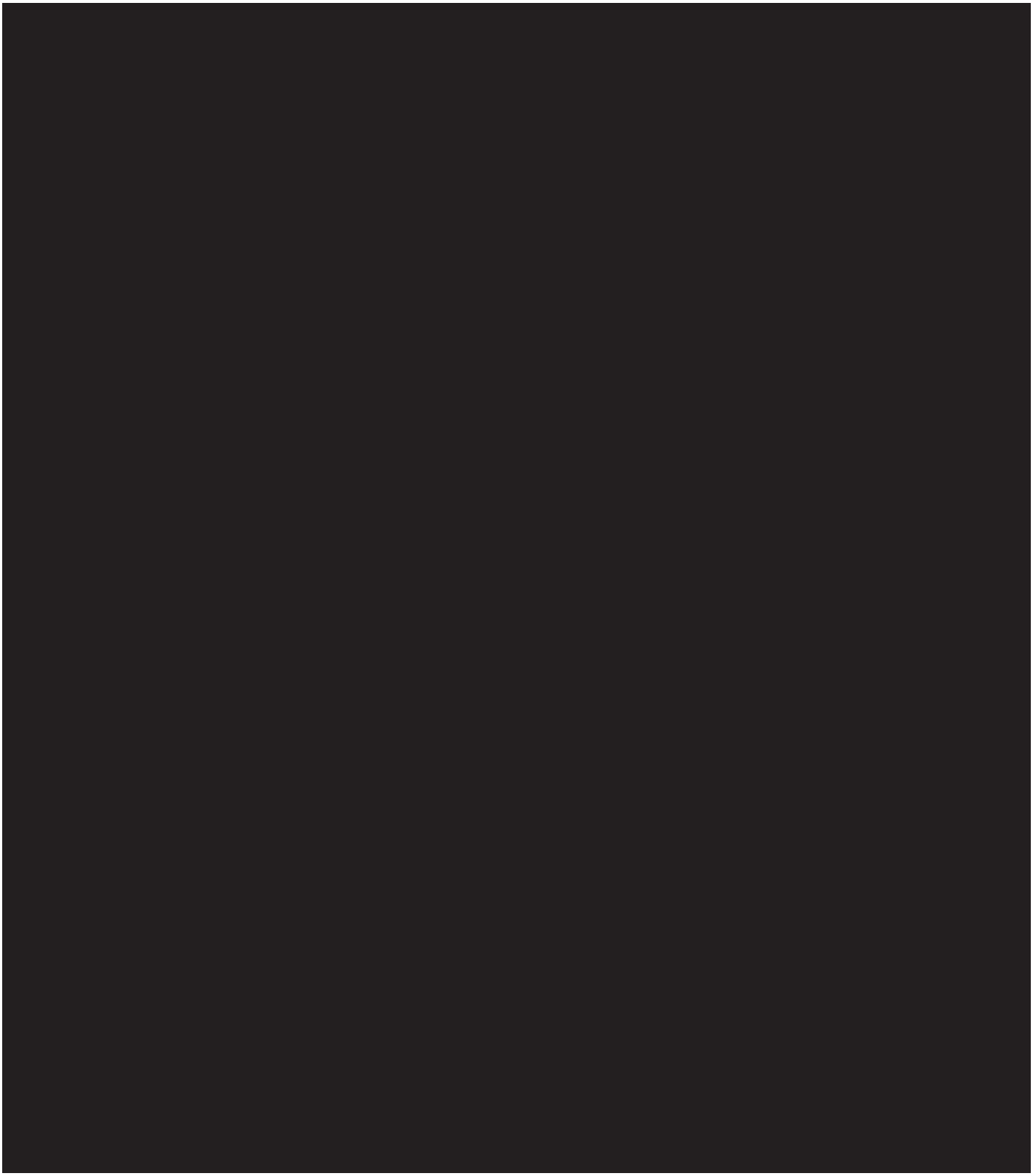
7.5.2.5 90-day mortality

Frequency of death by each time interval (day 0-7, day 8-30, day 31-90 and day >90) will be tabulated by treatment groups based on SS. The 90-day mortality cut-off date will be day 90. Comparisons between treatment groups regarding the binary endpoint variable will be performed using Chi-square (X^2) test. The unadjusted risk ratio between two treatment group and corresponding 95% confidence interval will be calculated to quantify the treatment effect for the following pair-wise comparisons of interest: tenecteplase vs alteplase. Wilson method [10] will be used to provide confidence intervals for single proportions. Wald method will be used to provide confidence interval for unadjusted risk ratio. No imputation is planned for the analysis.

7.5.2.6 mRS score of 5 or 6 at day90

Number of patients with mRS score of 5 or 6 at day90 will be tabulated in frequency tables by treatment groups based on FAS. The adjusted risk ratio between two treatment group and corresponding 95% confidence interval will be estimated using Log-binomial regression model including categorical treatment and continuous NIHSS at baseline, age and time to drug administration since onset of stroke symptoms as covariates.

Note that though it is defined as safety endpoint in CTP, all related analysis outputs will be presented in Section 15.2 together with other mRS score related efficacy endpoints.



7.7 EXTENT OF EXPOSURE

Only descriptive analyses are planned for this section. Total duration will be presented only for alteplase group. Actual dose received and actual dose received per kg will be presented by treatment group. The analysis will be performed on the SS.

In addition, time in study will be analysed descriptively on SS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on SS. The secondary and further safety endpoints are mentioned in Section 7.5 and 7.6.

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. For further details on summarization of AE data, please refer to the guidance [12].

The primary interest analysis of AEs will be based on the concept of treatment emergent (on-treatment period) AEs, i.e. AEs occurring between start of treatment and end of the REP.

AEs stopped before the start of bolus treatment administration will be assigned to ‘screening’ and AEs occurring after the end of REP to Visit 6 will be assigned to ‘post-treatment’. For details on the treatment definition, see Section 6.1. The frequency of all AEs collected from signing informed consent until study completion will also be summarized.

According to ICH E3, AEs classified as ‘other significant’ needs to be reported and will include those non-serious AEs with ‘action taken = discontinuation’ or ‘action taken = reduced’.

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by primary SOC and 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 (SAE)
- Drug-related AEs
- Drug-related SAEs
- AEs leading to treatment discontinuation
- AEs leading to death
- Other significant AEs (according to ICH E3 [13])
- 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 presented for both on-treatment period and the overall period (from inform consent to study completion).

7.8.2 Laboratory data

For continuous safety laboratory parameters original and standardized values will be summarised as well as the change from baseline. Frequency of patients with possible clinically significant abnormalities will also be summarised by treatment groups.

7.8.3 Vital signs

Descriptive statistics of vital sign will be presented over all measured time points for absolute value and change from baseline. Figures may be presented over specified time points if appropriate.

7.8.4 ECG

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

7.9 OTHER ANALYSIS

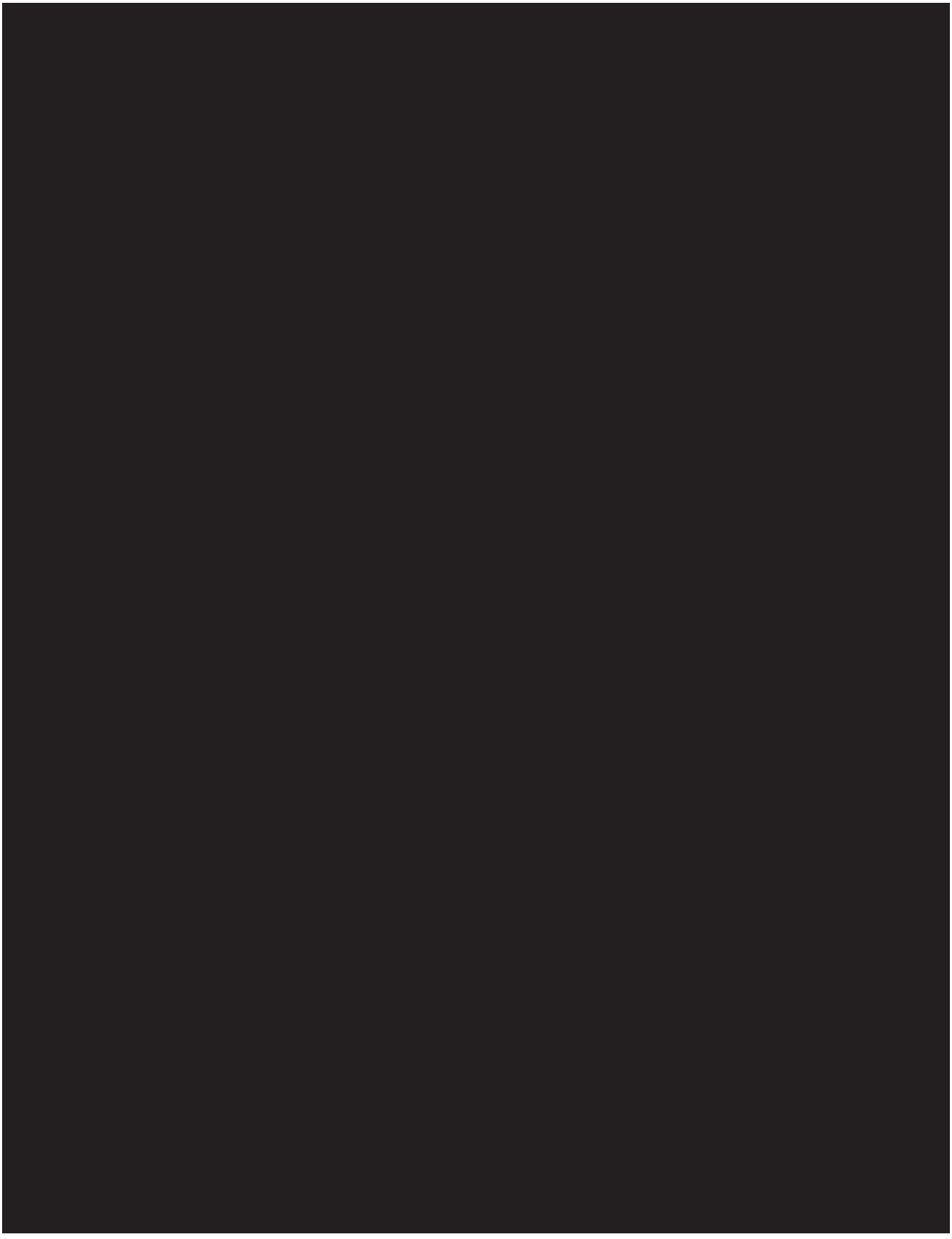
Not applicable.

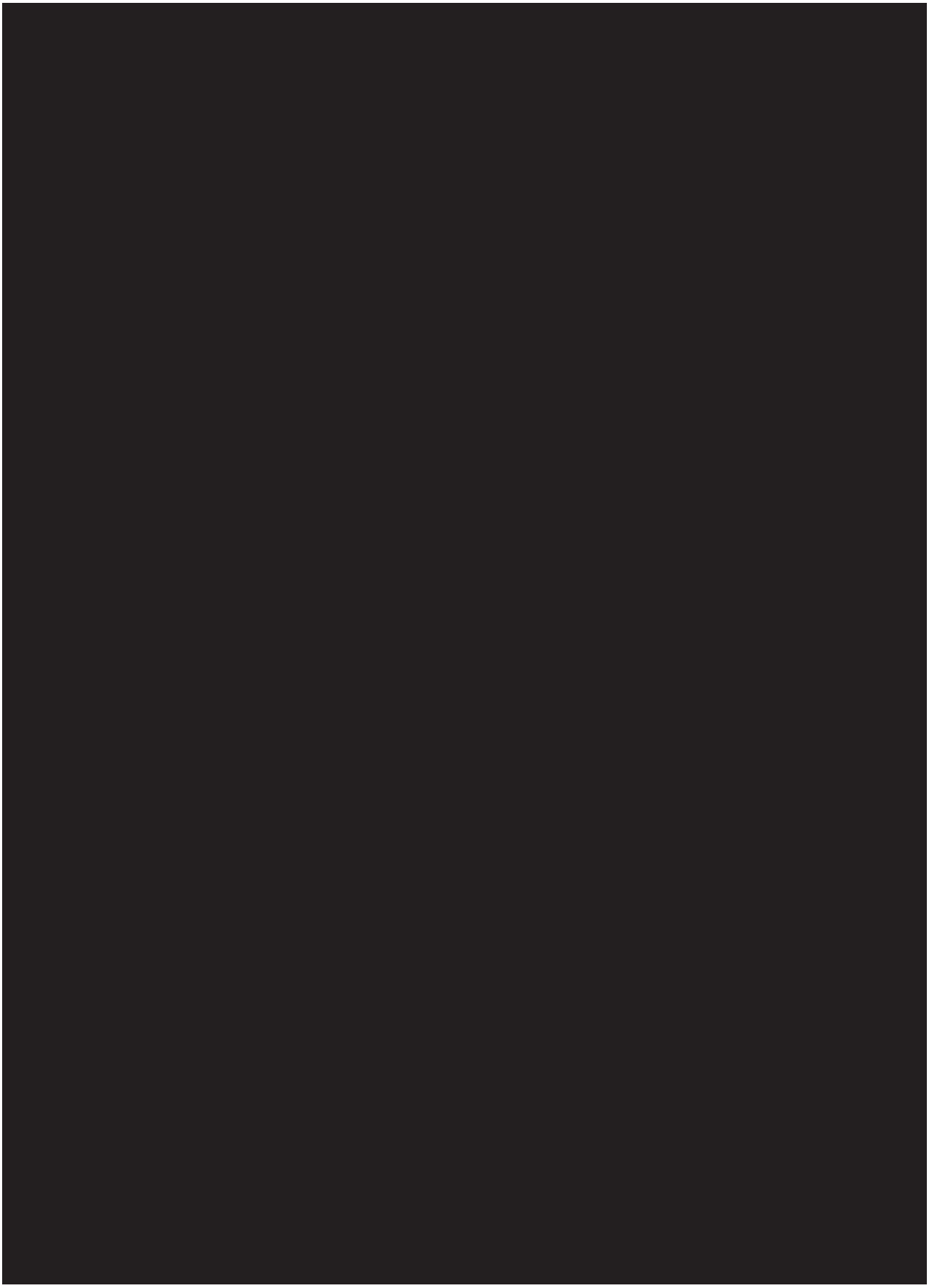
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

This trial is an open-label trial but the database is handled in blinded way. The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.

9. 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	*Anne Lott & Jerome P. Reiter. Wilson Confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data. The American Statistician 2020; 74:2, 109-115*
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	*Ge, Miaomiao & Durham, L. & Meyer, Dan & Xie, Wangang & Thomas, Neal. (2011). Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal - DRUG INF J. 45. 481-493.*
7	*Agresti A. Generalized odds ratios for ordinal data. Biometrics 1980; 36:59-67.*
8	*Howard G, Waller JL, Voeks JH. A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. Stroke 2012; 43:664-669.*
9	*Churilov L, Amup S, Johns H, et al. An improved method for simple, assumption-free ordinal analysis of the modified Rankin Scale using generalized odds ratios. Int J Stroke 2014; 9(8):999-1005.*
10	*Brown LD, Cai TT, DasGupta A. Confidence intervals for a binomial proportion and asymptotic expansions. Ann Stat 30 (1), 160 – 201 (2002).*
11	*Chan I S F, Zhang Z. "Test-based exact confidence intervals for the difference of two binomial proportions"[J]. Biometrics, 1999, 55(4): 1202-1209.*
12	*001-MCG-156: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", version 8.0; IDEA for CON.*
13	*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.*
14	*FDA: Guideline Adjusting for covariates in RCT for drugs and biological products.*





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	10-JUL-23	[redacted]	None	This is the final TSAP.
2.0	6-SEP-23		[redacted]	[redacted]