

# Statistical Analysis Plan

A Multicenter, Randomized, Blind Endpoint and Positive Drug Controlled Phase III Study of Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection in the Treatment of Patients with Acute Ischemic Stroke

## CRAD-001-03

<b>Study drug:</b>	Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection
<b>Control drug:</b>	Alteplase
<b>Indication:</b>	Acute ischemic stroke
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## Table of abbreviation

English abbreviation	The full name in Chinese
AE	不良事件
AIS	急性缺血性脑卒中
ALT	丙氨酸氨基转移酶
AST	门冬氨酸氨基转移酶
CI	置信区间
CREA	肌酐
CTCAE	不良事件通用术语标准
eCRF	电子病例报告表
FIB	纤维蛋白原
GEE	广义估计方程
ISTH	国际血栓与止血学会
mITT	修正的意向性治疗
IWRS	交互式网络应答系统
LOCF	最近一次观测向后结转
LSM	最小二乘均值
MedDRA	国际医学用语词典
MMRM	重复测量的混合效应模型
mRS	改良的 Rankin 量表
NCI	美国国立癌症研究所
NIHSS	美国国立卫生研究院卒中量表
OR	比数比
PT	首选术语
RD	率差
RR	比值
SAE	严重不良事件
SAP	统计分析计划
sICH	症状性颅内出血
SOC	系统器官分类
SS	安全性分析集
SUSAR	可疑且非预期严重不良反应
TBIL	总胆红素
TEAE	治疗期间发生的不良事件
TRAE	与治疗相关的不良事件
ULN	正常值上限
WHO	世界卫生组织

## 1. Summary of test

This statistical analysis plan (SAP) provides a reference for A Multicenter, Randomized, Blind Endpoint and Positive Drug Controlled Phase III Study of Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection in the Treatment of Patients with Acute Ischemic Stroke sponsored by Angde Biotech Pharmaceutical Co., Ltd. (Protocol No. CRAD-001-03) provided detailed descriptions of statistical analysis methods and data processing principles.

The SAP was developed on the basis of CRAD-001-03 protocol, version 2.2 (version date: November 17, 2022).

### 1.1 Purpose of the test

#### **Main purpose:**

To evaluate the efficacy of recombinant human tissue plasminogen kinase derivative for injection and alteplase in the treatment of patients with acute ischemic stroke within 4.5h of onset.

#### **Secondary purpose:**

To evaluate the safety of recombinant human tissue plasminogen kinase derivative for injection and alteplase in patients with acute ischemic stroke within 4.5 hours of onset.

### 1.2 Trial endpoint

#### 1.2.1 Efficacy endpoint

##### 1.2.1.1 Primay efficacy endpoint

Proportion of subjects with a mRS Score of 0-1 at 90 days after treatment.

##### 1.2.1.2 Secondary efficacy endpoint

- The proportion of subjects with NIHSS score  $\leq 1$  point or 4 points or more lower than baseline 24 hours and 7 days after treatment;
- The difference of NIHSS score from baseline to 24 hours and 7 days after treatment;
- The proportion of subjects with mRS Score 0-2 at 90 days after treatment;
- Continuous changes of mRS Scores at 30 days and 90 days after treatment;
- Proportion of subjects with Barthel index score  $\geq 95$  at 90 days after treatment.

### 1.2.2 Safety endpoint

- Vital signs, physical examination, laboratory examination, 12 lead electrocardiogram.
- Bleeding events according to category (ISTH criteria);
- All AE, SAE, SUSAR;

Of these, focus on the following events:

- All-cause death occurred within 7 days and 90 days after treatment;
- Symptomatic intracranial hemorrhage (SITS-MOST, ECASS III criteria);
- Post-treatment major bleeding events (ISTH criteria);
- Liver function tests within 7 days after treatment showed ALT $\geq$ 3 $\times$ ULN and TBIL $\geq$ 2 $\times$ ULN. Creatinine (CREA) increased to more than 3 times the baseline value or increased  $\geq$ 4 mg/dL (353.6 $\mu$ mol/L) within 7 days after treatment.

## 1.3 Design of the trial

### 1.3.1 General design of the trial

This study was a multi-center, randomized, blinded outcome, positive drug parallel controlled phase III trial of recombinant human tissue plasminogen kinase derivatives for injection in the treatment of acute ischemic stroke (AIS) within 4.5 hours of onset. Using the non-inferiority hypothesis, the difference between the test drug group and the positive drug alteplase group in the proportion of subjects with mRS Score 0-1 at 90 days after thrombolytic therapy as the main efficacy indicator was compared.

This study is only conducted in the Chinese population, multi-center participation, and 1412 AIS patients with onset within 4.5 hours are planned to be recruited, and the experimental group and the control group are assigned 1:1. After receiving thrombolytic drug treatment, subjects were required to undergo a series of safety and effectiveness checks. mRS Score and Barthel index score visits were conducted 90 days ( $\pm$ 7 days) after the start of thrombolytic drug treatment, and subjects were allowed to leave the group after the visit.

In this study, independent blind end-point evaluators were set up to evaluate the mRS Scale and Barthel index score at 30 days and 90 days after the initiation of thrombolysis in a blind manner.

The detailed test flow table is shown in the scheme test flow table.



### 1.3.2 Determination of sample size

The primary efficacy measure was the proportion of subjects with a mRS Score of 0-1 at 90 days after treatment using noninferiority statistics. According to history trial data of positive control drug alteplase [1] [2], its lower limit of the 95% confidence interval of risk ratio (RR) to placebo is 1.15, if consider  $\alpha$  value was 0.05, then the non-inferiority margin compared to the active comparator alteplase was 0.93. According to the data of previous trials of alteplase and the results of phase II clinical trials of recombinant human tissue plasminogen kinase derivatives for injection in the treatment of acute ischemic stroke, P=62.5% was selected as the primary efficacy effect of the alteplase group, assuming a true efficacy ratio of 1.05 in the experimental group and the control group, and a significance level ( $\alpha$ ) of 0.025 (one sided). The power ( $1-\beta$ ) was 80%. The experimental group and the control group were designed in a 1:1 ratio, and the dropout rate was expected to be about 15%, then, 706 subjects per group for a total of 1412 subjects were needed. According to the data of previous trials, the incidence of symptomatic intracranial hemorrhage was estimated to be about 1% with reference to SITS-MOST study [3], and the mortality rate was estimated to be about 5% with reference to NOR-TEST study [4]. Based on the sample size of 1412 cases, the probability of finding at least one death or symptomatic intracranial hemorrhage was greater than 99%.

### 1.3.3 Randomization and blinding

The randomization system IWRS was used to assign the random number. The randomization numbers of the subjects were generated by an independent statistician unrelated to the study using SAS9.4 or higher software. Simple stratified randomization was performed in 1:1 variable blocks according to the trial drug or control drug. After eligibility, the investigator accessed the randomization and trial drug management system IWRS and obtained a random number. Randomly assigned subjects who withdraw from the trial for any reason, regardless of whether a trial drug has been given, will retain their randomization number and cannot be replaced, and withdrawn subjects will not be able to re-participate in the trial.

Due to the different administration methods of the trial drug and the control drug, and the limited time window for the treatment of acute patients, it was not possible to perform a blinded design at the drug and clinical treatment levels. However, in order to make the evaluation of the primary end point more objective and reduce artificial bias as much as possible, The mRS And Barthel index scores at 30 days and 90 days after thrombolysis were assessed by independent blinded end-point assessors in each center.

2. Estimand

2.1 Main estimand

**The main clinical question of interest in this study was:** Is the clinical thrombolytic effect of recombinant human tissue plasminogen kinase derivative for injection not worse than that of alteplase in patients with acute ischemic stroke within 4.5h of onset?

**Definitions of the main estimand:**

- 1. **Target Population:** All randomly assigned patients with acute ischemic stroke who received at least one dose of a trial drug and who basically met the main eligibility requirements
- 2. **Target variable:** whether the subject's mRS Score reached 0-1 at 90 days after treatment.
- 3. **Treatment:** intravenous injection of recombinant human tissue plasminogen kinase derivative for injection (18 mg + 18 mg) or intravenous infusion of alteplase for injection 0.9 mg/kg (maximum dose 90mg).
- 4. **Concurrent events and handling strategies:**

Concurrent event	Handling strategy	Note
Use other thrombolytic and fibrinolytic drugs	Compound strategy	A patient in the use of an unplanned down other fiber after medicine treatment the curative effect of the data obtained will be better than not to use, so according to the most conservative no answer processing of data after remedial treatment.
Use of antiplatelet and anticoagulant drugs (within 24 hours after the start of thrombolysis)	Therapeutic strategy	It truly reflects actual clinical practice. mRS Scores will continue to be collected after the occurrence of a concomitant event,

		and the actual observed value of the mRS Score will be used for analysis regardless of whether the concomitant event occurred.
Intracranial endovascular therapy was carried out to treat the intracranial endovascular treatment for the purpose of acute ischemic stroke *	Compound strategy	A patient who had received an unplanned intracranial endovascular treatment would have had better efficacy data than none, so the data after supplemental treatment were treated as the most conservative nonresponse.
Not according to the plan to complete treatment (including two unfinished original human recombinant tissue type fibrinolytic enzyme kinase derivatives atenolol injection or not completed the plan's enzyme dosage drip, super window, the actual drug treatment and treatment plan is not consistent, dose of nonadherence, etc.)	Therapeutic strategy	It truly reflects actual clinical practice. mRS Scores will continue to be collected after the occurrence of a concomitant event, and the actual observed value of the mRS Score will be used for analysis regardless of whether the concomitant event occurred.

Note: \* Test process was carried out to treat the intracranial endovascular treatment for the purpose of acute ischemic stroke: including thrombolysis within 24 h after beginning, to treat the acute ischemic stroke after intracranial endovascular treatment for the purpose of routine use of antiplatelet and anticoagulant drugs.

- 5. Population level summary:** Risk ratio (RR) and its 95% bilateral confidence interval.

## 2.2 Secondary estimand

The target population, treatment, and concomitant events were the same as the primary estimand;

Concurrent events will be treated as:

1. Therapeutic strategies were used for these major estimated target concomitant events.
2. For the above primary estimated target concurrent events, the same as the primary estimated target.

In addition, in the above cases, when the death occurred in other indicators (NIHSS score, Barthel index score) except mRS Score, the composite variable strategy was adopted and the treatment was treated as no response.

Secondary efficacy index	Target variable	Group level summary
The proportion of patients with NIHSS score $\leq 1$ or a decrease of 4 or more points compared with baseline at 24 hours and 7 days after treatment	Whether the NIHSS score of the subjects was $\leq 1$ or decreased by 4 or more points compared with baseline at 24 hours and 7 days after treatment	Same as the main estimated target
Proportion of subjects with mRS Score 0-2 at 90 days after treatment	Whether the mRS Score of subjects reached 0-2 at 90 days after treatment	
Proportion of subjects with Barthel index score $\geq 95$ at 90 days after treatment	Whether the Barthel index score of the subjects was $\geq 95$ at 90 days after treatment	
Difference in NIHSS score from baseline at 24h and 7 days after treatment	Changes in NIHSS scores from baseline to 24h and 7 days after treatment	Differences between groups, means and their 95% CI
Continuous changes in mRS Scores at 30 days and 90 days after treatment	Distribution of mRS Score grades at 30 and 90 days after treatment	Differences in rank order between groups and their P values

## 3. Statistical analysis

### 3.1 Basic principle

The SAP contains all statistical analysis will be done with SAS v9.4 or above.

Unless otherwise specified, all study data will be summarized and tabulated

by treatment group and visit/time point (if applicable) :

The continuous variables will be statistically described by case number, mean value, standard deviation, median value, minimum and maximum values of the 1st quantile (Q1) and 3rd quantile (Q3). Categorical variables were described with the use of frequencies and percentages for each category, and missing values were not included in the calculation of percentages unless otherwise noted. In addition, if necessary, for continuous variables, according to the data, t-test will be performed and P values will be provided if the data are normally distributed, and rank sum test will be performed and P values will be provided if the data are not normally distributed. For categorical variables, chi-square or Fisher's exact test was performed and P values were provided if not otherwise specified.

The data processing and decimal place retention principles of descriptive statistics are shown in **Table 1**:

**Table 1 Basic descriptive statistics processing principles**

Name	Description	Number of decimal places(dp)
N	Number of subjects in the analysis	Always displayed as 0 dp
%	Percentage	Categorical data are shown as
Mean	Arithmetic mean	1 dp more than the original
SD	Standard deviation	2 dp more than the original
Median	Median value	1 dp more than the original
Min	Minimum value	Same as the original data
Max	Maximum value	Same as the original data
CI	Confidence interval	1 dp more than the statistic
Missing	Missing	Always displayed as 0 dp

The derived data and its statistics will be 1 decimal place more than the original data and corresponding statistics. P values are presented as three decimal places or "< 0.001".

Unless specified otherwise, all the hypothesis test will use the bilateral inspection, inspection level for 0.05.

### 3.2 Analysis data set

- Random population: All randomly assigned subjects.
- Modified Intention-To-Treat (mITT): All randomly assigned subjects with acute ischemic stroke who had received at least one dose of a trial drug and who basically met the main eligibility requirements.
- Safety Set (SS): SS including subjects who were screened successfully and received investigational product and had at least one post-treatment safety evaluation. SS was used for safety analysis in this

trial, and subjects were analyzed according to the group in which they actually received the drug.

### **3.3 Multicenter study**

No differences among centers will be considered, data from all participating centers will be analyzed together, and center will not be considered as a variable in statistical models.

### **3.4 Adjustment for covariates**

Age and baseline NIHSS were included as covariates in the model for the sensitivity analysis of the primary estimator and the secondary estimator, with the interaction between group and visit taken into account.

### **3.5 Multiple comparisons and multiplicity**

The analysis of the primary estimation target of the trial involved a comparison of only one primary end point between the two treatment groups and therefore did not require multiple comparisons or adjustment for multiplicity.

### **3.6 Subgroup analysis**

If the data permit, subgroup analysis will be performed for the main efficacy measures based on the following factors:

- Age (18-60 years, > 60 years)
- Thrombolytic time window ( $\leq 3h$ , 3~4.5h)
- Baseline NIHSS score ( $\leq 7$  points, >7 points)
- MRS baseline score (0 points, 1 point)

If applicable, exploratory analyses will also be performed on other demographics, baseline disease characteristics, and preexisting/concomitant disease subgroups. In addition, interaction p values will be calculated and corresponding forest plots will be drawn.

## **4. Principles of Data Processing**

### **4.1 Derived variable**

#### **4.1.1 Duration of onset**

Duration of onset (minutes)= (First investigational drug dosing date time - Onset date time) /60。

### 4.1.2 Baseline and change from baseline

Baseline was defined as the last nonmissing assessment/examination (including unscheduled visits) before the first dose of trial drug.

The change from baseline was calculated as the postbaseline assessment/examination value minus the baseline value.

### 4.1.3 Study days

Study days were defined as the number of days from the efficacy/safety assessment to the reference date. the first test with drug delivery date as the reference date. The reference date will be recorded as day 1.

Study days were calculated as follows:

- Study days = Date of assessment/examination - Date of reference + 1, If the evaluation/examination is after the reference date

OR

- Study days = Date of assessment/examination - Date of reference, If the evaluation/examination is prior to the reference date.

## 4.2 Missing data

### 4.2.1 Missing efficacy and safety data

In the efficacy analysis, if the subjects were lost to follow-up or the mRS Score was missing, the specific treatment methods were detailed in the efficacy analysis section 5.2.2.

Unless otherwise specified, missing data were treated as missing and were not imputed with any assumptions.

### 4.2.2 Missing/incomplete dates

#### Adverse events/concomitant medications

- If the date of adverse event/concomitant medication initiation was recorded only in the year and month, the date of adverse event/concomitant medication initiation was imputed to the first investigational drug administration date if the year and month were the same as the year and month of the first investigational drug administration date (if the imputed date of adverse event/concomitant medication initiation was later than the end date of the imputed date of adverse event/concomitant medication initiation was later than the end date of the imputed date of adverse event/concomitant medication initiation). The start date will be filled directly with the end date);

Otherwise, the start date of the adverse event/concomitant medication was filled in as the first day of the month when the adverse event/concomitant medication was started (day 1). If the start date of the imputed adverse event was earlier than the informed consent date, the start date was filled in directly as the informed consent date.

- If adverse events/drug combination start date only records the year, if the test for the first time to use drug delivery date and year of the same year, adverse events/drug combination start date will be filling test for the first time to use drug delivery date (if adverse events after filling/drug combination start date later than the end date, direct filling will start date to end date). Or adverse events/drug combination start date will begin filling/drug combination for adverse event was the first day of January (1), if fill the adverse events after the start date earlier than the date of informed consent, date directly fill the start date will be informed consent.
- If adverse events/drug combination end date is not complete, adverse events/drug combination end date will be populated for adverse events/drug combination end on the last day of that month or the last day (December 31), but no later than the end date/date of death of the two earliest date (if applicable).
- If the date was completely missing, no padding was performed
- Imputation judgements will be made only when TEAE cannot be judged and when the duration of AE is calculated.

#### Date of death

- If only the year of the date of death was recorded and the year was the same as the year of the last known date of the subject's survival, the missing month and day in the date of death was filled in by the last known date of the subject's survival +1, otherwise the first day of the year of the date of death (January 1) was used.
- If only record the year and month of the date of death, and month and year and the last known subjects were alive at the same year, month, date, using the last known subjects live date + 1 to populate the date of death, death or the date on the first day of that month (1).
- If the date of death was completely missing, the date of death was filled in using the last known subject alive date +1.



### 4.3 Visit window

All analyses performed according to visit/time point will be analyzed at the planned visit/time point, regardless of deviations from the visit window. Deviations from the use of the primary end point will be decided at the data review meeting.

## 5. Statistical analysis

### 5.1 Subjects

#### 5.1.1 Distribution of subjects

All screened subjects will be included in the analysis.

Subjects were considered to have failed screening if they withdrew from the study between the time of signing informed consent and before randomization. The total number and reasons of screening failure, screening success but random failure were reported, and the reasons for screening failure were listed. Subjects who failed screening will no longer be included in other analyses.

According to the randomized group, the number and proportion of randomized subjects who received medication were summarized, and the situation of randomized subjects who did not receive medication was listed.

According to the random group, the number and proportion of subjects who prematurely withdrew from the study due to different reasons were summarized for all randomized subjects, the reason of early exit will be in accordance with the order of the electronic case report form (eCRF) presented in the table. The completion of the test for the subjects of all random list.

The number and percentage of participants who were enrolled and who were not enrolled for various reasons in each analysis data set were summarized according to randomization group. The number of participants who were randomly selected was used as the denominator for the calculation of percentages. The table illustrates the distribution of each analysis data set and the reasons for exclusion from the analysis data set.

#### 5.1.2 Protocol deviation

Protocol deviation will be classified as mild and major deviations.

Based on randomized analysis set, Major protocol deviations were tabulated by classification for all subjects in each treatment group, Categories will be presented in tables by ordinal number on the PD listing. The major protocol deviations and all protocol deviations were tabulated separately.

### 5.1.3 Demographic and baseline characteristics

#### 5.1.3.1 Demographic

Based on the mITT, according to the treatment group of demographic (age, and age groups (18 ~ 60 years, and > 60 years), gender, ethnic, weight to summary the tabulation and corresponding data list. In addition, between-group comparisons were performed, and P values for t-tests or rank-sum tests were calculated for continuous variables. For categorical variables, P values for Fisher's exact probability tests will be calculated.

#### 5.1.3.2 Baseline disease characteristics

Based on the mITT, according to the treatment group of baseline disease characteristics to summary tabulation and list below. In addition, between-group comparisons were performed, and P values for t-tests or rank-sum tests were calculated for continuous variables. For categorical variables, P values for Fisher's exact probability tests will be calculated.

- Duration of onset (minutes)
- Thrombolytic time window ( $\leq 3h$ ,  $3\sim 4.5h$ ,  $>4.5h$ )
- Baseline NIHSS score
- Baseline NIHSS score group ( $\leq 7$  points,  $>7$  points)
- mRS baseline score (0, 1, 2 and above)
- TOAST classification
- Localization diagnosis.

#### 5.1.3.3 Other baseline characteristics

Based on mITT, the results of allergy, pregnancy examination, finger blood glucose, etc. of the subjects were listed according to the treatment group. Other tests and baseline are analyzed together in Section 5.3.

### 5.1.4 History of stroke

Previous stroke history was coded with the use of the International Dictionary of Medical Terms (MedDRA), version 25.1.

Based on the mITT, according to the classification system organs (SOC) and the preferred term (PT) to summary of history of stroke, calculate the number of cases and the percentage of the subjects.

Previous stroke history was tabulated according to treatment group.

### 5.1.5 Concomitant diseases, other past medical history, and history of trauma

Concomitant medical conditions, other previous medical conditions, and

history of trauma were coded with the use of the International Dictionary of Medical Terms (MedDRA), version 25.1.

Based on the mITT, according to the classification system organs (SOC) and the preferred term (PT) to carry on the summary of accompany disease, other previous medical history, calculated the number of cases and the percentage of the subjects.

List of concomitant diseases, other past medical history, and history of trauma for all mITT subjects according to treatment group.

#### **5.1.6 Previous surgical history**

Previous surgical history was coded with the use of the International Dictionary of Medical Terms (MedDRA), version 25.1.

Based on mITT, the previous surgical history was summarized by system organ classification (SOC) and preferred term (PT), and the number and percentage of subjects were calculated.

List of previous surgical history for all mITT subjects according to treatment group.

#### **5.1.7 Previous and concomitant medications**

Previous and concomitant medications were coded with the use of the WHO Drug Dictionary 2022 Sep 1, providing preferred drug names (PN) and Anatomical Therapeutic and Chemical Classification System (ATC) classifications.

Based on mITT, previous and combined medications were summarized according to ATC classification level 2 and PN, respectively, and the number and percentage of subjects were calculated:

- Previous medications, i.e., medications used only before administration of the first investigational product (i.e., discontinued before administration of the first investigational product)
- Concomitant medications, i.e., medications used during treatment (i.e., medications that were not discontinued before the first dose of a trial drug or started between the first dose of a trial drug and completion of the last treatment visit)

Medications were considered to be concomitant if the time of administration relative to the first dose of the investigational product could not be determined.

Based on the mITT, according to the treatment group of subjects always list and drug combination.

### 5.1.8 Combined with non-drug treatment

Nonpharmacologic treatments were coded with the use of MedDRA, version 25.1.

Based on the mITT, according to the classification system organs (SOC) and the preferred term (PT) to carry on the summary of not drug therapy, calculate the number and percentage of subjects:

- Concomitant non-drug therapy, i.e., non-drug therapy used during treatment (i.e., non-drug therapy not stopped before first administration of the trial drug or started between first administration of the trial drug and completion of the last treatment visit).

If the time of treatment relative to the first dose of the trial drug could not be determined, it was considered to be concomitant nonpharmacologic treatment.

Based on the mITT, according to the treatment group on the subjects' combined non-drug therapy to the list.

### 5.1.9 Medication adherence and drug exposure

According to treatment group, the drug exposure (total exposure, 1/2 exposure), dosing interval, and duration during the study were descriptively analyzed. "In addition, the number and percentage of subjects with interruptions and their different causes, as well as infusion reactions, will be analyzed in a pooled manner according to treatment group."

In addition, adherence to the investigational drug will be evaluated by calculating the proportion of the actual dose to the planned dose. Compliance calculation formula: Adherence (%) = actual dose/planned dose × 100%

According to the treatment group of participants' adherence to summary descriptions, and calculate the compliance < 80%, 80% to 120% and > 120% of the participants and the number of percentage.

List of administration of the trial drug according to treatment group.

## 5.2 Efficacy analysis

### 5.2.1 Main estimand

#### 5.2.1.1 Main analysis of the main estimand

Hypothesis tests for the proportion of subjects with a mRS Score of 0-1 at 90 days after treatment were as follows:

$$H_0: RR_{T/R} \leq 0.93$$

$$H_1: RR_{T/R} > 0.93.$$

Here,  $RR_{T/R}$  represents the risk ratio of the trial drug to the control drug.

Subjects who died within the corresponding post-treatment visit were considered to have a mRS Score of 6 at 90 days post-treatment. The mRS Score at 90 days after treatment was used to determine whether the subject had achieved a 90-day mRS Score response (0-1). For subjects with concurrent events, if the strategy was a treatment strategy, the mRS Score at 90 days after treatment would be collected and used to determine the outcome. The treatment method for missing data was the same as other missing methods. If the strategy is a composite strategy, the mRS Score will not be used to determine the outcome, and the non-response will be used directly.

For participants whose mRS Score response was still missing at 90 days after treatment, missing data were imputed with the use of multiple imputation. Multiple imputation will be performed with the use of the SAS program PROC MI to create five complete data sets based on the full conditional definition (FCS) method, with a seed number of 752571. The multiple imputation model will include treatment group, baseline mRS Score and determination of mRS Score response after each baseline, age, thrombolysis time, baseline and after each baseline NIHSS score, and sICH.

Based on the five complete data sets generated, the proportion of subjects achieving a mRS Score response (0-1) at 90 days after treatment in the five complete data sets was summarized according to treatment group, and the two-sided 95% confidence interval of the normal approximation Wald, the rate difference (RD) between groups and their corresponding 95% confidence intervals were summarized. The SAS program PROC MIANALYZE was used to combine the above results.

For 5 complete set of data set will use log binomial test relatively controlled drugs are calculated separately, and the risk ratio (RR), odd ratio (OR) and their corresponding 95% confidence interval. Analyses were combined with the use of the SAS program PROC MIANALYZE to obtain the final primary efficacy end point. Noninferiority would be shown if the lower limit of the 95% confidence interval of the RR was above the noninferiority margin of 0.93. After confirmed the Non-inferiority, will test Superiority. Superiority would be confirmed if the lower limit of the two-sided 95% confidence interval was higher than 1.

In addition, chi-square p-values were calculated for the five complete imputation data sets. By Wilson - Hilferty conversion of chi-square analysis results for standardization [5], continue using SAS PROC MIANALYZE to merge into the analysis of the results.

List of mRS Score data for all mITT subjects, according to treatment group.  
List of concomitant events.

### 5.2.1.2 Sensitivity analysis

Data if applicable, will plan the primary efficacy end point missing data

processing for the following sensitivity analysis:

- Sensitivity analysis 1: GEE model with visit, age and baseline NIHSS score as covariates was used to calculate the relative response rate (RR) and 95% confidence interval (CI) of the trial drug versus the control drug, considering the interaction between group and visit. The rate difference (RD), odds ratio (OR) and their corresponding 95% confidence intervals were also provided.
- Sensitivity analysis 2: NRI will be used to fill the missing data, then calculate experimental drug control and 90 days after drug treatment, mRS score 0-1 minute proportion of the subjects and the corresponding confidence interval, experimental drugs relative comparison of risk ratio (RR) and their corresponding 95% confidence interval. The rate difference (RD), odds ratio (OR) and their corresponding 95% confidence intervals were also provided, and the P value of the chi-square test or Fisher's exact probability test was calculated.
- Sensitivity analysis 3: LOCF will be used to fill the missing data, then calculate experimental drug control and 90 days after drug treatment, mRS score 0-1 minute proportion of the subjects and the corresponding confidence interval, experimental drugs relative comparison of risk ratio (RR) and their corresponding 95% confidence interval. The rate difference (RD), odds ratio (OR) and their corresponding 95% confidence intervals were also provided, and the P value of the chi-square test or Fisher's exact probability test was calculated.
- Sensitivity analysis 4: No imputation will be used, then calculate experimental drug control and 90 days after drug treatment, mRS score 0-1 minute proportion of the subjects and the corresponding confidence interval, experimental drugs relative comparison of risk ratio (RR) and their corresponding 95% confidence interval. The rate difference (RD), odds ratio (OR) and their corresponding 95% confidence intervals were also provided, and the P value of the chi-square test or Fisher's exact probability test was calculated.
- Sensitivity analysis 5: The tipping point analysis (TPA) method [6] to estimate main goal analysis results of robustness. For all possible combinations of missing data, the relative response ratio (RR) of the trial drug versus the control drug and its corresponding 95% confidence interval were calculated. The proportion of combinations in which the lower limit of the statistical confidence interval was higher than the noninferiority margin of 0.93 was calculated.

### 5.2.1.3 Additional analyses

To assess the impact of different companion event handling strategies on the results, the primary efficacy analysis will also be repeated based on the treatment strategy for all concomitant events, and the missing handling of concomitant event data converted to the treatment strategy will be handled in the same way as other missing data handling strategies, using multiple imputation.

### 5.2.1.4 Subgroup analysis

Analyses of mRS Scores in different subgroups of subjects based on the subgroups in the 3.6 definition will also be performed if data are applicable. Corresponding forest plots were drawn based on the subgroup results.

## 5.2.2 Secondary estimand

5.2.2.1 The proportion of patients with NIHSS score  $\leq 1$  or a decrease of 4 or more points compared with baseline at 24 hours and 7 days after treatment

Follow the concurrent event handling method 1: Subjects who died within the corresponding visit after treatment were treated as failure after treatment. For all other cooccurring events, actual observations after cooccurring events were collected on the basis of the treatment strategy.

Calculated separately according to the supervision, testing drugs and controlled 24 h after drug treatment, NIHSS score 7 days 1 minute or less, or a baseline to reduce more than 4 points and the proportion of the subjects and corresponding confidence interval, experimental drugs relative comparison of risk ratio (RR) and their corresponding 95% confidence interval. The rate difference (RD), odds ratio (OR) and their corresponding 95% confidence intervals were also provided, and the P value of the chi-square test or Fisher's exact probability test was calculated.

In addition, in order to account for the effect of missing data and covariates, the GEE model was used, with treatment group and visit as independent variables, age and baseline NIHSS score as covariates, and the interaction between group and visit. The relative response rate (RR), rate difference (RD), odds ratio (OR) and 95% confidence interval (CI) of the test drug versus the control drug were calculated.

Follow the concurrent event handling method 2: To assess the impact of different concurrent event treatment strategies on the results, the statistical analysis will be repeated in the same manner as for treatment Method 1, using the same concurrent event treatment strategy as for the primary estimation objective. Subjects who died within the corresponding visit after treatment were



treated as failure after treatment.

The response was determined based on the NIHSS score at 24 hours and 7 days after treatment ( $\text{NIHSS} \leq 1$  or a decrease of 4 or more points from baseline). For subjects with incident, if the strategy for the therapy strategy, will continue to collect and use the 24 h, NIHSS score 7 days after treatment, after using NIHSS score to judge the results. If the strategy is a composite variable strategy, the NIHSS score will not be used to determine the post-outcome, and the failure treatment will be used directly.

#### 5.2.2.2 Difference in NIHSS score from baseline at 24h and 7 days after treatment

Follow the concurrent event handling method 1: A patient who died within the corresponding post-treatment visit was considered to have a post-treatment score of 42. For all other cooccurring events, actual observations after cooccurring events were collected on the basis of the treatment strategy.

Observed values and changes from baseline were tabulated for each visit according to treatment group with the use of student's t-test or the nonparametric rank-sum test.

Repeated measurement of mixed effect model (MMRM) is analyzed, with each visit after baseline NIHSS a baseline change as the dependent variable, in the treatment group, visit as independent variables, age, baseline NIHSS score as the covariate, interaction and consider the treatment group and supervision, subjects within the variance - covariance structure for structure without structural variance (UN). Based on the model, the least squares mean (LSM) and standard error (SE) of each treatment group, as well as the difference, SE and corresponding 95% confidence interval (CI) and P value of LSM between the two groups were reported. If the covariance structure in the model for the UN model convergence, when you can choose other possible covariance structure such as Toelitz, autoregressive (1) (AR (1)) and so on, eventually AIC value minimum covariance structure will be used in the final model.

Follow the concurrent event handling method 2: To assess the impact of different concurrent event treatment strategies on the results, the statistical analysis will be repeated in the same manner as for treatment Method 1, using the same concurrent event treatment strategy as for the primary estimation objective. A patient who died within the corresponding post-treatment visit was considered to have a post-treatment score of 42.

For subjects with concurrent events, if the strategy was a composite strategy, the original value of NIHSS score after treatment was used if it was  $>$  NIHSS baseline, such as  $\leq$  baseline or missing baseline. If the strategy was therapeutic, the NIHSS score would continue to be collected and used.



### 5.2.2.3 Proportion of subjects with mRS Score 0-2 at 90 days after treatment

Follow the concurrent event handling method 1: Actual observations after concomitant events were collected on the basis of the treatment strategy for all concomitant events.

The proportion of subjects with a mRS Score of 0-2 at 90 days after treatment was analyzed using statistical methods similar to those used in the main analysis of the primary efficacy end point.

Follow the concurrent event handling method 2: To assess the impact of different concomitant event management strategies on outcomes, the proportion of subjects with a mRS Score of 0-2 at 90 days post-treatment will be analyzed using the same concomitant event management strategies and statistical methods as the primary estimation objective.

### 5.2.2.4 Serial changes in mRS Scores at 30 and 90 days after treatment

Follow the concurrent event handling method 1: Actual observations after concomitant events were collected on the basis of the treatment strategy for all concomitant events.

Subjects who died within the corresponding post-treatment visit were considered to have a mRS Score of 6 at 90 days post-treatment. According to treatment group, the number and percentage of subjects in each category with mRS Score (0-6) at each visit were calculated, and the nonparametric rank sum test was performed. In addition, we used ordinal logistic analysis, included visit in the model, included age and baseline NIHSS score as covariates, and accounted for the interaction between group and visit, and provided odds ratios and 95% confidence intervals.

According to treatment group, a bar graph of mRS Score distribution at 90 days after treatment was drawn.

Follow the concurrent event handling method 2: To assess the impact of different concurrent event treatment strategies on the results, the statistical analysis will be repeated in the same manner as for treatment Method 1, using the same concurrent event treatment strategy as for the primary estimation objective.

Subjects who died within the corresponding post-treatment visit were considered to have a mRS Score of 6 at 90 days post-treatment. If the concomitant event strategy was a treatment strategy, mRS Scores at 30 days and 90 days after treatment would be collected and used. If the concomitant event strategy was a composite variable strategy, the mRS Score  $\leq 3$  at 30 and 90 days after treatment for the concomitant event was carried forward to 3, and the original value after the concomitant event was still used for the subjects with the mRS Score  $> 3$ . The missing value after the concomitant event was assigned by the median of the same type of non-missing mRS Score.

#### 5.2.2.5 Proportion of subjects with Barthel index score $\geq 95$ at 90 days after treatment

Follow the concurrent event handling method 1: Subjects who died within the corresponding visit after treatment were treated as failure after treatment. For all other cooccurring events, actual observations after cooccurring events were collected on the basis of the treatment strategy.

The proportion of subjects with a Barthel index score  $\geq 95$  at 90 days after treatment was analyzed using statistical methods similar to those used for the analysis of the 5.2.2.1 secondary efficacy end point.

Follow the concurrent event handling method 2: To assess the impact of different concurrent event treatment strategies on the results, the statistical analysis will be repeated in the same manner as for treatment Method 1, using the same concurrent event treatment strategy as for the primary estimation objective. Subjects who died within the corresponding visit after treatment were treated as failure after treatment.

The response was determined based on the Barthel index score at 90 days after treatment (Barthel index score  $\geq 95$ ). For subjects with concomitant events, if the strategy is a treatment strategy, the Barthel index score will continue to be collected and used 90 days after treatment, and the Barthel index score will be used to determine the outcome. If the strategy is a composite variable strategy, the Barthel index score will not be used to determine the subsequent outcome, and the failure treatment will be used directly.

### 5.3 Safety analysis

All safety analyses will be based on the safety analysis set.

#### 5.3.1 Adverse event (AE)

AE were coded according to MedDRA version 25.1, and severity levels of AE were determined according to NCI CTCAE 5.0.

Adverse events will be classified as:

- Pretreatment adverse events were defined as adverse events that occurred between the time the subject signed the informed consent and the time before the initiation of the investigational drug or as a preexisting medical exacerbation between the time the subject signed the informed consent and the time before the initiation of the investigational drug.
- Treatment/medication emergence or worsening adverse events (TEAE) : refers to all adverse medical events that occur in clinical trial subjects after receiving the investigational drug, including the deterioration of

existing symptoms/signs after entering the trial.

If adverse events compared with the test for the first time during treatment with drug delivery time not sure, are regarded as TEAE.

Only TEAE were summarized, but a list of data was provided for AE during all study periods.

#### 5.3.1.1 TEAE summary sheet

The TEAE summary table is presented, and the number, percentage, and number of subjects with the following categories of TEAs in each treatment group are reported according to all TEAs.

- All TEAE
- CTCAE Level 3 and above TEAE
- TEAE that cause adjustment of the investigational drug product
  - TEAE that result in a reduction in the dose of the investigational drug
  - TEAE that cause temporary withdrawal of the investigational drug
  - TEAE that result in discontinuation of administration of the investigational drug
- Bleeding Events
  - Post-treatment major bleeding events (ISTH criteria)
  - Clinically relevant nonmajor bleeding events (ISTH criteria)
  - Minor bleeding (ISTH criteria)
- Intracranial hemorrhage
  - Symptomatic intracranial hemorrhage (ECASSIII criteria)
  - Symptomatic intracranial hemorrhage (SITS-MOST criteria)
- Nonintracranial bleeding events
- Adverse events of special interest
- Liver function tests showed  $ALT \geq 3 \times ULN$  and  $TBIL \geq 2 \times ULN$  within 7 days after treatment
- Creatinine (CREA) increased to more than three times the baseline value or increased to  $\geq 4$  mg/dL ( $353.6 \mu\text{mol/L}$ ) in renal function tests associated with the investigational drug product within 7 days after treatment
- TEAE that resulted in early withdrawal of the subject

- Serious TEAE (SAE)
- TEAE that cause death
- SUSAR

The above summary analysis will be repeated for TEAE other than those related to drug coagulation mechanisms. The preferred term (PT) for TEAE related to drug coagulation mechanisms will be determined by the blinded data review committee.

#### 5.3.1.2 TRAE summary sheet

A summary table of treatment-related adverse events (TRAE) is provided. According to the all report to TRAE respectively in each treatment group the following categories TRAE percentage of cases, subjects.

- All TRAE
- CTCAE Level 3 and above TEAE
- TEAE that cause adjustment of the investigational drug product
  - TEAE that result in a reduction in the dose of the investigational drug
  - TEAE that cause temporary withdrawal of the investigational drug
  - TEAE that result in discontinuation of administration of the investigational drug
- Bleeding events related to the trial product
  - Post-treatment major bleeding events related to the investigational product (ISTH criteria)
  - Clinically relevant nonmajor bleeding events related to the investigational product (ISTH criteria)
  - Minor bleeding related to the investigational product (ISTH criteria)
- Intracranial hemorrhage associated with the trial product
  - Symptomatic intracranial hemorrhage associated with investigational product (ECASS/IIIIII criteria)
  - Symptomatic intracranial hemorrhage associated with investigational product (SITS-MOST criteria)
- Nonintracranial bleeding events related to the trial product
- Adverse events of special interest related to the investigational product

- Liver function test ALT $\geq$ 3 $\times$ ULN and TBIL $\geq$ 2 $\times$ ULN within 7 days after treatment related to the investigational drug
- Creatinine (CREA) increased to more than three times the baseline value or increased to  $\geq$ 4 mg/dL (353.6 $\mu$ mol/L) in renal function tests associated with the investigational drug product within 7 days after treatment
- TRAE that resulted in early withdrawal of the subject
- Serious TRAE (SAE)
- TEAE that cause death

The above summary analysis will be repeated for TRAE other than those related to drug clotting mechanisms. The preferred term (PT) to be included in the TRAE related to the drug's mechanism of coagulation will ultimately be determined by the blinded data review board.

#### 5.3.1.3 TEAE were analyzed according to SOC and PT

The number, percentage, and number of subjects with the following TEAE in each treatment group were summarized according to MedDRA SOC and PT:

- All TEAE
- TEAE associated with investigational drug products

##### 5.3.1.3.1 SAE

The number, percentage, and number of subjects with the following SAEs in each treatment group were summarized according to MedDRA SOC and PT.

- Serious TEAE
- Serious TEAE associated with the investigational product.

According to treatment group, all SAE that occurred during the study period were tabulated.

##### 5.3.1.3.2 Other important TEAE

The number, percentage, and number of subjects with the following important TEAEs in each treatment group were summarized according to MedDRA SOC and PT:

- CTCAE Level 3 and above TEAE
  - TEAE of CTCAE level 3 or above related to investigational drug products
- TEAE that result in a reduction in the dose of the investigational drug

- TEAE that cause temporary withdrawal of the investigational drug
- TEAE that result in termination of administration of the investigational drug.

The above important TEAE were tabulated separately according to treatment group.

#### 5.3.1.4 TEAE were analyzed according to SOC, PT, and severity (CTCAE classification)

The number and percentage of subjects who experienced the following TEAEs in each treatment group were summarized according to MedDRA SOC, PT, and severity (CTCAE grades 1-5). If multiple TEAEs of the same SOC or PT occur in the same subject, the subject will be counted only once according to the highest CTCAE grade at the corresponding SOC or PT level.

- All TEAE
- TEAE associated with investigational product.

#### 5.3.1.5 Death

According to treatment group, the causes of death (hemorrhage, intracranial hemorrhage, symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage) and the time of occurrence of different causes of death were summarized and described:

- All death
- Death within 7 days after treatment
- Death within 90 days after treatment.

According to treatment group, causes of death (bleeding, intracranial hemorrhage, symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage) associated with the investigational product and the timing of their occurrence were summarized as follows:

- All deaths related to the investigational product
- Death related to the investigational product within 7 days after treatment
- Death related to the investigational product within 90 days after treatment.

The number and percentage of subjects with TEAE below each treatment group were summarized according to MedDRA SOC and PT, and the data were tabulated.

- All TEAE that resulted in death
- TEAE leading to death associated with the investigational drug.

The number and percentage of deaths and censoring within 90 days, as data permit, are also described separately for each treatment group. The Kaplan-Meier method was used to estimate median 90-day OS and 95% two-sided confidence intervals. Kaplan-Meier curves were plotted for the two treatment groups.

#### 5.3.1.6 Bleeding events (including intracranial hemorrhage and non-intracranial hemorrhage)

The number, percentage, and number of subjects with TEAE under each treatment group were summarized according to MedDRA PT, and the data were tabulated.

- Intracranial hemorrhage
- Intracranial hemorrhage associated with the trial product
- ECASSIII criteria for symptomatic intracranial hemorrhage
- ECASSIII criteria for symptomatic intracranial hemorrhage associated with the investigational product
- SITS-MOST criteria for symptomatic intracranial hemorrhage
- SITS-MOST criteria for symptomatic intracranial hemorrhage associated with the investigational product

The number and percentage of subjects with TEaes below each treatment group were summarized according to MedDRA SOC and PT and severity (CTCAE classification), and the number and percentage of subjects with TEaes below each treatment group were summarized according to ISTH criteria, and the data were tabulated.

- Nonintracranial bleeding events
- Nonintracranial bleeding events related to the trial product

PT for intracranial hemorrhage and common bleeding events (incidence >10%) will describe time to first occurrence, outcome, and duration:

Time to first occurrence (Day) = The time when this PT AE first occurred - Time of first trial drug administration + 1.

The duration is the sum of the time that the PT AE occurred. Duration was defined as the time from the initial occurrence of an AE to its end. Only those recovered/resolved without sequelae and those recovered/resolved with sequelae were counted.

#### 5.3.2 Laboratory tests

Laboratory tests included blood routine, blood biochemistry, urine routine, coagulation function, stool routine and occult blood, etc.

Data from different laboratories are summarized as follows:

- Quantitative laboratory results and changes from baseline were summarized at scheduled visits
- Changes from baseline in clinical significance were summarized according to the worst outcome at the visit and during the study period

Laboratory test results and abnormal values were tabulated according to treatment group and visit (including scheduled visits and unscheduled visits).

### **5.3.3 Vital signs**

Vital signs were summarized as follows:

- Results across vital signs and changes from baseline were summarized at scheduled visits
- Changes from baseline in the clinical significance of different vital signs were summarized according to the worst outcome during the study period.

According to the treatment group and the supervision/time point of the subjects' vital signs list (including plan supervision and outbound).

### **5.3.4 12-lead electrocardiogram (ECG)**

12-lead electrocardiograms were summarized as follows:

- ECG parameters and changes from baseline were summarized at scheduled visits
- Changes from baseline in clinical significance were summarized according to the worst outcome at the visit and during the study period.

List of ECG results (including scheduled and unscheduled visits) for subjects by treatment group and visit.

### **5.3.5 Imaging examination**

List of imaging findings (including scheduled and unscheduled visits) according to treatment group and visit.

### **5.3.6 Physical examination**

Physical examinations were summarized as follows:

- Changes from baseline in clinical significance were summarized according to visit.

List of physical examination results (including scheduled and unscheduled visits) according to treatment group and visit.



## 6. Planned analysis

### 6.1 Interim analysis

No interim analyses were planned.

### 6.2 Final analysis

The final analysis will be performed at the end of the entire trial.

## 7. Deviations from the protocol plan analysis

There are no changes in the statistical analysis plan to the analyses that were planned in the protocol.

## 8. Statistical analysis table/list/chart

The statistical analysis table/list/chart template will be provided in a separate file.

## 9. References

- [1] Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke[J]. New England journal of medicine, 2008, 359(13): 1317-1329.
- [2] Koroshetz W J . Tissue Plasminogen Activator for Acute Ischemic Stroke[J]. N Engl J Med, 1995, 334(21):1581.
- [3] Wahlgren N, Ahmed N, Eriksson N, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[J]. Stroke, 2008, 39(12):3316-3322.
- [4] Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial[J]. Lancet Neurol, 2017, 16(10):781-788.
- [5] Bohdana Ratitch, Quintiles, et al. Analysis Results from Multiply Imputed Categorical Data. PharmaSUG 2013, Paper SP03.
- [6] O'Kelly, M. and Ratitch, B., Clinical Trials with Missing Data, A Guide for Practitioners. Wiley, 2014.