# Endovascular Treatment With or Without Intravenous Thrombolysis in Acute Ischemic Stroke Due to Basilar Artery Occlusion: A Multicentre, Prospective, Randomized Controlled Trial (The BEST-BAO trial)

## Statistical Analysis Plan

Version: Draft V1.1 (Version Date: 2025-01-05)

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|---|---|
| **Study Type:** | Investigator-Initiated Trail |
| **Sponsor:** | Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China |
| **Statistical Analysis Unit:** | Clinical Research Institute, Peking University |
| **Contract Research Organization:** | JetMed (Beijing) Co., Ltd |

**Statistical Analysis Plan Signature Page**

**Study Title:** Endovascular Treatment With or Without Intravenous Thrombolysis in Acute Ischemic Stroke Due to Basilar Artery Occlusion: A Multicentre, Prospective, Randomized Controlled Trial (The BEST-BAO trial)

**Sponsor:** Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China

**Statistical Unit:** Clinical Research Institute, Peking University
**Version:** Draft V1.0 (Version Date: 2025-01-05)

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**Version Update Log**

| Version | Date |
|---|---|
| V1.0 | 2023-5-6 |

# Contents

## 1. Study design and protocol overview

This is a multicenter, prospective, open-label, blinded-endpoint, randomized controlled clinical trial. The content of the Statistical Analysis Plan is based on Clinical Trial Protocol Version 1.1 (Protocol Number: BEST-BAO-A, Version Date: 2024-12-09).

### 1.1 Study title

Endovascular treatment with or without intravenous thrombolysis in acute ischemic stroke due to basilar artery occlusion: A multicentre, prospective, randomized controlled trial..

### 1.2 Study objective

To assess the efficacy and safety of IVT followed by EVT and EVT alone in the treatment of patients with AIS-BAO who are eligible for both treatment strategies within 4.5 hours of symptom onset.

### 1.3 Overview of study design

This is a multicentre, prospective, open-label, blinded endpoint evaluation, randomized controlled trial (PROBE design). Based on previous observational studies, this trial primarily aims to validate the superiority of IVT followed by EVT over EVT alone. However, given the limited prior data and evidence from the anterior circulation, this trial will also investigate the non-inferiority of EVT alone comparing with IVT followed by EVT in case the two strategies demonstrate similar efficacy. An interim analysis will be conducted when 1/3 of the sample size (114 patients) has completed primary endpoint follow-up. The interim analysis will focus on sample size re-estimation based on conditional power calculated by the data and safety monitoring board (DSMB), which will provide recommendations on whether to adjust the sample size.

### 1.4 Study intervention

In accordance with the 2019 AHA/ASA guidelines for early management of AIS and recommendations from the steering committee (SC): In EVT alone group, EVT will be performed as quickly as possible. In IVT followed by EVT group, patients will receive IVT with alteplase (0.9 mg/kg, maximum 90 mg in one hour) before EVT. Efforts will be made to minimize delays in EVT initiation due to IVT administration. EVT techniques include retrievable stent thrombectomy, thrombus aspiration, balloon angioplasty, stent implantation, or combinations thereof. The specific EVT approach will be at the discretion of the treatment team.

### 1.5 Sample size

Currently, no large-scale randomized controlled trials (RCTs) exist in this field. Therefore, the calculation of the sample size for this study will be based on the results of the RESCUE-RE registry study conducted in the Chinese population. According to the study, the proportion of patients achieving a mRS score ≤ 2 at 90 days post-procedure was 42.03% in the IVT followed by EVT group and 26.14% in the EVT alone group.

Based on the superiority hypothesis, the study aims to determine whether the proportion of patients achieving a modified Rankin Scale (mRS) score of ≤2 at 90 days is higher in the IVT followed by EVT group compared to the EVT alone group. The statistical hypotheses are defined as follows:

Null Hypothesis $H_0: p_T - p_C \leq 0$

Alternative Hypothesis $H_1: p_T - p_C > 0$

$\alpha = 0.025$ (per side),

Assuming a one-sided type I error rate of 0.025 and a statistical power of 80%, with equal allocation between the two groups (1:1), each group will require 136 patients (a total of 272 patients). Considering an anticipated dropout rate of approximately 20%, the final sample size will be adjusted to 340 patients, with 170 patients per group.

Given limited reference data and evidence suggesting the non-inferiority of EVT alone in the anterior circulation, an interim analysis will be conducted after one-third (114) of patients have completed follow-up for the primary endpoint. At this stage, the Data and Safety Monitoring Board (DSMB) will perform a sample size re-estimation based on the efficacy data obtained from both groups.

If the interim analysis the efficacy of the two groups is found to be similar, the study hypothesis will be adjusted to a non-inferiority hypothesis, aiming to verify whether EVT alone is non-inferior to IVT followed by EVT. The specific statistic hypotheses are as follows:

Null Hypothesis $H_0: p_T - p_C \leq -\Delta$

Alternative Hypothesis $H_1: p_T - p_C > -\Delta$

$\alpha = 0.025$ (per side),

In this context, $p_T$ represents the proportion of patients in the IVT followed by EVT group achieving a 90-day mRS score of ≤ 2, while $p_c$ represents the proportion in the EVT alone group. Δ denotes the non-inferiority margin, defined as a positive value. Assuming that the efficacy of the two groups is equivalent, with both achieving a 90-day mRS score of ≤2 in 42.03% of patients, and under the conditions of a one-sided type I error rate of 0.025 and a non-inferiority margin of -15%, the current sample size of 170 patients per group provides 80% power to detect non-inferiority.

### 1.6 Randomization and blinding

The randomization process will use a web-based randomization system. Patients can be randomized (Appendix 16) when AIS-BAO is confirmed by CTA, MRA, or DSA.

Before a patient is registered in the study database, assigned groups and treatment allocation will remain inaccessible, and patients cannot be excluded from the study after the allocation is revealed. Both patients and treating physicians will be aware of the assigned treatment group. However, trained investigators, who are blinded to assigned groups and treatment allocation, will record endpoint-related information using standardized forms and procedures, and details of the interviews. These trained evaluators will assess mRS outcomes and evaluate neuroimaging results in a blinded manner. Information related to assigned groups and treatment allocation will be maintained separately from the study database. The SC will not be informed of interim analysis results on the efficacy and safety. Independent trial statisticians will combine treatment allocation data with study database for reporting to the DSMB.

### 1.7 Planned analyses

One interim analysis (involving hypothesis testing adjustments and sample size re-estimation) and one final analysis are planned.

### 1.8 Visit schedule

| Assessment/Step | Baseline | Treatment/ Intervention | Follow-up period[1] | | | | |
|---|---|---|---|---|---|---|---|
| | | | 18–24 hrs after procedure | 24–72 hrs after procedure | 5–7 days after stroke onset | 30±7 days after stroke onset | 90±14 days after stroke onset |
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | |
| Randomization | X | | | | | | |
| Demographics[2] | X | | | | | | |
| Medical History | X | | | | | | |
| Vital Signs[3] | X | X | X | X | X | | |
| Clinical Lab Tests[4] | X | | | X | X | | |
| CT/CTA or MRI/MRA or CT/DSA | X | | | X[5] | | | |
| CT/MRI (Head) | | | | | X | | |
| mRS Score | X | | X | X | X | X | X |
| NIHSS Score | X | | X | X | X | | |
| GCS Score | X | | X | X | X | | |
| IVT/EVT[6] | | X | | | | | |
| Vascular Recanalization | | X | | X | | | |
| eTICI Score | | X | | | | | |
| mAOL Score | X | | | X | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PC-ASPECTS Score | X | | | X | | | |
| PMI Score | X | | | | | | |
| PC-CS Score | X | | | | | | |
| BATMAN Score | X | | | | | | |
| BI Score | | | | | | X | X |
| EQ-5D-5L Score | | | | | | X | X |
| Concomitant Medications | X | X | X | X | X | X | X |
| Death | | X | X | X | X | X | X |
| ICH/sICH | | X | | X | X | | |
| Procedure-Related Complications | | X | X | X | X | X | X |
| New Territory Embolization | | X | | | | | |
| New Infarction | | | | X | X | | |
| AE/SAE | | X | X | X | X | X | X |

**Abbreviations:** h, hours; CT, Computed tomography; CTA, Computed tomographic angiography; MRI, Magnetic resonance imaging; MRA, Magnetic resonance angiography; DSA, Digital subtraction angiography; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; EVT, Endovascular treatment; IVT, Intravenous thrombolysis; eTICI, Extended thrombolysis in cerebral infarction score; mAOL, Modified arterial occlusion lesion score; PC-ASPECTS, Posterior circulation acute stroke prognosis early CT score; PMI, Pons-midbrain index; PC-CS, Posterior circulation collateral score; BATMAN, Basilar artery on CTA score; BI, Barthel index; EQ-5D-5L, EuroQoL five dimensions five levels health questionnaire; ICH, Intracranial hemorrhage; sICH, Symptomatic intracranial hemorrhage; AE, Adverse event; SAE, Serious adverse event.

**Notes:**

(1) Follow-Up: At 30±7 days and 90±14 days, follow-ups are conducted through telephone,

video calls, or in-person visits.

(2) Demographics: Includes basic patient information such as sex, age, BMI, etc.

(3) Vital Signs: Covers temperature, heart rate, respiratory rate, and blood pressure.

(4) Clinical Laboratory Tests: Encompasses blood biochemistry, complete blood count, and coagulation parameters.

(5) Imaging Follow-Up: Investigators are required to complete imaging evaluations at 24–72 hours after EVT procedure. If clinical deterioration necessitates earlier imaging, assessments can be conducted within 24 hours. In such cases, angiography (CTA or MRA) should be completed as synchronously as possible. In addition, given logistical constraints such as insurance policies and patient safety during transportation, the 24–72-hour imaging requirement for these cases can be waived.

(6) IVT/EVT: Includes thrombolytic drug details (type, dose, timing, and route), time intervals from symptom onset to various procedural steps, and specifics of devices and sedation/anesthesia used during the procedure..

## 2. Evaluation criteria

### 2.1 Efficacy Endpoints

#### 2.1.1 Primary Endpoint

The primary endpoint of this trial is the proportion of patients achieving a mRS score ≤ 2 at 90 days after stroke onset. The mRS is the preferred parameter for assessing disability in stroke-related clinical trials. It is an ordinal scale with 7 levels, ranging from 0 to 6, where a score of 6 indicates death.

Assessments will be conducted by trained and independent investigators who are blinded to group assignments and the treatments received. These assessments will be based on standardized follow-up reports completed by blinded study personnel, through either outpatient visits or telephone interviews.

#### 2.1.2 Secondary endpoints

The secondary endpoints are as following:

(1) Proportions of patients with mRS = 0 or 1 at 90 days after stroke onset.

(2) Proportions of patients with mRS = 0–3 at 90 days after stroke onset.

(3) mRS score at 90 days after stroke onset.

(4) NIHSS score at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(5) Proportions of patients with a NIHSS score = 0 or 1, a NIHSS score = 0–2, a NIHSS score improvement ≥ 4 points, and a NIHSS score improvement ≥ 8 points at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset.

(6) Glasgow coma scale score (GCS) at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(7) Barthel Index score (BI) and proportions of patients with BI = 95–100 at 30 and 90 days after stroke onset.

(8) EQ-5D-5L score at 90 days after stroke onset.

(9) eTICI score and successful reperfusion rates before and after EVT.

(10) mAOL score and recanalization rates at 24–72 hours after procedure.

(11) PC-ASPECTS score at 24–72 hours after procedure and 5–7 days after stroke onset.

(12) Lesion volume based on quantitative imaging detection at 24–72 hours after procedure and 5–7 days after stroke onset.

### 2.2 Safety endpoints

The safety endpoints include:

(1) All-cause mortality within 7, 30, and 90 days after stroke onset.

(2) Proportions of patients with intracranial hemorrhage and symptomatic intracranial hemorrhage at 24–72 hours after procedure and 5–7 days after stroke onset.

(3) Proportions of patients with new regional cerebral embolisms during EVT.

(4) Proportions of patients with new cerebral infarction at 24–72 hours after procedure and 5–7 days after stroke onset.

(5) EVT procedure-related complications within 90 days after stroke onset.

(6) Other serious adverse events within 90 days after stroke onset.

## 3. Statistical analysis

### 3.1 Analysis datasets

#### 3.1.1 Intention-to-treat population (ITT)

The ITT population includes all randomized subjects, and the analysis will be conducted based on their randomized treatment groups according to the intention-to-treat principle.

#### 3.1.2 Modified intention-to-treat population (m-ITT)

The m-ITT population includes all randomized subjects who received either IVT followed by EVT or EVT alone treatment. The analysis will be conducted based on their randomized treatment groups following the intention-to-treat principle.

#### 3.1.3 As treated set (AT)

The AT population is defined the same as the m-ITT population but will be analyzed based on the actual treatment received.

#### 3.1.4 Per-protocol set (PPS)

The PPS population includes subjects in the m-ITT population who did not experience any significant protocol deviations, as determined by the sponsor.

#### 3.1.5 Safety analysis set (SS)

The SS population includes all subjects who received either IVT followed by EVT or EVT alone treatment and had at least one safety follow-up.

### 3.2 General principles of statistical analysis

#### 3.2.1 Analysis software and data transfer standards

Sample size calculation and statistical analyses will be performed using SAS 9.4 (or a later version). Analysis datasets will be generated following CDISC standards (SDTM Implementation Guide Version 3.2 and ADaM Implementation Guide Version 1.1). Statistical tables, figures, and listings will be generated in RTF file format.

#### 3.2.2 Reporting standards for analysis results

The ITT, m-ITT, and PPS datasets will be analyzed according to the randomized treatment groups, while the AT and SS datasets will be analyzed based on the actual interventions received. Issues related to cases or data handling not explicitly described in the clinical trial protocol will be resolved following case discussions.

Continuous variables will be described using the mean, standard deviation, median, quartiles, minimum, and maximum values. Categorical and ordinal data will be summarized using frequencies and percentages. Statistical measures and the number of decimal places will be reported as outlined in the table below:

| Name | Description | Decimal Places (dp) |
|---|---|---|
| Quantitative Data | | |
| N | Number of subjects without missing results | 0 dp |
| Mean | Arithmetic mean | Raw data decimal places + 1 dp |

| | | |
|---|---|---|
| SD | Standard deviation | Raw data decimal places + 1 dp |
| Median | Median value | Raw data decimal places |
| Q1 | 25th percentile (first quartile) | Raw data decimal places |
| Q3 | 75th percentile (third quartile) | Raw data decimal places |
| Min | Minimum value | Raw data decimal places |
| Max | Maximum value | Raw data decimal places |
| Missing | Number of missing cases | 0 dp; if the percentage frequency is less than 0.1%, the percentage will be displayed to the first non-zero digit. For example, if the percentage is "0.000523%", it will be displayed as "0.0005%" instead of "0.0%". |
| Qualitative (Categorical and Ordinal) data | | |
| n | Number of subjects with a specific evaluation indicator value | 0 dp |
| % | Percentage (0-100%) | 1 dp |
| Statistical measures | | |
| 95% CI | 95% confidence interval | Raw data decimal places + 2 dp |

The comparison of baseline characteristics between the two groups will be conducted using appropriate statistical methods according to the type of data. For quantitative variables, an independent samples t-test will be used if normality and homogeneity of variance are satisfied; otherwise, the Wilcoxon rank-sum test will be applied. For categorical data, a chi-square test will be used if all expected cell counts are ≥ 5, a continuity-corrected chi-square test will be used if one expected cell count is between 1 and 5, and Fisher's exact test will be applied if more than one expected cell count is between 1 and 5, or if any expected cell count is < 1. For ordinal data, the Wilcoxon rank-sum test will be used without adjusting for center effects, while the Cochran-Mantel-Haenszel (CMH) test will be applied if adjustments for center effects are needed.

Unless otherwise specified, all statistical tests will be two-sided, with a significance level of 0.05 (two-sided). P-values will be reported to three decimal places, and values less than 0.001 will be reported as "P < 0.001".

### 3.2.3 Rules for handling missing data

Any requested data that is not provided will be considered as missing data.

Missing data will be displayed as " " in the listings. If data is recorded as "Not Applicable" (NA) or "Not Known" (NK), such data will appear in the listings as per their original record. However, for statistical analysis, they will be treated as missing data.

**Handling of missing efficacy data**

The primary efficacy analysis will be conducted based on the m-ITT population, and every subject must have a 90-day mRS score. If a subject dies before 90 days, they will not be considered missing and will be assigned the highest mRS score of 6 for evaluation. If the 90-day mRS value is missing but the subject's survival is confirmed within 90 days, the last available observation (e.g., from day 5 or discharge) will be carried forward to impute the missing value. For subjects with an unknown survival status at 90 days, the worst possible score (mRS = 6) will be assigned.

**Handling of Incomplete Dates**

For **AE dates** or the relationship of an AE to the study drug, missing dates will be handled as follows:

**1) AE start date:**

- If the year and month are known and the month/year are earlier than the first study drug administration, the last day of the known month will be used.

- If the year and month are known and the month/year are the same as the first study drug administration, the AE start date will be the same as the date of the first study drug administration (i.e., "xx month xx day").

- If the year and month are known and the month/year are later than the first study drug administration, the first day of the known month will be used.

- If only the year is known and it is earlier than the year of first study drug administration, December 31 of that year will be used.

- If only the year is known and it is the same as the year of first study drug administration, the AE start date will be the date of the first study drug administration (i.e., "xx month xx day").

- If only the year is known and it is later than the year of first study drug administration, January 1 of that year will be used.

- If the year, month, and day are all missing, the date of the first study drug administration will be used as the AE start date.

2) AE end date

- If the year and month are known, the last day of the known month will be used.

- If only the year is known, December 31 of that year will be used.

- If the imputed start date is after the imputed end date, the end date will be adjusted to match the start date.

- In all other cases, the data will be treated as missing.

**For CM (concomitant medication) dates, missing data will be handled as follows:**

1) **Start date of CM**:

- If the year and month are known, the first day of the known month will be used.

- If only the year is known, January 1 of that year will be used.

- If the year, month, and day are all missing, no imputation will be performed for the start date.

2) **End date of CM**:

- If the year and month are known, the last day of the known month will be used.

- If only the year is known, December 31 of that year will be used.

- If the imputed end date is after the last study visit date, the last study visit date will be used as the end date.

- If the year, month, and day are all missing, no imputation will be performed for the end date.

If the relationship between an AE and the study drug is missing, the AE will be classified as drug-related for the purpose of summary reporting.

For all other missing data in this study, no imputation will be performed, and the data will be analyzed and described in their original state as collected.

#### 3.2.4 Baseline definition

Unless otherwise specified, baseline values are defined as the last measurement obtained during the screening period or before the first administration of the study drug.

#### 3.2.5 Data derivation and transformation

Age (years)=(Date of informed consent−Date of birth+1)/365.25. The result will be rounded down to the nearest integer.

### 3.3 Multiplicity

This study does not involve early termination due to efficacy during interim analysis. Therefore, there are no issues related to multiplicity.

### 3.4 Interim Analysis

An interim analysis is planned once 1/3 (114 subjects) of the total population has completed the follow-up for the primary endpoint. During this interim analysis, the DSMB will conduct a sample size re-estimation based on the efficacy data obtained from both groups.

If the efficacy advantage of the IVT followed by EVT group over the EVT alone group is less than anticipated, the sample size will be appropriately increased. The DSMB will calculate the **conditional power** from the current data and provide recommendations to the BEST-BAO research team regarding sample size adjustments or modifications to the study hypothesis. The maximum increase in sample size will not exceed 20% of the original planned sample size.

If the efficacy of the two groups is found to be similar, the study hypothesis will be adjusted to a **non-inferiority hypothesis** to determine whether EVT alone is non-inferior to IVT followed by EVT. Assuming both groups achieve similar efficacy, with 42.03% of patients achieving a 90-day mRS $\leq 2$, and with a one-sided type I error rate of 0.025 and a non-inferiority margin of -15%, the current sample size of 170 patients per group will provide 80% power to demonstrate non-inferiority.

### 3.5 Trial completion and subject distribution analysis

Based on the screening population, the trial will summarize the screening process and reasons for screening failures. Using the randomized population (ITT set), the trial will summarize randomization and trial completion, including reasons for early termination. The number and percentage of subjects in each treatment group and site will be calculated. A list of subjects who failed screening will be provided, along with a list of all randomized subjects and their clinical trial completion status (ITT set).

The inclusion of subjects in each analysis dataset (m-ITT, PPS, SS) will also be summarized based on the randomized population (ITT set), with the number of subjects in each dataset calculated by treatment group and site. A list of all subjects included in the analysis datasets (ITT set) will also be provided.

The trial will summarize major protocol deviations based on the randomized population (ITT set), with the number and percentage of subjects with major protocol deviations calculated by treatment group. A list of all subjects with major protocol deviations (ITT set) will be provided.

A subject distribution flowchart will also be created.

### 3.6 Demographic and baseline analysis

Demographic and other baseline characteristic analyses will be performed based on the m-ITT population.

Baseline demographic characteristics (e.g., age, sex, ethnicity, height, weight) will be statistically described by treatment group. Vital signs, baseline imaging data, and laboratory test results will also be described by treatment group. A list of all subjects' baseline demographic data (m-ITT set) will be provided.

Previous medical history and current medical history will be coded using the **medical dictionary for regulatory activities (MedDRA V25.0)** and classified by **system organ class (SOC)** and **preferred term (PT)**. Previous/concomitant medical history will be summarized by SOC and PT, with the number and percentage of subjects in each category calculated by treatment group. A list of all subjects' past/concomitant medical history (m-ITT set) will be provided.

### 3.7 Concomitant medications, treatments, and previous procedures/surgeries

Concomitant medications and treatments/procedures during the clinical trial are defined as all non-investigational or control interventions/drugs and other treatments used during the clinical trial period.

Previous procedures/surgeries are defined as those with an end date earlier than the first administration of the investigational drug.

Previous and concomitant treatments/procedures during the clinical trial will be coded using the **MedDRA V25.0** and **SOC** and **PT**. Previous concomitant medications and concomitant medications during the study will be coded using the **world health organization drug dictionary (WHODrug Global 2022.03)**, with appropriate medication terms and ATC codes selected.

Based on the m-ITT analysis set, previous treatments/procedures will be summarized by SOC and PT, with the number and percentage of subjects calculated by treatment group. A list of all subjects' past treatments/procedures (m-ITT set) will be provided.

Based on the m-ITT analysis set, concomitant treatments/procedures during the clinical trial will be summarized by SOC and PT, with the number and percentage of subjects calculated by treatment group. Concomitant medications will be summarized using ATC codes, with the number and percentage of subjects calculated by treatment group. A list of all subjects' concomitant medications and treatments/procedures during the clinical trial (m-ITT set) will be provided.

### 3.8 Use of thrombolytic drugs and thrombectomy Procedures

Using the m-ITT set, the actual dosage, type, and administration time of IVT thrombolytic drugs will be described.

Additionally, based on the m-ITT set, the timeline for each treatment stage will be described by treatment group, including time from symptom onset to emergency admission, CT/MR, randomization, initiation of IVT, initiation of EVT, first successful reperfusion, and end of procedure. Details of vascular device types, specifications, quantities, and usage sequence will be recorded, as well as the type of anesthesia (if used) and sedation.

Vascular recanalization outcomes, post-procedure diagnoses, eTICI grading, collateral circulation scores, and other relevant data will also be described by treatment group.

A list of all subjects' thrombolytic drug use and thrombectomy procedure details (m-ITT set) will be provided.

### 3.9 Efficacy analysis

Efficacy analysis will be performed on the m-ITT, AT, and PPS datasets. The m-ITT dataset will be the primary analysis set for efficacy evaluation, while the AT and PPS datasets will serve as sensitivity analyses.

#### 3.9.1 Primary efficacy endpoint

The primary efficacy endpoint, "the proportion of patients with mRS ≤ 2 at 90 days after onset," will be statistically described by treatment group. The 95% confidence intervals (CIs) will be calculated using the exact Clopper-Pearson method. Additionally, a bar chart will be used to display the distribution of mRS scores.

When using a superiority hypothesis test, the specific statistical hypotheses are as follows:

Null hypothesis $H_0: p_T - p_C \leq 0$

Alternative hypothesis $H_1: p_T - p_C > 0$

$\alpha = 0.025$ (one side)

If the hypothesis is adjusted to a non-inferiority hypothesis after the interim analysis, the specific statistical hypotheses are as follows:

Null hypothesis $H_0: p_T - p_C \leq -15\%$

Alternative hypothesis $H_1: p_T - p_C > -15\%$

$\alpha = 0.025$ (one side)

Here, $p_T$ represent the proportions of patients with mRS ≤ 2 in the IVT followed by EVT and EVT alone groups, respectively.

A log-binomial model will be used, assuming the primary endpoint follows a binomial distribution. A log-link function will be applied, with covariates including age, pre-stroke mRS, time from onset to randomization, stroke severity (NIHSS score), and collateral circulation. Adjusted and unadjusted risk difference (RD) and risk ratio (RR) with their 95% confidence intervals will be reported.

For superiority, if the lower bound of the 95% CI of the adjusted RD > 0, superiority is established.

For non-inferiority, if the lower bound of the 95% CI of the adjusted RD > -15%, non-inferiority is established.

Additionally, Chi-square tests (expected cell count ≥ 5), continuity-corrected chi-square tests (1 expected cell count between 1 and 5), or Fisher's exact test (≥ 1 expected cell count < 5 or any expected cell count < 1) will also be used for group comparisons, and P-values will be reported.

The mRS score used in the primary analysis will be based on centralized assessments. If centralized assessments are missing for certain subjects, local investigator assessments will be used by default. Sensitivity analyses will also use local assessments to evaluate the robustness of the results.

A list of all primary efficacy endpoint data for all visits (m-ITT, AT, PPS sets) will be provided.

#### 3.9.2 Secondary efficacy endpoints

The secondary efficacy endpoints are as following:

(1) Proportions of patients with mRS = 0 or 1 at 90 days after stroke onset.

(2) Proportions of patients with mRS = 0–3 at 90 days after stroke onset.

(3) mRS score at 90 days after stroke onset.

(4) NIHSS score at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(5) Proportions of patients with a NIHSS score = 0 or 1, a NIHSS score = 0–2, a NIHSS score improvement ≥ 4 points, and a NIHSS score improvement ≥ 8 points at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset.

(6) Glasgow coma scale score (GCS) at 18–24 hours after procedure, 24–74 hours after procedure, and 5–7 days after stroke onset and their changes from baseline.

(7) Barthel Index score (BI) and proportions of patients with BI = 95–100 at 30 and 90 days after stroke onset.

(8) EQ-5D-5L score at 90 days after stroke onset.

(9) eTICI score and successful reperfusion rates before and after EVT.

(10) mAOL score and recanalization rates at 24–72 hours after procedure.

(11) PC-ASPECTS score at 24–72 hours after procedure and 5–7 days after stroke onset.

(12) Lesion volume based on quantitative imaging detection at 24–72 hours after procedure and 5–7 days after stroke onset.

For categorical endpoints (1, 2, 5, 7, 9, and 10), proportions will be calculated with 95% CI using the exact Clopper-Pearson method. Group comparisons will use chi-square tests, continuity-corrected chi-square tests, or Fisher's exact test, as appropriate, and P-values will be reported. RD and RR with 95% CIs will also be calculated. Both unadjusted and adjusted results will be reported. Covariates include age, pre-stroke mRS, time from onset to randomization, NIHSS score, and collateral circulation.

For continuous endpoints (4, 6, 7, 8, 11, and 12), group comparisons will use independent samples t-tests (if normality and homogeneity of variance are satisfied) or Wilcoxon rank-sum tests (if not). Mean differences with 95% Cis will also be calculated. Both unadjusted and adjusted results will be reported. Covariates include age, pre-stroke mRS, time from onset to randomization, NIHSS score, and collateral circulation.

For endpoint (3), shift analysis will be performed using ordinal logistic regression to calculate the common odds ratio and its 95% CI. Both unadjusted and adjusted results will be reported. Covariates include age, pre-stroke mRS, time from onset to randomization, NIHSS score, and collateral circulation.

A list of secondary efficacy endpoints for all visits (m-ITT, AT, PPS sets) will be provided.

### 3.9.3 Subgroup analysis

Subgroup analysis of the primary efficacy endpoint will be conducted based on the following factors (m-ITT set):

(1) Age
(2) Sex
(3) Medication history
(4) Pre-stroke mRS score
(5) Baseline stroke severity (NIHSS score)
(6) Blood glucose level at admission
(7) Baseline infarct size (PC-ASPECTS score and quantitative measurement)
(8) Baseline collateral circulation status (PC-CS and BATMAN scores)
(9) Stroke etiology
(10) Location of basilar artery occlusion
(11) Time from symptom onset to randomization

(12) Time from randomization to groin puncture
(13) Time from randomization to guiding catheter insertion into the vascular puncture sheath
(14) Time from randomization to cerebrovascular reperfusion

### 3.10 Safety analysis

Safety analysis will be performed using the SS dataset.

All adverse events (AEs) reported during the clinical trial will be summarized. AEs will be coded using MedDRA and classified by SOC and PT. For incidence rate calculations, if a subject experiences multiple different AEs, they will be counted as one case for the overall incidence rate. If the same AE occurs multiple times in the same subject, the subject will still be counted as one case for the incidence calculation of that AE. For severity analysis, only the most severe occurrence of the same AE in a subject will be included. Additionally, if a subject experiences multiple AEs within the same SOC and PT, they will only be counted once for the incidence rate calculation within that SOC and PT.

The incidence, number of cases, and rate of all safety endpoints will be summarized. Exact Clopper-Pearson 95% CIs will be calculated for incidence rates. Group comparisons will use chi-square tests, continuity-corrected chi-square tests, or Fisher's exact test, as appropriate, with P-values reported. RD and RR with 95% CIs will also be calculated.

Mortality events will be analyzed using Kaplan-Meier methodology, with median survival time and 95% CIs reported. Kaplan-Meier survival curves will be plotted, and group comparisons will use the log-rank test with P-values reported.

A list of all AEs, serious AEs, adverse reactions, and serious adverse reactions (SS dataset) will be provided.

## 4. Statistical tables and figures

Statistical tables and figures are included in the "Attachment (TFLs Shell)."

## 5. References

1. Nie, X., et al., *Endovascular treatment with or without intravenous alteplase for acute ischaemic stroke due to basilar artery occlusion.* Stroke Vasc Neurol, 2022. **7**(3): p. 190-199.