Description of programmatic changes

Reteplase versus alteplase for acute ischemic stroke within 4.5 hours (RAISE): Rationale and design of a multicenter, prospective, randomized, open-label, blinded-endpoint, controlled phase 3 non-inferiority trial

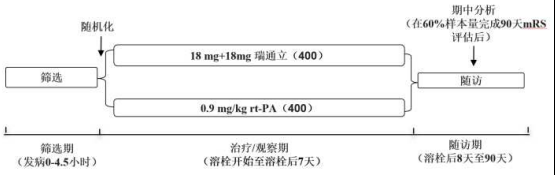
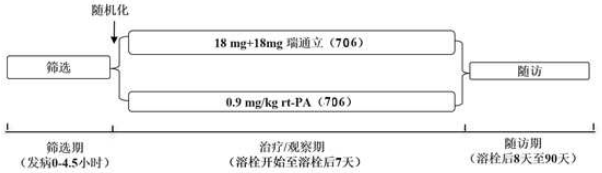
Project Name: Reteplase versus alteplase for acute ischemic stroke within 4.5 hours (RAISE): Rationale and design of a multicenter, prospective, randomized, open-label, blinded-endpoint, controlled phase 3 non-inferiority trial			
Sponsor: China Resources Angde Biotech Pharma Co., Ltd			
Principal investigator: Wang Yongjun			
First revision			
Version number/Version date before revision: V1.0/2021.10.25			
Revised Version Number/Version Date: V1.1/2021.11.14			
Modify item	Content of the original research program	Content of the revised research program	Note

Version number/version date on cover page and signature page	Version No.: V 1.0 Version Date: October 25, 2021	Version No.: V1.1 Version Date: November 14, 2021	
Protocol Synopsis	Protocol Version No./Version Date: V1.0 2021/10/25	Program version number/version date: V1.1 2021/11/14	
Version number/date in the corner of the page	Version No.: V 1.0 Version Date: 2021/10/25	Version No.: V 1.1 Version Date: 2021/11/14	
7.3.8 Chapter,Laboratory examination	-	Add "Biological samples such as blood, urine and feces collected in this study will be analyzed in the laboratories of each clinical trial center. Biological samples remaining after completion of this examination will be disposed of by the clinical trial centers in accordance with the relevant regulations for the management of medical waste in that center. All biological samples will not be used for any testing not related to the trial protocol agreed by the ethics committee."	Modified in accordance with the review of the Ethics Committee
Second revision			
Version number/Version date before revision: V1.1/2021.11.14			
Revised Version Number/Version Date: V1.2/2021.11.23			
Modify item	Content of the original research program	Content of the revised research program	Note

Version number/version date on cover page and signature page	Version No.: V 1.1 Version Date: November 14, 2021	Version No.: V 1.2 Version Date: November 23, 2021	
Protocol Synopsis	Program version number/version date: V1.1 2021/11/14	Program version number/version date: V1.2 2021/11/23	
Version number/date in the corner of the page	Version No.: V1.1 Version Date: 2021/11/14	Version No.: V 1.2 Version Date: 2021/11/23	
Table of contents	Appendix 1 to Appendix 4	Appendix 1 to Appendix 5	Add "Appendix 5: Post-thrombolytic Adverse Reaction Contingency Plan Reference"
Appendix 5	None	Add "Appendix 5: Post-thrombolytic Adverse Reaction Contingency Plan Reference"	Increase by ethical opinion
Third revision			
Version number/Version date before revision: V1.2/2021.11.23			
Revised Version Number/Version Date: V2.0/2022.01.05			

Modify item	Content of the original research program	Content of the revised research program	Note
Version number/version date on cover page and signature page	Version No.: V 1.2 Version Date: November 23, 2021	Version No.: V 2.0 Version Date: January 5, 2022	-
Protocol Synopsis	Program version number/version date: V1.2 2021/11/23	Program version number/version date: V 2.0 2022/1/5	-
Version number/date in the corner of the page	Version No.: V1.2 Version Date: 2021/11/23	Version No.: V 2.0 Version Date: 2022/1/5	-
Table of contents	3.9 Interim Analysis	cancel	Revised in accordance with the comments of the Center for Drug Control and Prevention
Table of contents	10.2 Interim Analysis	cancel	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol Synopsis, Experimental design	The study plans to enroll 800 patients with AIS within 4.5h of onset	This study plans to enroll 1,412 patients with AIS within 4.5 h of seizure	Revised in accordance with the comments of the Center for Drug Control and Prevention

Protocol Synopsis/Experimental design	1) Safety assessment: safety assessment on cumulative data from ongoing clinical trials to ensure the safety of subjects; and 2) Efficacy assessment: independent assessment of efficacy results of interim data analysis, and comments on sample size re-estimation of interim analysis, etc.	Amend to read: "Safety assessment of cumulative data from ongoing clinical trials to ensure subjects' safety."	IDMC duties de-emphasize mid-period analysis validity assessment
Protocol Synopsis	Legal representative	Replace with "guardian."	Modified in accordance with the 2020 edition of the GCP
Protocol Synopsis/Statistical Hypothesiss/Sample Size Estimation	The efficacy rate relative ratio (RR) is 1.30 compared to placebo. Considering the value of f as 0.5, the non-inferiority boundary for RR is 0.87 compared to alteplase.	Change to "The lower limit of the 95% confidence interval for the efficacy rate relative ratio (RR) is 1.15 compared to placebo. Considering the value of f as 0.5, the non-inferiority boundary for RR is 0.93 compared to alteplase. ."	Revised in accordance with the comments of the Center for Drug Enforcement, revising the non-inferiority thresholds
Protocol Synopsis/Statistical Hypothesiss/Sample Size Estimation	Test power (1-β) of 90%, and 1:1 ratio between two groups, considering the effect of an interim analysis (planned to be done once at 60% sample size, using the O'Brien Fleming Class I Error Consumption Function), and expecting a dropout rate of approximately 15%, that is, 400 subjects in each group and a total of 800 subjects.	Change to " test power (1-β) of 80%, and 1:1 ratio between two groups, expecting a dropout rate of approximately 15%, that is, 706 subjects in each group and a total of 1412 subjects. Referring to previous research SITS-MOST study[7], the estimated incidence of symptomatic intracranial hemorrhage is approximately 1%. Referring to NOR-TEST study[8], the estimated incidence of death is approximately 5%. the probability of observing at least one death or symptomatic intracranial hemorrhage is greater than 99% with a sample size of 1412."	Revised to remove midterm analysis in accordance with CTRC comments
Protocol Synopsis/Statistical analysis	The efficacy rate relative ratio (RR) of the two groups and its corresponding 95.24% confidence interval will be calculated. If the lower limit of the 95.24% confidence interval for RR is higher than the non-inferiority margin of 0.87, it proves that non-inferiority has been achieved. Following the confirmation of non inferiority, further superiority test will be conducted. If the lower limit of the bilateral 95.24% confidence interval is higher than 1, then superiority is confirmed. The rate difference between the groups, odds ratios (ORs), and their corresponding 95.24% confidence intervals will	Replace with "The relative effectiveness ratio (RR) of the test drug relative to the control drug and its corresponding 95% confidence interval. If the lower limit of the 95% confidence interval of the RR is higher than the non-inferiority threshold of 0.93, non-inferiority will be demonstrated. After confirming non-inferiority, further tests of superiority will be done. If the lower limit of the bilateral 95% confidence interval is higher than 1, then the superiority is confirmed. The rate difference between the groups, the ratio of ratios (OR) and their corresponding 95% confidence intervals will also be calculated, as well as the p-value of the chi-square or Fisher exact	Revised in accordance with the comments of the Center for Drug Control and Prevention

	also be calculated, and P-values from chi-square or Fisher exact probability test will be calculated. In addition, the GEE model will be used, in which age and baseline NIHSS score as covariates are included, to calculate the efficacy rate relative ratio (RR) of the investigational drug to the control drug, rate difference (RD) between the groups, odds ratio (OR) and its corresponding 95.24% confidence interval.	probability test. In addition, a GEE model will be used, in which age at inclusion and baseline NIHSS score will be included as covariates, and the relative effectiveness ratio (RR), between-group rate difference (RD), and ratio ratio (OR) of the test drug relative to the control drug and their corresponding 95% confidence intervals will be calculated."	
Protocol Synopsis/Statistical analysis	Interim analysis: One interim analysis is set up during the trial. The interim analysis will be performed by the IDMC. Details will be specified in the IDMC charter. The interim analysis will be performed at the 90-day mRS score after 60% of patient have completed treatment. Using the O'Brien Fleming type 1 error spending function, type 1 error spending at the time of the interim analysis will be approximately 0.00381 unilaterally. Condition efficacy will be calculated based on the efficacy ratios at the time of the interim analysis, and when condition efficacy ranges from 50%-80%, sample size adjustments will be made using the Mehta & Pocock method. Based on the O'Brien Fleming type 1 error spending function, the type 1 error boundary at final analysis will be approximately 0.02380 unilaterally.	cancel	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol Synopsis/Trial flow chart			Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol Synopsis/Trial flow chart Column 1	Signing of the ICF	Add superscript "a" in upper right corner	-
Protocol Synopsis/ the Trial flow chart	-	Add a row for "Fingerstick glucose m" and label the corresponding "Screening period" column thereafter with an "X".	Refinement of the Trial flow chart

Protocol Synopsis/the Trial flow chart/Notes Section	-	In order to correspond with the trial flow chart, the new content "a) If the patient have already undergone laboratory tests and imaging tests (e.g., emergency examination) related to this study after the onset of stroke (-4.5h~0h) and before signing the informed consent form for this study, they do not need to repeat the tests after signing the informed consent form, and the data of this pre-informed test can be used as the data of the screening period. . m) means that the blood glucose result can be used as a reference for the screening period enrollment criteria, and if it is not possible to decide whether a patient should be enrolled based on this result, it is up to the investigator to decide whether to wait for the blood biochemistry and glucose test result to be issued before enrolling the patient."	Add annotations for specific test processes
Protocol Synopsis/the Trial flow chart/Notes Section	The test reports of blood biochemistry, coagulation, and pregnancy test are not required after sample collection.	Amend to read: "Blood biochemistry, coagulation and pregnancy tests may be performed without waiting for the return of the laboratory order after the specimen has been collected."	-
Protocol Synopsis/the Trial flow chart/Notes Section	Based on which the investigators determine that the subject is no longer eligible for thrombolysis	Read "If, in the judgment of the investigator, the subject can no longer receive thrombolytic therapy."	-
Protocol/3.1 Overall Design	In this study conducted only in Chinese population with multicenter participation, 800 patients with AIS within 4.5h of onset are planned to be enrolled and allocated into the trial group and control group in a 1:1 ratio.	This study was conducted only in the Chinese population, with multicenter participation, and was planned to recruit 1412 patients with AIS within 4.5 h of seizure, with a 1:1 allocation between the test group and the control group.	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol/3.8 Independent Data Monitoring Board	1) Safety assessment: safety assessment on cumulative data from ongoing clinical trials to ensure the safety of subjects; and 2) Efficacy assessment: independent assessment of efficacy results of interim data analysis, and comments on sample size re-estimation of interim analysis, etc.	Amend to read: "Safety assessment of cumulative data from ongoing clinical trials to ensure the safety of patient."	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol/3.9 Interim analysis	3.9 Interim Analysis One interim analysis is set up during the trial. The interim analysis will be performed by the IDMC. Details will be specified in the IDMC charter. The interim analysis will be performed at the 90-day mRS score after 60% of	cancel	Revised in accordance with the comments of the Center for Drug Control and Prevention

	patient have completed treatment. Using the O'Brien Fleming type 1 error spending function, type 1 error spending at the time of the interim analysis will be approximately 0.00381 unilaterally. Condition efficacy will be calculated based on the efficacy ratios at the time of the interim analysis, and when condition efficacy ranges from 50%-80%, sample size adjustments will be made using the Mehta & Pocock method. Based on the O'Brien Fleming type 1 error spending function, the type 1 error boundary at final analysis will be approximately 0.02380 unilaterally. See the Interim Analysis Plan for details.		
Protocol/4.1 Inclusion criteria	Legal representative	Replace with "guardian"	Modified in accordance with the 2020 edition of the GCP
Protocol/6.1 Screening period	Legal guardian	Replace with "guardian"	Modified in accordance with the 2020 edition of the GCP
Protocol/6.1 Screening period	-	Added content "1) Patient who have already undergone laboratory tests and imaging tests related to this study (e.g., emergency room examination) after the onset of this stroke (-4.5 to 0 h) and before signing the informed consent form for this study do not need to repeat the tests after signing the informed consent form, and the data of this pre-informed test can be used as the data of the screening period.2) The result of the finger blood glucose can be used as a reference for the screening period enrollment criteria, and if it is not possible to decide whether a patient should be enrolled based on this result, it is up to the investigator to decide whether to wait for the results of the blood biochemistry glucose test to be available before enrolling the patient."	Improvement of the test process
ProtocolTable 2 List of laboratory inspection items	-	1. Added "Glucose (GLU)" to blood biochemistry tests.; 2. Added note under Blood Biochemistry Tests "Collection of only one of the blood biochemistry tests, urea and urea nitrogen, is sufficient."; 3. New test, "fingerstick blood glucose".	Improvement of laboratory testing programs

Protocol/8.10. Serious adverse events	7) The expected disease progression of the malignant tumor itself and its corresponding signs and symptoms should not be reported as SAEs unless they result in the subject's death.	cancel	In this trial, malignant tumor disease progression was reported as SAE
Protocol/10.1. Statistical Hypothesiss and sample size estimation	The efficacy rate relative ratio (RR) is 1.30 compared to placebo. Considering the value of f as 0.5, the non-inferiority boundary for RR is 0.87 compared to alteplase. Based on previous trial data of alteplase and the results of Phase II clinical study for recombinant human tissue-type plasminogen activator derivative in the treatment of acute ischemic stroke, a primary efficacy level of P=62.5% is selected for the alteplase group. Assuming a true efficacy ratio of 1.05 between the experimental group and control group, one-sided significance level (α) of 0.025, test power (1-β) of 90%, and 1:1 ratio between two groups, considering the effect of an interim analysis (planned to be done once at 60% sample size, using the O'Brien Fleming Class I Error Consumption Function), and expecting a dropout rate of approximately 15%, that is, 400 subjects in each group and a total of 800 subjects.	was changed to "The lower line of the 95% confidence interval for its relative placebo relative effectiveness ratio (RR) was 1.15, and the non-inferiority test cut-off value relative to the positive control drug alteplase was 0.93 if a value of 0.5 was considered for f. Based on the data of the previous alteplase trial and the phase II of the treatment of acute ischemic stroke by injectable recombinant human tissue-type plasminogen activator derivative clinical study results, P=62.5% was selected as the primary efficacy level for the alteplase group, assuming a true efficacy ratio of 1.05 for the test group to the control group, a significance level (α) of unilateral 0.025, and a test efficacy (1-β) of 80%, and a test group to control group designed in a 1:1 ratio with an expected dropout rate of approximately 15%, which would be 706 cases in each group and a total of 1412 patient."	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol/10.2.Interim analysis	10.2. Interim Analysis One interim analysis is set up during the trial. The interim analysis will be performed by the IDMC. Details will be specified in the IDMC charter.	cancel	Revised in accordance with the comments of the Center for Drug Control and Prevention

	The interim analysis will be performed at the 90-day mRS score after 60% of patient have completed treatment. Using O'Brien Fleming type 1 error spending function, the type 1 error boundary at interim analysis will be approximately 0.00381 unilaterally. Condition efficacy will be calculated based on the efficacy ratios at the time of the interim analysis, and when condition efficacy ranges from 50%-80%, sample size adjustments will be made using the Mehta & Pocock method. Based on the O'Brien Fleming type 1 error spending function, the type 1 error boundary at final analysis will be approximately 0.02380 unilaterally.		
Protocol/10.3.1. Efficacy Analysis	The efficacy rate relative ratio (RR) of the two groups and its corresponding 95.24% confidence interval will be calculated. If the lower limit of the 95.24% confidence interval for RR is higher than the non-inferiority margin of 0.87, it proves that non-inferiority has been achieved. Following the confirmation of non inferiority, further superiority test will be conducted. If the lower limit of the bilateral 95.24% confidence interval is higher than 1, then superiority is confirmed. The rate difference between the groups, odds ratios (ORs), and their corresponding 95.24% confidence intervals will also be calculated, and P-values from chi-square or Fisher exact probability test will be calculated. In addition, the GEE model will be used, in which age and baseline NIHSS score as covariates are included, to calculate the efficacy rate relative ratio (RR) of the investigational drug to the control drug, rate difference (RD) between the groups, odds ratio (OR) and its corresponding 95.24% confidence interval.	Replace with "The relative effectiveness ratio (RR) of the test drug relative to the control drug and its corresponding 95% confidence interval. If the lower limit of the 95% confidence interval of the RR is higher than the non-inferiority threshold of 0.93, non-inferiority will be demonstrated. After confirming non-inferiority, further tests of superiority will be done. If the lower limit of the bilateral 95% confidence interval is higher than 1, then the superiority is confirmed. The rate difference between the groups, the ratio of ratios (OR) and their corresponding 95% confidence intervals will also be calculated, as well as the p-value of the chi-square or Fisher exact probability test. In addition, a GEE model will be used, in which age at inclusion and baseline NIHSS score will be included as covariates, and the relative effectiveness ratio (RR), between-group rate difference (RD), and ratio ratio (OR) of the test drug relative to the control drug and their corresponding 95% confidence intervals will be calculated."	Revised in accordance with the comments of the Center for Drug Control and Prevention
Protocol/11.5. Data review meeting	There is an interim analysis for this study. For the data range to be analyzed and cut-off date, the data management team will cooperate with the project team to complete the corresponding data cleaning requirements as specified in the IDMC charter.	cancel	Revised in accordance with the comments of the Center for Drug Control

			and Prevention
Appendix 5	At the same time, the responsible director of neurology department at this site should be contacted for professional evaluation of the subjects' condition. If necessary, the respective responsible personnel should be contacted to ensure the safety and rights of the subjects.	Change to "Also contact the neurologist in charge of the specialty at the Center, who will evaluate the subject's condition, and also contact the person in charge of the appropriate specialty if needed, in order to protect the subject's safety and rights."	Improve the emergency plan
Appendix 5	Discontinue administration immediately	Amend to read: "In the judgment of the investigator, the administration of the drug may be suspended."	Improve the emergency plan
Appendix 5	Stop thrombolysis immediately	Read "In the judgment of the investigator, thrombolysis may be suspended."	Improve the emergency plan
Appendix 5	Stop thrombolysis immediately	Read "In the judgment of the investigator, thrombolysis may be suspended."	Improve the emergency plan
Fourth revision			
Version number/Version date before revision: V2.0/2022.01.05			
Revised Version Number/Version Date: V2.1/2022.08.29			

Modify item	Content of the original research program	Content of the revised research program	Note
Version number/version date on cover page and signature page	Version No.: V 2.0 Version Date: January 5, 2022	Version No.: V2.1 Version Date: August 29, 2022	-
Protocol Synopsis	Program version number/version date: V2.0 2022/1/5	Program version number/version date: V 2.1 2022/8/29	-
Version number/date in the corner of the page	Version No.: V 2.0 Version Date: 2022/1/5	Version No.: V2.1 Version Date: 2022/8/29	-
abbreviations	-	Delete "FAS" and "PPS" and add "CEC" and "ITT".	Modify accordingly to the Protocol
Protocol Synopsis/Add "Estimands"; Protocol/Add a section on "Estimands "	-	**Protocol Synopsis:** Add an "Estimands" section between "Study Objective" and "Study Design", which consists of a "Primary Estimands" and a "Secondary Estimands" section; **Protocol:** "Estimands" section is added between "Objectives" section and "Study Design" section, which consists of two parts: "Primary Estimand" and "Secondary Estimand". Primary EstimandSecondary Estimand "Primary Estimand" includes "Definition of the Primary Estimand" and "basis for selecting the corresponding treatment strategy for the Intercurrent events", and the "Secondary Estimand" is detailed in the statistical analysis plan. The "Primary Estimand" is based on the main trial objective and the main efficacy indicators, and includes the following elements: **The primary clinical question:** To investigate whether the clinical thrombolytic effect of recombinant human tissue-type plasminogen activator derivative for injection is non-inferior to alteplase in the patients with acute ischemic stroke.Recombinant Human Tissue-	In order to promote the technical standards of drug registration in line with international standards, China's National Drug Administration (NMPA) has decided to apply the ICH "E9(R1): Estimand and Sensitivity

type Plasminogen Activator Derivative

TARGET POPULATION: All randomized patients with acute ischemic stroke who have received at least one dose of the study drugs and meet the basic inclusion criteria.

TARGET VARIABLE: The proportion of participants achieving a modified Ranking Scale (mRS) score of 0-1 at day 90 after treatment..

TREATMENT: Intravenous injection of recombinant human tissue-type plasminogen activator derivative for injection (18mg + 18mg) or intravenous infusion of alteplase for injection at a dose of 0.9mg/kg (the maximum dose of 90mg)..

Intercurrent Events and corresponding treatment strategy:

Intercurrent Event	**Treatment Strategy**	**Note**
Use of other thrombolytic and fibrinolytic drugs	treatment policy strategy	A true reflection of actual clinical practice. The mRS scores will continue to be collected after an intercurrent event occurs and will be analyzed using the actual observations of the mRS scores regardless of whether or not that intercurrent event occurs.
Use of antiplatelets and anticoagulants (within 24h of thrombolysis)	treatment policy strategy	
Intracranial endovascular treatment performed during the trial for treating the acute ischemic stroke*	treatment policy strategy	
Failure to complete treatment per protocol requirements(including failure to complete two injections of recombinant human tissue-type plasminogen activator derivative or failure to complete the planned dosage titration of alteplase, treatment window overruns, inconsistencies between the actual treatment medication and the plan, and non-adherence to treatment dosage,,	treatment policy strategy	

Analysis in Clinical Trials" guidelines and require the implementation of the guidelines in clinical studies of drugs initiated after January 25, 2022.

The NMPA has decided to apply the ICH "E9(R1): Estimand and Sensitivity Analysis in Clinical Trials" guideline, and requires that it be implemented in the clinical studies of drugs initiated after January 25, 2022.

According to the guideline, the estimation objective should identify the clinical question of primary interest and clearly define its five attributes (target population, target variable, treatment,

		etc.)			intercurrent events and their management strategies, and population-level aggregation). The purpose of adding this section is to list as comprehensively as possible the intercurrent events (e.g., use of banned drugs, failure to complete treatment according to the plan, etc.) that may occur in the target population during the clinical trial in the protocol, and to stipulate the corresponding treatment strategies in advance, so as to ensure a more objective and realistic reflection of the efficacy of the test drug. The treatment strategies for intercurrent events include
		Notes: : * Endovascular treatment with the aim of treating the current acute ischemic stroke was performed during the trial: routine use of antiplatelets and anticoagulants after intracranial endovascular treatment with the aim of treating the current acute ischemic stroke was performed, including within 24 h after the start of thrombolysis. **Population-level summary:** relative efficiency ratios (RR) and their 95% two-sided confidence intervals. All of the above intercurrent events were managed using the treatment policy strategy, as the use of this strategy is a true reflection of actual clinical practice and is in line with the ITT principles of ICH E9.			

			treatment policy strategy, hypothetical strategy, composite variable strategy, on-treatment strategy, and main level strategy. Among them, the treatment policy strategy means that the values of the relevant variables will be used regardless of whether an intercurrent event occurs or not.
Protocol Synopsis/ Experimental Design; Protocol/ Added 4.9 independent Clinical Event Committees	-	Added: "**The Establishment of An** Independent Clinical Events Committee (CEC) A CEC will be established in this study, consisting of clinical experts in the field who are independent from the project. The CEC will make blinded adjudication on important clinical events on a case-by-case basis to ensure the scientific and rational judgment of these events. Its composition, responsibilities, operating procedures, and cycle of operation will be specifically described in the relevant charter."	To ensure the scientific and rational nature of the incident judgment, increase the CEC
Protocol Synopsis/ Add references; Protocol/ Add references.	acute ischemic stroke according to the diagnosis criteria for stroke issued by the World Health Organization (WHO)	acute ischemic stroke according to the diagnosis criteria for stroke issued by the World Health Organization (WHO) [3] .	Addition of source documents

Protocol Synopsis/ Early Withdrawal Criteria; Protocol/5.3.2. Withdrawal determined by the investigator	Protocol Synopsis: Subjects may voluntarily withdraw from the study under the following circumstances: • Subjects withdraw their consent; • Subjects are lost to follow-up and cannot be contacted by at least three attempts; • Subjects who undergo endovascular treatment before or after administration of the investigational drug or active comparator are considered to withdraw voluntarily from the study and will no longer be followed up; • Subjects voluntarily withdraw from the study due to adverse events or abnormal laboratory results. The investigators may terminate the participation of subjects in the study under the following circumstances: • Subjects experiences a serious protocol violation, which, in the opinion of the investigator, seriously affects the evaluation of the primary endpoint of the study; • Subjects become pregnant (or the partners become pregnant) or are suspected to be pregnant (or the partners are pregnant); • Subjects are allergic to the investigational drug; • Subjects experience adverse events that lead to the subjects cannot continue to participate in this clinical study; • Subjects are found not to be eligible as patients with acute ischemic stroke after thrombolytic therapy; • Participants with other conditions requiring withdrawal from the study as determined by the investigator. Protocol: 4.3. Subjects' Withdrawal from the Study 4.3.1. Voluntary Withdrawal 1) Subjects withdraw their consent; 2) Subjects are lost to follow-up and cannot be contacted by at least three attempts; 3) Subjects who undergo endovascular treatment before or after administration of the investigational drug or active	Protocol Synopsis: Subjects may voluntarily withdraw from the study under the following circumstances: • Withdrawal of consent by the subject; • The subject is lost to follow-up and cannot be contacted after at least 3 attempts. The investigator may withdraw the subject early from the study under the following circumstances: •Subjects become pregnant (or the partners are pregnant) or are suspected to be pregnant (or the partners are pregnant); • Subjects are found not to be eligible as patients with acute ischemic stroke after randomization. • Subjects have other conditions in which the investigators determine the need for the subjects to withdraw from the study after randomization and prior to the start of thrombolysis. Protocol: 5.3. Patient withdrew from the study 5.3.1. Patient withdrew themselves 1) Withdrawal of consent by the subject; 2) Patient were lost to visit and could not be contacted after at least 3 attempts. 5.3.2. Researcher-determined withdrawal 1) Occurrence of pregnancy or suspected pregnancy in the subject; 2) Patient who proved not to be acute ischemic stroke after randomization; 3) Other circumstances that, in the judgment of the investigator, required withdrawal from the trial after patient were randomized and before thrombolytic therapy was initiated.	With the addition of the estimand target, the early exit criteria will need to be modified accordingly to avoid missing data

	comparator are considered to withdraw voluntarily from the study and will no longer be followed up; 4) Subjects voluntarily withdraw from the study due to adverse events or abnormal laboratory results. 4.3.2. Withdrawal Determined by the Investigators 1) Subjects experiences a serious protocol violation, which, in the opinion of the investigator, seriously affects the evaluation of the primary endpoint of the study; 2) Subjects become pregnant (or the partners become pregnant) or are suspected to be pregnant (or the partners are pregnant); 3) Subjects are allergic to the investigational drug; 4) Subjects experience adverse events that lead to the subjects cannot continue to participate in this clinical study; 5) Subjects are found not to be eligible as patients with acute ischemic stroke after thrombolytic therapy; 6) Participants with other conditions requiring withdrawal from the study as determined by the investigator.		
Protocol Synopsis/ Trial Termination	-	Added: 4) Major errors found in the trial design during the trial make it difficult to evaluate the drug, or significant deviations occurring during the implementation of the protocol affect the final evaluation of the drug; Other entries are renumbered accordingly.	Revise to make summary and body presentation consistent
Protocol Synopsis/ Statistical Analysis; Protocol/11.2. Statistical analysis of the population.	**Protocol Synopsis:** ➢ Full analysis set (FAS): All subjects who are randomized and have received the investigational drug will be included in the FAS, which will be used for the analysis of patient distribution, demographic and baseline characteristics, and for the primary analysis of efficacy indicators. Subjects will be analyzed according to the group to which they are randomized. ➢ Per Protocol Set (PPS): All randomized subjects who have received the investigational drug without major protocol violations constitute the PPS of this study. The PPS is also used as the	**Protocol Synopsis：** ➢ Intent-to-treat set (ITT): Including all participants who are randomized, receive study drug., meet the basic inclusion criteria.. ➢ Safety analysis set (SS): All participants who are randomized, receive study drug, and provide any evaluable post-treatment safety data,. SS will be used to analyze the safety data. Patients will be as 'treated' (i.e. according to the drug the patient received, rather than the drug to which the patient may have been randomized). **Protocol：** 11.2.1. Intentional Healing Set（Intention-To-Treat，ITT）	Modified according to E9R1 guidelines; Written error modification

	primary analysis set, in which the patient disposition, demographic and baseline characteristics should be reported. ➢ Safety analysis set (SS): All subjects who are randomized, have received investigational drug, and have at least one post-treatment safety evaluation will be included in the SS. SS will be used to analyze the safety data. Patients will be as 'treated'(i.e. according to the drug the patient received, rather than the drug to which the patient may have been randomized) **Protocol:** 10.2.1. Full analysis set (FAS) All subjects who are randomized and have received the investigational drug will be included in the FAS, which will be used for the analysis of patient distribution, demographic and baseline characteristics, and for the primary analysis of efficacy indicators. Subjects will be analyzed according to the group to which they are randomized. 10.2.2. Per Protocol Set (PPS) All randomized subjects who have received the investigational drug without major protocol violations constitute the PPS of this study. The PPS is also used as the primary analysis set, in which the patient disposition, demographic and baseline characteristics should be reported. 10.2.3. Safety Set (SS) All participants who have been screened successfully, receive investigational drug, and have at least one post-treatment safety evaluation will be included in the SS. SS will be used to analyze the safety data. Patients will be as 'treated'(i.e. according to the drug the patient received, rather than the drug to which the patient may have been randomized)	Including all participants who are randomized, receive study drug., meet the basic inclusion criteria.11.2.2. Security Analysis Set（Safety Set, SS） All participants who are randomized, receive study drug, and provide any evaluable post-treatment safety data,. SS will be used to analyze the safety data. Patients will be as 'treated' (i.e. according to the drug the patient received, rather than the drug to which the patient may have been randomized).	
Protocol Synopsis/ Statistical Analysis; Protocol/11.3.1. Efficacy Analysis.	Analysis of Primary Efficacy Variables The primary efficacy analysis of this study will be conducted in the FAS population, and the primary endpoint is the proportion of subjects with a mRS score of 0-1 at 90	Primary Estimand Analysis For subjects with intercurrent events, mRS scores will be collected continuely at day 90 after treatment based on the treatment policy strategy. Multiple imputation method will be used for patients with	Modified in accordance with E9R1 guidelines

	days after treatment. The proportion of subjects who have received the investigational drug and the control drug, the corresponding confidence intervals, as well as efficacy rate relative ratio (RR) of the two groups and its corresponding 95% confidence interval will be calculated. If the lower limit of the 95% confidence interval for RR is higher than the non-inferiority margin of 0.93, it proves that non-inferiority has been achieved. Following the confirmation of non inferiority, further superiority test will be conducted. If the lower limit of the bilateral 95% confidence interval is higher than 1, then superiority is confirmed. The rate difference between the groups, odds ratios (ORs), and their corresponding 95% confidence intervals will also be calculated, and P-values from chi-square or Fisher exact probability test will be calculated. In addition, the GEE model will be used, in which age and baseline NIHSS score as covariates are included, to calculate the efficacy rate relative ratio (RR) of the investigational drug to the control drug, rate difference (RD) between the groups, odds ratio (OR) and its corresponding 95% confidence interval. Analysis of secondary efficacy endpoints For dichotomous efficacy endpoints, the same methods will be used as primary efficacy; the ordinal logistic regression will be used for the ordinal and categorical variables; the observed values and changes from baseline will be summarized, and t-test or non-parametric test will be performed for continuous endpoints.	missing mRS score at day 90. The proportion of patients with a mRS score of 0-1 at day 90 after treatment and corresponding confidence intervals, as well as efficacy rate relative ratio (RR) of two groupsand its corresponding 95% confidence interval, will be calculated. If the lower limit of the 95% confidence interval for RR is higher than the non-inferiority margin of 0.93, it proves that non-inferiority has been achieved. Following the confirmation of non inferiority, further superiority test will be conducted. If the lower limit of the bilateral 95% confidence interval is higher than 1, then superiority is confirmed. If applicable, different methods for primary estimand will be considered and sensitivity analysis will also be conducted to evaluate the robustness of the results. The GEE model will be used, in which age and baseline NIHSS score as covariates are included, to calculate the efficacy rate relative ratio (RR) of the investigational drug to the control drug and its corresponding 95% confidence interval. Meanwhile, sensitivity analysis will be conducted based on different missing data assumptions to evaluate the robustness of non-inferior results using different processing strategies. The detailed description of sensitivity analysis will be presented in the statistical analysis plan. In addition, in terms of the intercurrent events of "use of other thrombolytic and defibrase drugs" and "intracranial endovascular treatment performed during the trial for treating the acute ischemic stroke", treatment policy strategy will be used as supplementary analysis, in which the actual observed mRS score at day 90 after treatment will be used, in order to evaluate the impact of intercurrent events on efficacy. Analysis of Other Efficacy endpoints For dichotomous efficacy endpoints, the same methods will be used as primary efficacy; the rank sum test will be used for the ordinal and categorical variables; the observed values and changes from baseline will be summarized, and t-test or non-parametric rank sum test will be performed for continuous endpoints. Sensitivity analysis for other efficacy endpoints will be described in the statistical analysis plan.	
Trial flow chart/Remarks a); Protocol/7.1 Screening period	If the subject has undergone laboratory tests and imaging examinations (such as emergency examinations) related to this study before signing the informed consent form (-4.5h~0h) and after the onset of this stroke, there is no need to repeat them after signing the informed consent form. The	Patient who had already undergone laboratory tests, imaging (e.g., emergency room examination), and 12-lead electrocardiography (to ensure traceability) related to this study at our study center after the onset of the current stroke (-4.5h to 0h) and before signing the informed consent form for this study did not need to repeat the tests	Improvement of the test process

	data prior to the informed consent can be used as screening-period data.	after signing the informed consent form, and the data from this pre-informed examination could be used as screening period data.	
Trial flow chart/remark d)	See section 7.3.2 of this protocol for the remaining inquiries during the screening period.	The remainder of the screening period should be asked about in section 8.3.2 of this program.	Modified in accordance with section numbering in the main Protocolme
Pilot Program Flow Sheet/Remarks e); Protocol/8.3.3. Vital signs	Study flowchart: vital signs include body temperature, heart rate, respiration, and blood pressure. Visits will be conducted during the screening period, at 24h, 72h, 7 days, 30 days, and 90 days after thrombolysis. Continuous monitoring shall be conducted within 24h after thrombolysis. If abnormalities occur, the investigators shall record and report them as AEs. If visits are made via telephone within 30 or 90 days after thrombolysis, then this examination is not necessary. Protocol: vital signs include blood pressure, heart rate, respiratory rate, and body temperature. Visits will be conducted during the screening period, at 24h, 72h, 7 days, 30 days, and 90 days after thrombolysis. Within 24h after thrombolysis, monitoring will be performed according to the requirements of each study site. If abnormalities occur, the investigators shall record and report them as AEs. If visits are made via telephone within 30 or 90 days after thrombolysis, then this examination is not necessary.	Trial flow chart: vital signs included temperature, heart rate, respiration, and blood pressure. Visits were performed during the screening period, 24h after the start of thrombolysis, 72h, 7 days, 30 days and 90 days after the start of thrombolysis. Continuous monitoring was performed for 24h after thrombolysis initiation, and any clinically significant abnormalities were recorded by the investigator and reported to the AE. This examination was not required if the 30-day and 90-day visits after thrombolysis initiation were performed by telephone voice or video. Protocol: Vital signs include blood pressure, heart rate, respiratory rate and temperature. Visits will be performed during the screening period, 24h after the start of thrombolysis, 72h, 7 days, 30 days, and 90 days after the start of thrombolysis. Monitoring will be done as required by each study hospital within 24h after the start of thrombolysis, and any clinically significant abnormality will be recorded by the investigator and reported to the AE. This test is not required if the 30 and 90 days after the start of thrombolysis is a telephone voice or video visit.	Improve the rigor of expression and the process of experimentation
Trial flow chart/Remark g); Protocol/7.2 Treatment period	CT is preferred for cranial imaging examination at 24h after thrombolysis; If the investigators believe that further examination is necessary after CT (in case of hemorrhage or other conditions), a cranial MRI examination can be added.	CT was preferred for cranial imaging 24h-36h after thrombolysis was initiated; MRI of the head could be added if the investigator felt that further examination (e.g., in the presence of hemorrhage or other conditions) was necessary after CT; direct MRI of the head was acceptable if the investigator judged that it was necessary based on the patient's condition.	Improve the rigor of expression and the process of experimentation

Trial flow chart/Remarks i) ; Protocol/7.1 Screening period	-	Added: If the patient has no history of thrombocytopenia, intravenous thrombolytic therapy may be initiated until a platelet count is obtained; intravenous thrombolysis should be discontinued once routine blood tests result in a platelet count of <100 × 109/L during thrombolysis.	Improvement of the test process
Trial flow chart/Remark k); Protocol/7.2 Treatment period; Protocol/7.2 Treatment period	Study flowchart: k) Stool routine +occult blood: The first collected stool samples are tested within 24h to 7 days after thrombolysis. In case of abnormalities, continuous collection will be conducted in the later stage. Protocol/Page 42/Line 9: collect the first stool sample within 24h and 7 days after thrombolysis, and continue to collect the sample if abnormalities occur; Protocol/Page 42/Line 23: collect the first stool sample within 24h to 7 days after administration, and continue to collect the sample if abnormalities occur	Trial flow chart： k) Stool routine + occult blood: testing of the first stool sample collected between 24h and 7 days after the start of thrombolysis, with continued collection at a later stage if clinically significant abnormalities are present; Protocol text/page 42/line 9 modified: first stool sample collected between 24h and 7 days after initiation of thrombolysis, and continued at a later date if clinically significant abnormalities occur; Protocol text/page 42/line 23 modified: first stool sample collected between 24h and 7 days after drug administration, or continued at a later date if clinically significant abnormalities occur	Increased rigor of expression
Trial flow chart/Remarks l) ; Protocol/7.1 Screening period	During the screening period, the test reports of blood biochemistry, coagulation, and pregnancy test are not required after sample collection	Blood biochemistry and coagulation during the screening period can be done without waiting for the return of the labs after specimen collection	Improvement of the test process
Pilot flow chart, column 2 of table	X[1]	Delete the corner marker in the upper right corner of the "X".	Modified according to content
Trial flow chart/line 1 of the table/add a comment q for "Follow-up period".	-	Add to the notes： q) Follow-up period visits may be conducted by telephone voice or video	Improvement of the test process
Protocol/4.2. Randomization	simple stratified randomization will be performed by 1:1 ratio for two groups.	Randomized according to 1:1 variable block groups of test or control drugs	correct a clerical error

Protocol/4.10. Trial Completion and early termination	3.9. Trial Termination and Early Termination 3.9.1. Trial Termination The completion of all stages of the study for subjects, including the last visit or last study procedure in the study schedule, is considered as the completion of the study. The completion of the last visit of the last subject is considered the end of the clinical study. The last visit includes additional unplanned visit due to adverse events.	4.10. Completion and early termination of trials 4.10.1. Completion of the test A subject was considered to have completed the study when the subject completed all phases of the study, including the last visit or last study procedure in the study schedule. The end of the last visit for the last subject was considered completion of the clinical trial. The final visit included additional unscheduled visits due to the occurrence of adverse events.	Changes to make it consistent with the presentation of the summary
Protocol/5.4.Provisions for Screening Failure	The information that should be recorded for subjects who fail in screening include demographics, reasons for failure in screening, eligibility criteria for subjects and any serious adverse events, and be entered into eCRF.	Information including demographics, reason for screening failure, subject eligibility criteria, and any adverse events should be recorded for patient who fail screening and entered into the eCRF.	Modify the content of information to be recorded for patients who fail screening
Protocol/5.5.Subject Allocation and Numbering	If a subject withdraws from this study, his/her screening number/randomization number cannot be reused, and he/she cannot participate in this study again	If a subject withdraws from the study, his/her screening number/randomization number cannot be reused and the withdrawing subject cannot participate in the study again	Consistency with previous statement
Protocol/6.5.Combined Medication and Treatment	The CRA should promptly be contacted for any issues with the combination therapy	If the investigator has any questions about the combination of treatments, he or she should contact the supervisor in a timely manner	Improved accuracy of expression
Protocol/7.2.Treatment Period	If abnormalities occur, the investigators shall record and report them as AEs	If clinically significant abnormalities occur, they are recorded by the investigator and reported to the AE	Increased rigor of expression
Protocol/7.2.Treatment Period	which the investigators believe that thrombolysis cannot continue	Those in whom the investigators felt the abnormality was clinically significant leading to no further thrombolysis	Increased rigor of expression
Protocol/7.2.Treatment Period	Under no special circumstances, cranial CT is re-performed 24h after the start of thrombolysis	If there are no special circumstances, repeat the cranial CT 24h-36h after the start of thrombolysis.	Improvement of the test process

Protocol/7.2.Treatment Period	12-lead electrocardiogram (24h to 36h after thrombolysis)	12-lead ECG (24h-36h after start of thrombolysis)	Improved accuracy of expression
Protocol/7.2.Treatment Period	-	Added: Note: If the visit is considered to be conducted by telephone voice or video, a vital signs check is not required.	Improvement of the test process
Protocol/8.3.2.Medical History, Treatment History, and Allergy History	➢ Medical history includes past and current medical history	➢ Medical history includes history of previous serious illness and current medical history	bring together
Protocol/8.3.6.Cranial CT or MRI Examination	24h after thrombolysis, CT should be performed for cranial examination as much as possible in order to find post-thrombolysis intracranial hemorrhage in time	24h-36h after the start of thrombolysis, try to use CT for cranial detection and timely detection of post-thrombolysis intracranial hemorrhage	Improvement of the test process; improvement of the accuracy of presentation
Protocol/8.3.8.Laboratory Tests	Laboratory tests include blood routine, urine routine, stool routine+occult blood, blood biochemistry, coagulation function, and pregnancy test (for women of childbearing age)	Laboratory tests including routine blood, urine, stool + occult blood, blood biochemistry, coagulation, fingerstick blood glucose and pregnancy test (women of childbearing age)	Refinement of laboratory tests to correspond to the flowchart
Protocol/9.3.Record of Adverse Event	If an exact diagnosis cannot be determined, individual signs and symptoms should be recorded separately. Each diagnosis/symptom should be recorded separately.	If it cannot be recorded as a definitive diagnosis, separate signs and symptoms should be recorded separately; when a later diagnosis is definitive, the record is updated and the diagnosis replaces the previous signs/symptoms.	Improved accuracy of expression
Protocol/9.3.Record of Adverse Event	If adverse events of the same type occur more than once in a subject and a correlation can be found between the preceding and following event (the progression of previous adverse event or recurrence), it is recommended to record the same adverse event in the medical record and explain the severity based on previous records (such as intermittent gingival bleeding within a day).	If the same category of adverse event occurs more than once in a subject, it is recommended that it be documented in the medical record as the same adverse event if the before and after are related (judged by the investigator to be a progression or intermittent recurrence of a previous adverse event), and that the severity be described in conjunction with the previous record (e.g., intermittent gingival bleeding over the course of a day).	Improved accuracy of expression
Protocol/9.3.Record of Adverse Event	1） The investigator should strictly judge whether the subject have "recovered". If laboratory abnormalities turn to normal, the AE can only be judged to be terminated after repeated tests showing normal. In the case of short-term	1）Judgment of AE regression by the investigator	Describe how to determine AE regression based on clinical

	fluctuating changes, it is not recommended to record AE as "terminated".		practice
Protocol/9.3.Record of Adverse Event	Not improved/sustained: The event has not remitted and is still ongoing. If the AE outcome is "sustained", at least 2 follow-ups are required for the investigators to determines that there are no signs of deterioration.	Failure to improve/continuing: event has not resolved and is still ongoing. If "persistent" is used as the AE outcome. There must be at least 2 follow-up examinations with no signs of deterioration in the judgment of the investigator.	Make the definitions of "not improving" and "persistent" clear, respectively.
Protocol/9.10.Serious Adverse Event	The following are not considered as hospitalization or not required to be reported as SAEs: emergency room visit; hospital stays for observation within 24h; hospitalization for routine examinations (hospitalization less than 24h); hospitalization for social reasons (e.g., hospitalization for unattended care); hospitalization for planned surgery on a date agreed prior to entry of study. If the subject has disease prior to participation in the study and the disease does not worsen during the study, the hospitalization and/or surgical treatment that are planned prior to the study performed are not considered as an AE.	The following are not hospitalizations or not reported as SAEs due to hospitalization: emergency room stay; hospitalization for observation within 24 h; hospitalization for routine care with a stay of less than 24 h; hospitalization for social reasons (e.g., hospitalization due to unavailability of care); hospitalization due to a surgery for which a date has been agreed upon prior to the study; and hospitalization and/or surgical treatment that has been planned prior to the trial that was performed when the subject already had a disease prior to participation in the trial and the disease did not exacerbate during the trial.	Improved accuracy of expression
Protocol/10.Risk Control and Management	During the administration, a regular safety examination will be conducted, mainly including vital signs, physical examination, blood routine, blood biochemistry (liver function, kidney function, electrolytes, etc.), etc.	A safety check will be conducted periodically during the dosing period, mainly including: vital signs, physical examination, blood routine, blood biochemistry (liver function, kidney function, etc.), etc.	Deletion of non-included checks
Protocol/13.Clinical Monitoring	verify that all medical reports, records and documents provided by the investigator are traceable, legible, synchronously recorded, original, accurate and complete, dated and study numbered	Verify that all medical reports, records and documents provided by the researcher are traceable, legible, synchronized, original, accurate and complete, and dated	Modified in accordance with the recording of documents in practice
Protocol/18.2.Patient' Benefits	Compensation for transportation costs and nutritional compensation will be distributed to subjects in multiple times according to the progress of the subject completing the study.	Transportation reimbursement will be issued to patient based on their progress in completing the trial.	Modification of compensation and its modalities in the light of the actual situation

References	-	The following references have been added: [3] WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke–1989: Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989, 20:1407–1421.	New references added
Appendix 3: National Institutes of Health Stroke Scale（NIH Stroke Scale，NIHSS）	• 1a rating scale: 2= Not alert; requires repeated stimulation to attend, or is obtunded and requires strong/painful stimuli to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic • 1b- Line 4 of the checklist: Patients unable to speak due to endotracheal intubation, orotreacheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. • 1c- Line 3 of the checklist: Substitute another one step command (stretch the tongue) if the hands cannot be used. • 2 Optimal Gaze - Checklist: Only horizontal movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scared, but caloric testing is not done. If the patient's conjugate eye deviation can be overcome by automatic or reflexive activity, score 1 point. If a patient has an isolated peripheral nerve paresis (CN III , IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other impairments of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy. rating scale: 1=Partial gaze palsy: gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is present.	• 1a Modification of scoring items: 2 = Not alert; requires repeated stimulation for attention or is unresponsive requires strong or painful stimulation for activity (non-repetitive fixed movements) 3 = Only reflexive movements or autonomic reflex manifestations or complete unresponsiveness, flaccidity, absence of reflexes • 1bAmendments to line 4 of the check: Inability to speak due to tracheal intubation, oral tracheal trauma, severe dysarthria from any cause, speech disorders, or any other cause not secondary to aphasia is recorded as 1 point. • 1cAmendments to line 3 of the check: If the hand is not available, replace it with another one-step instruction. • 2 Optimal Gaze - Check Item Modification: Test horizontal eye movements only. Score casual or reflex (head-eye reflex) eye movements, but do not do the hot and cold water test. Score 1 point for isolated peripheral nerve palsy (III, IV, VI cranial nerves). Gaze is examinable in all aphasic individuals. Those with ocular trauma, bandage wrapping, long-standing blindness, or other visual or visual field abnormalities should be examined for reflex movements, as determined by the examiner. Making eye contact with the patient and then moving from one side to the other occasionally reveals partial gaze paralysis. Modification of scoring items: 1 = Partial gaze palsy; abnormal gaze in one or both eyes without forced deviation or complete gaze palsy 2 = Forced deviation, or complete gaze paralysis that cannot be overcome by head-eye reflexes • 3 Field of view - check item line 7 change: At this point do bilateral simultaneous stimulation, if there is unilateral	Standardizing the presentation of rating scales

	2=Forced deviation or total gaze paresis not overcome by the oculocephalic maneuver. • 3 Visual field - check item line 7: Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11. • 4 Facial paralysis - check item line 3: Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. • 5 Upper Extremity Exercise - Checklist: The limb is placed in the appropriate position: extend the arms (palms down)90 degrees (if sitting) or 45 degrees (if supine). Drift is scored based on whether the arm falls before 10 seconds. Guide aphasic patients using voice or gestures, without using noxious stimuli. The rater can lift the patient's arm to the required position and encourage the patient to persevere. rating scale: 1=Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. • 6 Lower Extremity Exercise - Checklist: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored based on whether the leg falls before 5 seconds. Guide aphasic patients using voice or gestures, without using noxious stimuli. The rater can lift the patient's leg to the required position and encourage the patient to persevere. rating scale: 1= Drift; leg falls by the end of the 5-second period but does not hit bed. • 7 Limb ataxia-examination items: This item is aimed at finding evidence of a bilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness.	neglect, mark 1 point, this result is used in article 11. • 4 Facial paralysis - change in line 3 of the checklist: For patients who responded poorly or were unable to understand, scoring was based on the symmetry of expression during painful stimuli. • 5 Upper Extremity Exercise - Check Item Modification: Place the limb in the appropriate position: extended arm (palm down) 90° (seated) or 45° (supine). Score if the upper limb falls within 10 seconds. Use a sharp tone of voice or gesture to guide the aphasic person without using pain stimuli. Modification of scoring items: 1 = Swaying: limb placed at 90° (or 45°) but downward in less than 10 seconds; does not strike bed or other supports • 6 Lower Extremity Exercise - Check Item Modification: Place the limb in the proper position: raise the leg 30° (must be in supine position). Score if the lower limb drops within 5 seconds. Use voice or gestures to guide the aphasic person without pain stimulation. Modification of scoring items: 1 = Wobbling: lower limbs fall close to 5 seconds but do not hit the bed • 7 Limb ataxia - modification of test items: The goal is to find evidence of unilateral cerebellar lesions. The examination is performed with eyes open. If there is a visual defect, ensure that the examination is performed in an unimpaired field of vision. Bilateral finger-nose tests and heel-knee-shin tests are performed. Motor disorders are only counted as ataxia if they exceed limb weakness. • 9 Best Language-Checkpoint Modification: If a visual deficit interferes with the test, have the patient identify objects placed in the hand, repeat and converse. • 11 The name of the test has been changed to: loss of sensation or loss of attention (formerly known as neglect) Modification of scoring items: 2 = Severe lateral inattention or loss of attention to more than one sensory test; does not recognize one's own hand or is oriented to only one side of space	

	• 9 Best Language - Checklist: If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and pronounce. • 11 Name of check item: Neglect rating scale: 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space		
Protocol Synopsis/Study Design; Trial Flow Chartt/Remarks at f), j), n). Protocol	The expression "post-thrombolysis" in that context	Amend to read "after thrombolysis has begun".	Improved accuracy of expression
The fifth revision			
Version number/Version date before revision: V2.1/2022.08.29			
Revised Version Number/Version Date: V2.2/2022.11.17			
Modify item	Content of the original research program	Content of the revised research program	Note
Version number/version date on cover page and signature page	Version No.: V2.1 Version Date: August 29, 2022	Version No.: V2.2 Version Date: November 17, 2022	-

<table>
<tr><td>Protocol Synopsis</td><td>Protocol Version No./Version Date: V2.1 2022/8/29</td><td>Program version number/version date: V 2.2 2022/11/17</td><td>-</td></tr>
<tr><td>Version number/date in the corner of the page</td><td>Version No.: V2.1 Version Date: 2022/8/29</td><td>Version No.: V2.2 Version Date: 2022/11/17</td><td>-</td></tr>
<tr><td>Protocol Synopsis/Estimated Objective;
Protocol/3.1.Primary Estimated Objective</td><td>Intercurrent Events and corresponding treatment strategy：
<table>
<tr><th>Intercurrent Event</th><th>Treatment Strategy</th><th>Note</th></tr>
<tr><td>Use of other thrombolytic and fibrinolytic drugs</td><td>treatment policy strategy</td><td rowspan="4">A true reflection of actual clinical practice. The mRS scores will continue to be collected after an intercurrent event occurs and will be analyzed using the actual observations of the mRS scores regardless of whether or not that intercurrent event</td></tr>
<tr><td>Use of antiplatelets and anticoagulants (within 24h of thrombolysis)</td><td>treatment policy strategy</td></tr>
<tr><td>Intracranial endovascular treatment performed during the trial for treating the acute ischemic stroke*</td><td>treatment policy strategy</td></tr>
<tr><td>Failure to complete treatment per protocol requirements(including failure to complete two injections of recombinant human tissue-type plasminogen activator derivative or failure to complete the planned dosage titration of alteplase, treatment window overruns, inconsistencies between</td><td>treatment policy strategy</td></tr>
</table></td><td>Intercurrent events and corresponding treatment strategy:
<table>
<tr><th>Intercurrent Event</th><th>Treatment Strategy</th><th>Note</th></tr>
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<tr><td>Use of antiplatelets and anticoagulants (within 24h of thrombolysis)</td><td>treatment policy strategy</td><td>A true reflection of actual clinical practice. The mRS scores will continue to be collected after an intercurrent event occurs and will be analyzed using the actual observations of the mRS scores regardless of whether or not that intercurrent event occurs.</td></tr>
<tr><td>Intracranial endovascular treatment performed during the trial for treating the acute ischemic stroke*</td><td>Composite strategy</td><td>treat as non-responsive</td></tr>
<tr><td>Failure to complete treatment per protocol</td><td>treatment policy</td><td>A true reflection of actual clinical</td></tr>
</table></td><td>In accordance with the CDE communication, the treatment strategies of "use of other thrombolytic and fibrinolytic drugs" and "intracranial endovascular therapy for the purpose of treating the current acute ischemic stroke was performed during the trial" were changed to a composite strategy.</td></tr>
</table>

	the actual treatment medication and the plan, and non-adherence to treatment dosage,, etc.)		occurs.
	requirements(including failure to complete two injections of recombinant human tissue-type plasminogen activator derivative or failure to complete the planned dosage titration of alteplase, treatment window overruns, inconsistencies between the actual treatment medication and the plan, and non-adherence to treatment dosage,, etc.)Recombinant Human Tissue-type Plasminogen Activator Derivative	strategy	practice. The mRS scores will continue to be collected after an intercurrent event occurs and will be analyzed using the actual observations of the mRS scores regardless of whether or not that intercurrent event occurs.
Protocol Synopsis/Statistical Hypothesis/ Sample Size Estimation; Protocol/11.1.Statistical Hypothesis and Sample Size Estimation	-	Added: Based on information from previous trials, the expected incidence of symptomatic intracranial hemorrhage was approximately 1% with reference to the SITS-MOST study [7], and the expected incidence of death was approximately 5% with reference to the NOR-TEST study [8], which based on a sample size of 1,412 cases found that the probability of at least one death or symptomatic intracranial hemorrhage was greater than 99%.	Increase the safety basis for sample size calculations based on CDE communications .
Protocol Synopsis/Statistical Analysis/Primary Estimated Objective Analysis; Protocol/11.3.1.Efficacy Analysis	-	Added: A sensitivity analysis based on different missing data assumptions will also be conducted to assess whether different treatments of missing data may have an impact on the robustness of the non-inferiority results.	Addition of MNAR's sensitivity analysis description
Protocol Synopsis/Statistical Analysis/Primary Estimated Objective Analysis; Protocol/11.3.1.Efficacy	-	Added: In addition, for the intercurrent events "Use of other thrombolytic and fibrinolytic drugs" and "Intracranial endovascular therapy for the purpose of treating the current acute ischemic stroke", a treatment policy strategy will be used as a complementary analysis to assess the impact of confirming the intercurrent event on the assessment of efficacy. The effect of confirming intercurrent events	Add description of supplemental analysis per CDE requirements

Analysis		on the assessment of efficacy will also be assessed using the actual observed 90-day post-treatment mRS scores in the analyses.	
Protocol/11.3.1.Efficacy Analysis	1) Use of other thrombolytic and defibrase drugs: herapeutic strategy Rationale: This intercurrent event is consistent with clinical practice and is related to the treatment of the subject, is part of the treatment, and is consistent with the ITT principle in ICH E9 (This principle asserts that the effectiveness of an interventional treatment can be best assessed by evaluating the subject based on their intent (i.e., the planned treatment regimen), rather than the actual treatment given. The result is that patient assigned to a treatment group should be followed, evaluated, and analyzed as members of that group, regardless of their compliance with the planned course of treatment.) 。 Therefore, even if patients were on thrombolytic and fibrinolytic medications, they were continued to be followed up and the follow-up data were included in the analysis.	1) Use of other thrombolytic and anti-fibrinolytic drugs: composite strategy Rationale: The use of other thrombolytic and anti-fibrinolytic drugs by the subject is considered to be a poor thrombolytic effect or even failure of the previously tested drugs, so a combination strategy is used and will be treated as non-response.	Change the treatment strategy for "Use other thrombolytic and anti-fibrinolytic drugs" from a treatment policy strategy to a combination strategy and change the selection strategy accordingly, as required by the CDE.
Protocol/11.3.1.Efficacy Analysis	3) Intracranial endovascular treatment performed during the trial for treating AIS: treatment policy strategy Rationale: This event is consistent with clinical practice, and if endovascular therapy is performed after thrombolysis, it is part of the treatment, in accordance with the ITT principles of ICH E9, so even if the patient underwent endovascular therapy during the course of the trial, follow-up will be continued and follow-up data will be included in the analysis.	3) Intracranial endovascular treatment for the purpose of treating the current acute ischemic stroke was performed during the course of the trial: composite strategy Rationale: Patient who underwent intracranial endovascular treatment during the course of the trial for the purpose of treating the current acute ischemic stroke are considered to have had poor or even failed thrombolysis with drugs in the previous trial, and therefore a composite strategy is used, and will be treated as non-responsive.	Change the treatment strategy for "Intracranial endovascular therapy for the purpose of treating the current acute ischemic stroke was administered during the trial" from a treatment policy strategy to a combination strategy and change the

			selection strategy accordingly, as required by the CDE.
Protocol	-	1. Reorder literature [11] to literature [7]; 2. Add literature [8].	Adaptation of documentation to program content.