

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

**Trial Protocol**

Protocol Version: V2.2    Version Date: November 17, 2022

<b>Clinical Trial Approval No.</b>	2017L00263
<b>/Clinical Trial Notification:</b>	
<b>Acceptance No.:</b>	CXSL1500077LU
<b>Protocol No.:</b>	CRAD-001-03
<b>Investigational Drug:</b>	Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection
<b>Clinical Trial Phase:</b>	Phase III
<b>Major Study Site for Clinical Trial:</b>	Beijing Tiantan Hospital, Capital Medical University
<b>Principle Investigator:</b>	Yongjun Wang
<b>Sponsor:</b>	China Resources Angde Biotech Pharma Co., Ltd
<b>Declaration of Compliance:</b>	This trial will be conducted in strict accordance with the requirements of Good Clinical Practice (GCP)

DC AMS PHARMA Co., Ltd.

Protocol No.:XXX

Confidentiality Statement

All information contained in this protocol is proprietary to China Resources Angde Biotech Pharma Co., Ltd. Therefore, it is only provided for review by the sponsor, investigators, collaborating investigators, ethics committees, and regulatory authorities and relevant medical institutions. Any unauthorized individuals who come across this study protocol are requested to delete, abandon, or block access to the document. Except for necessary explanations provided to potential study participants when obtaining their informed consent, it is strictly prohibited to disclose any information to a third party unrelated to this study without written approval from the sponsor.

## Protocol Signature Page

We have read the study protocol for A Multicenter, Randomized, Blind Endpoint and Positive Drug Controlled Phase III Study of Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection in the Treatment of Patients with Acute Ischemic Stroke, with protocol No. CRAD-001-03 and version No.V2.2 (dated November 17, 2022). We have reviewed and confirmed this clinical trial protocol and agreed to conduct the clinical trial according to this protocol.

We will keep confidential this clinical trial protocol and related information.

**Sponsor:** China Resources Angde Biotech Pharma Co., Ltd

**Address:** No. 78, Ejiao Street, DongEShandong

**Project Leader of the Sponsor (Printed) :** Haifeng Liu **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY

## Investigator's Statement

- 1) I agree to personally participate in or directly supervise this clinical study.
- 2) I have received the Investigator's Brochure and I have learned the preclinical study conducted for the investigational drug.
- 3) I have read the study protocol for A Multicenter, Randomized, Blind Endpoint and Positive Drug Controlled Phase III Study of Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection in the Treatment of Patients with Acute Ischemic Stroke, with protocol No. CRAD-001-03 and version No.V2.2 (dated November 17, 2022). The study will be conducted in accordance with the principles of the Helsinki Declaration and the ethical and scientific principles defined by Good Clinical Practice (GCP). I agree to conduct this clinical study according to the protocol's design and requirements, and any modifications to the protocol will be made only after notifying the sponsor. Its implementation will be subject to the approval by the ethics committees, except for necessary measures that are required to protect the safety, rights, and interests of the subjects.
- 4) I will ensure that all subjects provide written informed consent before entering the study, in accordance with GCP requirements.
- 5) I will be responsible for making medical decisions related to the clinical trial and ensuring that subjects receive timely and appropriate treatment in case of any adverse event during the trial. I will also comply with the relevant national regulations to record and report serious adverse events.
- 6) I guarantee that data will be entered into the study records authentically, accurately, completely, and in a timely manner. I will accept the inspections and auditings conducted by CRA or auditors assigned by the sponsor and inspections conducted by the drug regulatory authorities to ensure the quality of the clinical trial.
- 7) I commit to keeping confidential subjects' information and related matters. I have been informed that any breach of this commitment may result in legal liability.
- 8) I agree to disclose my full name and profession to the sponsor and consent to the disclosure of expenses related to the clinical study upon request. I also agree to refrain from engaging in any commercial or economic activities related to this trial.

**Leading Site for the Clinical Trial:** Beijing Tiantan Hospital, Capital Medical University

**Principle Investigator (Printed):** Yongjun Wang **(Signature):** \_\_\_\_\_

**Date of Signature::** \_\_\_\_\_DD\_\_\_\_\_MM\_\_\_\_\_YY

## Protocol Signature Page

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**Contract Research Organization:** Nanjing CR Medicon Technology Co., Ltd.

**Project Leader (Printed):** Xingmiao Ma **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY

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**Contract Research Organization:** Beijing Highthink Pharmaceutical Technology Service Co., Ltd.

**Project Leader (Printed):** Xianlian Wang **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY

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**Contract Research Organization:** Beijing Borrun Technology Service Co., Ltd.

**Project Leader (Printed):** Xiaocui Fu **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY



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**Data Management Company:** Nanjing CR Medicon Technology Co., Ltd.

**Project Leader (Printed):** Tingting Zhang **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY

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**Statistical Analysis Company:** Nanjing CR Medicon Technology Co., Ltd.

**Project Leader (Printed):** Bing Sun **(Signature):** \_\_\_\_\_

**Date of Signature:** \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ Y

## Protocol Signature Page

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

Trial No.: CRAD-001-03

Investigational Drug: Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection

Protocol Version: V2.2

Version Date: November 17, 2022

### Protocol Drafter/Reviser:

Name(Printed): Xinming Liu (Signature)\_\_\_\_\_

Date of Signature: \_\_\_\_\_ DD \_\_\_\_\_ MM \_\_\_\_\_ YY

Title: Medical Manager Unit: China Resources BioPharmaceutical Co., Ltd

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Abbreviations

English Abbreviation	English Full Name	Chinese Full Name
AE	Adverse Event	不良事件
AIS	Acute Ischemic Stroke	急性缺血性脑卒中
ALB	Albumin	白蛋白
ALT	Alanine Transaminase	丙氨酸氨基转移酶
APTT	Activated Partial Thromboplastin Time	活化部分凝血活酶时间
AST	Aspartate Transaminase	门冬氨酸氨基转移酶
BUN	Blood Urea Nitrogen	尿素氮
CDE	Center for Drug Evaluation	药品审评中心
CEC	Clinical Event Committee	临床事件委员会
CK	Creatine Kinase	肌酸激酶
CREA	Creatinine	肌酐
CRF	Case Report Form	病例报告表
CT	Computed Tomography	电子计算机断层扫描
CTCAE	Common Terminology Criteria for Adverse Events	不良事件通用术语标准
eCRF	Electronic Case Report Form	电子病例报告表
EDC	Electronic Data Collection	电子数据采集系统
FIB	Fibrinogen	纤维蛋白原
GCP	Good Clinical Practice	药物临床试验质量管理规范
GLU	Glucose	葡萄糖
HCG	Human Chorionic Gonadotropin	人绒毛膜促性腺激素
HGB	Hemoglobin	血红蛋白
IDMC	Independent Data Monitoring Committee	独立数据监查委员会
INR	International Normalized Ratio	国际标准化比值
ISTH	International Society of Thrombosis and Hemostasis	国际血栓与止血学会
ITT	Intention -To -Treat	意向性治疗
MedDRA	Medical Dictionary for Regulatory Activities	国际医学用语词典
MRI	Magnetic Resonance Imaging	磁共振成像
mRS	Modified Rankin Scale	改良的 Rankin 量表
NCI	National Cancer Institute	美国国立癌症研究所
NIHSS	National Institutes of Health Stroke Scale	美国国立卫生研究院卒中量表
NMPA	National Medical Products Administration	国家药品监督管理局
OR	Odds ratio	比数比
PLT	Platelet	血小板
PT	Prothrombin Time	凝血酶原时间
PT	Preferred Term	首选术语
RBC	Red Blood Cell	红细胞
RD	Rate Difference	组间率差
RR	Rate Ratio	比值
rt-PA	recombinant Human Tissue Plasminogen Activator	重组人组织纤维蛋白溶酶原激活剂
SAE	Serious Adverse Event	严重不良事件
SDV	Source Document Verification	原始资料核查
SAP	Statistical Analysis Plan	统计分析计划
SK	Streptokinase	链激酶

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English Abbreviation	English Full Name	Chinese Full Name
SOC	System Organ Class	系统器官分类
SOP	Standard Operating Procedure	标准操作流程
SUSAR	Suspicious and Unexpected Serious Adverse Reactions	可疑且非预期严重不良反应
SS	Safety Set	安全性分析集
TC	Total Cholesterol	总胆固醇
TEAE	Treatment Emergent Adverse Event	治疗期间发生的不良事件
TG	Triglyceride	甘油三酯
TP	Total Protein	总蛋白
TT	Thrombin Time	凝血酶时间
TBIL	Total Bilirubin	总胆红素
UK	Urokinase	尿激酶
ULN	Upper Limit of Normal	正常值上限
UREA	Urea	尿素
WBC	White Blood Cell	白细胞
WHO	World Health Organization	世界卫生组织



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Protocol No.: CRAD-001-03

Protocol Synopsis

<b>Clinical Trial Basic Information</b>	Registration Category: Therapeutic Biological Products - Category 2.2 Clinical Trial Protocol No.: CRAD-001-03 Protocol Version/Version Date: V2.2 November 17, 2022 Clinical Trial Phase: Phase III Investigational Drug: Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection Sponsor: China Resources Angde Biotech Pharma Co., Ltd
<b>Study Title</b>	A Multicenter, Randomized, Blind Endpoint and Positive Drug Controlled Phase III Study of Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection in the Treatment of Patients with Acute Ischemic Stroke
<b>Study Objective</b>	<b>Primary Objective:</b> To evaluate the effectiveness of recombinant human tissue-type plasminogen activator derivative for injection versus alteplase in the treatment of patients with acute ischemic stroke within 4.5h of onset. <b>Secondary Objective:</b> To evaluate the safety of recombinant human tissue-type plasminogen activator derivative for injection versus alteplase in the treatment of patients with acute ischemic stroke within 4.5h of onset.
<b>Estimands</b>	<b>Primary Estimand</b> The primary clinical question is 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. Definition of Primary Estimand 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

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	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 defibrase drugs	Composite strategy	Treated as no response
	Use of antiplatelet and anticoagulant drugs (within 24 hours of thrombolysis):	treatment policy strategy	Reflecting real-world clinical practice. The mRS score will continue to be collected after the occurrence of the intercurrent events. Regardless of whether or not such events occur, the actual observed values of mRS scores will be used for analysis.
	Intracranial endovascular treatment performed during the trial for treating the acute ischemic stroke*	Composite strategy	Treated as no response
	Failure to complete treatment per protocol requirements (including uncompleted two injections of recombinant human tissue-type plasminogen activator derivative or uncompleted infusion of planned	treatment policy strategy	Reflecting real-world clinical practice. The mRS score will continue to be collected after the occurrence of

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	<div><div><div><div><div></div><div>dosage of alteplase, treatment beyond the specified window, inconsistency between actual treatment drug and planned treatment drug, non-compliance of treatment dosage, etc.)</div></div><div></div><div><div>the intercurrent events. Regardless of whether or not such events occur, the actual observed values of mRS scores will be used for analysis.</div></div></div></div></div>
	<div><p>Note: *Intracranial endovascular treatment for this acute ischemic stroke is performed during the trial, including the routine use of antiplatelet and anticoagulant drugs within 24h after thrombolysis for the treatment of this acute ischemic stroke.</p><p>Population-Level Summary: relative ratio (RR) of efficacy rate and its bilateral 95% confidence interval.</p><p><b>Secondary Estimand:</b> See Statistical Analysis Plan for details.</p></div>
<b>Study Design</b>	<div><p><b>Overall Design</b></p><p>This is a multicenter, randomized, blind endpoint and positive drug parallel controlled phase III study of recombinant human tissue-type plasminogen activator derivative for injection compared with alteplase in the treatment of acute ischemic stroke (AIS) within 4.5h of onset (hereafter referred to as "Reteplase"), with the primary objective of evaluating the effectiveness of the investigational drug based on mRS at day 90 after treatment.</p><p>This study plans to recruit 1412 cases with acute ischemic stroke within 4.5h of onset. Eligible subjects will be randomized in a 1:1 ratio to either the investigational drug group or control drug alteplase group. After receiving thrombolytic treatment, subjects will undergo a series of safety and efficacy assessments. At day 90 (±7 days) after the start of thrombolysis, subjects will be visited using mRS score and Barthel Index score. Following the completion of the follow-up visit, subjects may withdraw from the study.</p><p>In this study, independent blind endpoint evaluators are set at each study site to assess mRS score and Barthel Index score at day 30 and day 90 after thrombolysis in a</p></div>

	<p>blinded manner.</p> <p><b>Population Selection and Rationale:</b></p> <p>Patients with AIS within 4.5h of onset are selected as the study population.</p> <p>According to the Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition <sup>[1]</sup>, the current consensus has been reached that the time window for effectively salvaging the penumbra tissue is within 4.5h or 6h. Alteplase has been approved for marketing in multiple countries and for the treatment of AIS patients within 4.5h of stroke onset in China and Europe. With reference to the Technical Guidelines for Clinical Trials of Drugs for Acute Ischemic Stroke Treatment <sup>[2]</sup> issued by Center for Drug Evaluation (CDE) in 2018, intravenous thrombolytic drugs are recommended to be used by subjects who have had a stroke within 4.5h.</p> <p><b>Dosage Selection and Rationale</b></p> <p>Considering the efficacy and safety resulting from Phase II clinical trial and the historical data of the positive drug, a dosage of 18mg + 18mg is selected as the Phase III administration dosage.</p> <p><b>The Establishment of an Independent Data Monitoring Committee (IDMC)</b></p> <p>An independent data monitoring committee (IDMC) will be established in this study, whose responsibility includes conducting safety assessment on cumulative data from the ongoing clinical trial to ensure subjects’ safety.</p> <p>The IDMC consists of clinical experts and statistical experts in the relevant field. Its composition, operating procedures, and cycle of operation will be described in the relevant charter in detail.</p> <p><b>The Establishment of An Independent Clinical Event Committee (CEC):</b></p> <p>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.</p>
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Study Population	Patients with acute ischemic stroke within 4.5h of onset and aged between 18 and 80 (including two endpoints) are considered as the study population.
Inclusion Criteria	<p><b>Patients who meet all of the following criteria may be considered for enrollment:</b></p> <ol style="list-style-type: none"><li>1) Aged <math>\geq 18</math> and <math>\leq 80</math> at the time of signing the informed consent form, either males or females;</li><li>2) Within 4.5 hours after the onset of symptoms of neurological impairment due to acute ischemic stroke according to the diagnosis criteria for stroke issued by the World Health Organization (WHO)<sup>[3]</sup>, Onset time refers to the time the patient was last known to be well.</li><li>3) <math>4 \leq \text{NIHSS score} \leq 25</math> before thrombolysis.</li><li>4) Fertile men and women of childbearing age who have no childbearing plan from the date of enrollment to 3 months after thrombolysis administration and are willing to take effective contraceptive measures.</li><li>5) Understand and follow the procedures of clinical trial, participate voluntarily, and sign the informed consent (which can be signed voluntarily by the person or guardian).</li></ol>
Exclusion Criteria	<p><b>Patients who meet any of the following criteria may not be enrolled:</b></p> <ol style="list-style-type: none"><li>1) Patients are known to be allergic to investigational drugs (recombinant human tissue-type plasminogen activator derivative for injection, alteplase) or similar components, or materials used for imaging examinations.</li><li>2) Body weight <math>&gt;120\text{kg}</math> or <math>&lt;45\text{kg}</math>;</li><li>3) The onset of stroke symptoms cannot be ascertained.;</li><li>4) mRS score <math>\geq 2</math> before the onset of the current stroke;</li><li>5) 1a (level of consciousness) of NIHSS score <math>\geq 2</math> at screening;</li><li>6) Intracranial hemorrhage history (including parenchymal / intraventricular / subarachnoid hemorrhage, subdural / external hematoma, etc.);</li><li>7) CT/MRI imaging shows signs of intracranial hemorrhage or subarachnoid hemorrhage is suspected despite normal CT/MRI;</li><li>8) Severe head trauma , clinically symptomatic stroke history, or other severe trauma in the last 3 months.</li><li>9) Patients with intracranial tumor, arteriovenous malformation and aneurysm found before enrollment;</li></ol>

	<div>10) Intracranial surgery, intraspinal surgery or other major surgeries within 3 months before enrollment(based on the assessment of the investigators);</div> <div>11) Gastrointestinal or urinary system hemorrhage within the past 3 weeks;</div> <div>12) Patients with active visceral hemorrhage;</div> <div>13) Aortic arch dissection confirmed by pre-study examination or medical history;</div> <div>14) Arterial puncture at the site that is not easily compressed to stop bleeding within the last week;</div> <div>15) Acute hemorrhage tendency, including but not limited to the following: 1) Platelet count less than <math>100 \times 10^9/L</math>; 2) patients received low molecular heparin within 24h before onset; 3) use of thrombin inhibitors or factor Xa inhibitor within 48 hours before onset; 4) taking oral anticoagulant drugs with an INR &gt; 1.7 or PT&gt;15s;</div> <div>16) Actively treated but uncontrolled hypertension, defined as systolic blood pressure &gt;185 mmHg and/or diastolic blood pressure &gt;110 mmHg;</div> <div>17) Blood glucose &lt;50 mg/dl (equivalent to 2.78mmol/L) or &gt;400 mg/dl (equivalent to 22.2mmol/L) during screening;</div> <div>18) Large cerebral infarction on CT or MRI;</div> <div>19) Severe liver impairment, including liver failure, cirrhosis, portal hypertension (esophageal varices), and active hepatitis;</div> <div>20) Patients with bacterial endocarditis, pericarditis or acute pancreatitis at enrollment;</div> <div>21) History of gastrointestinal ulcers, esophageal varices, aneurysms, or arterial / venous malformations within 3 months before enrollment;</div> <div>22) Unable or unwilling to cooperate due to epileptic seizures during stroke episodes, or other mental illnesses;</div> <div>23) Planned or received endovascular treatment after the onset of the current stroke;</div> <div>24) Patients have to take or desire to continue to take the restrictive drugs specified in the protocol or any drug that may interfere with the test results;</div> <div>25) With an expected survival time less than 1 year due to other diseases;</div>
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	<p>26) Have participated in other clinical trials within 30 days prior to randomization or are participating in other clinical trials;</p> <p>27) Females are in pregnancy or lactation, or have a positive pregnancy test result;</p> <p>28) Considered by the investigator to have other conditions that might affect compliance or preclude participation in this study.</p>
<p><b>Early Withdrawal Criteria</b></p>	<p>During the trial, subjects may withdraw their consent and request to discontinue their participation. When subjects withdraw the informed consent and request to terminate the trial treatment, they should complete subsequent safety and efficacy visits as much as possible.</p> <p><b>Subjects may voluntarily withdraw from the study under the following circumstances:</b></p> <ul style="list-style-type: none"><li>• Subjects withdraw their consent.</li><li>• Subjects are lost to follow-up and cannot be contacted by at least three attempts.</li></ul> <p><b>The investigators may terminate the participation of subjects in the study under the following circumstances:</b></p> <ul style="list-style-type: none"><li>• Subjects become pregnant (or the partners are pregnant) or are suspected to be pregnant (or the partners are pregnant);</li><li>• Subjects are found not to be eligible as patients with acute ischemic stroke after randomization.</li><li>• 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.</li></ul>
<p><b>Trial Termination</b></p>	<p>Trial termination includes both trial completion and premature termination, and if either condition is met, the trial is stopped.</p> <p>Trial completion is defined as the time when the last subject completes the final visit. The sponsor has the right to terminate the trial in advance at any time point during the entire trial period for valid reasons.</p> <p>Premature termination of the trial refers to the discontinuation of the entire trial or part of the trial, as the clinical trial has not yet completed studies of all subjects as per the</p>

	<p>protocol. The premature termination primarily aims to protect the rights of the subjects, ensure the quality of the trial, and avoid unnecessary economic losses.</p> <p>Generally, the trial is not terminated early unless for valid reasons. However, if any of the following circumstances occur, the entire trial (or a specific site) may be terminated prematurely:</p> <p>1) The total sample size of competitive enrollment has met the requirements of the trial, but the site has not completed the planned enrollment as per the contract and/or all subjects at the site have completed the study.</p> <p>2) The investigators at the site fail to comply with the protocol, GCP <sup>[4]</sup>, etc.</p> <p>3) New information is obtained that indicates an unfavorable risk-benefit evaluation of the investigational drug, including sufficient evidence suggesting lack of efficacy or unacceptable safety.</p> <p>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.</p> <p>5) The sponsor considers it inappropriate to continue the clinical trial for medical, ethical, or commercial reasons.</p> <p>6) Slow subject enrollment makes it impossible to complete the study within an acceptable time period.</p> <p>7) The National Medical Products Administration or an ethics committee orders the termination of the trial for some reason.</p> <p>In the event of premature termination of the clinical trial, all relevant parties (the sponsor, investigators, ethics committees, clinical trial institutions, and regulatory authorities) should be promptly notified in written form.</p>
<b>Trial Grouping and Dosing Regimen</b>	<p>The enrolled subjects are randomly assigned to two groups in a 1:1 ratio:</p> <p><b>Investigational Drug Group:</b> Recombinant human tissue-type plasminogen activator derivative for injection (18mg + 18mg) is injected intravenously at two doses, 18mg for the first intravenous injection and 18mg for the second intravenous injection 30 minutes later. Each slow injection lasts at least 2 minutes.</p>



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	<p>The subjects are monitored closely during the medication and within 24h of medication.</p> <p>Note: Timing is started from the completion of the first intravenous injection. The second intravenous injection of the investigational drug should start 30 (±5) minutes after the completion of the first injection.</p> <p><b>Control Drug Group:</b> Alteplase for injection is administered via intravenous infusion at a dose of 0.9mg/kg (with a maximum dose of 90mg). 10% of the dose is administered via intravenous injection within 1min, followed by continuous intravenous infusion of the remaining dose for 1h. The subjects are monitored closely during the medication and within 24h of medication.</p> <p>The subjects are monitored with reference to Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition.</p>
Test Drugs	<p><b>Investigational Drug:</b></p> <ul style="list-style-type: none"><li>• <b>Name:</b> Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection</li><li>• <b>Trade Name:</b> Reteplase;</li><li>• <b>Specification:</b> 18mg/10ml/vial;</li><li>• <b>Character:</b> White or almost white freeze-dried powder injection;</li><li>• <b>Route of Administration:</b> Intravenous injection;</li><li>• <b>Storage Conditions:</b> Keep it sealed and away from light at 2-8 °C for storage and transportation. Do not freeze;</li><li>• <b>Expiry Date:</b> As indicated by the actual batch;</li><li>• <b>Excipient Ingredients:</b> L-arginine, phosphate, and Tween80;</li><li>• <b>Packaging:</b> butyl rubber stopper, glass vial, 1 vial/box;</li><li>• <b>Manufacturer:</b> China Resources Angde Biotech Pharma Co., Ltd.</li><li>• <b>Supplier:</b> China Resources Angde Biotech Pharma Co., Ltd.</li></ul> <p><b>Control Drug:</b></p> <ul style="list-style-type: none"><li>• <b>Name:</b> Alteplase for Injection;</li><li>• <b>Trade Name:</b> Actilyse;</li><li>• <b>Specification:</b> 20mg/vial, 50mg/vial;</li></ul>

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	<ul style="list-style-type: none"><li>• <b>Route of Administration:</b> Intravenous injection+intravenous infusion;</li><li>• <b>Storage Conditions:</b> keep it in the original packaging, away from light, at 25°C below. Following solution preparation, it is recommended to use it immediately. The prepared solution has been proven to remain stable for 24h at 2-8° C. Do not freeze;</li><li>• <b>Expiry Date:</b> As indicated by the actual batch;</li><li>• <b>Excipient Ingredients:</b> L-arginine, phosphate, poloxamer 188, and water for injection;</li><li>• <b>Packaging:</b> Colorless glass vial, 1 vial/box (including diluent);</li><li>• <b>Manufacturer:</b> Boehringer Ingelhim Shanghai Pharmaceuticals Co., Ltd;</li><li>• <b>Supplier:</b> China Resources Angde Biotech Pharma Co., Ltd.</li></ul>
Evaluation endpoints	<p><b>Efficacy endpoints:</b></p> <ul style="list-style-type: none"><li>➤ <b>Primary efficacy endpoint:</b> The proportion of patients with mRS score of 0-1 at day 90 after treatment.</li><li>➤ <b>Secondary efficacy endpoints:</b></li><li>➤ The proportion of patients with NIHSS score ≤1 or decreasing ≥4 from baseline at 24h and day 7 after treatment;</li><li>➤ The difference in NIHSS scores from baseline at 24h and day 7 after treatment;</li><li>➤ The proportion of patients with mRS score of 0-2 at day 90 after treatment;</li><li>➤ Continuous changes in mRS scores at day 30 and 90 after treatment.</li><li>➤ The proportion of patients with Barthel Index scores ≥95 at day 90 after treatment.</li></ul> <p><b>Safety endpoints:</b></p> <ul style="list-style-type: none"><li>➤ Vital signs, physical examinations, laboratory tests, 12-lead electrocardiograms.</li><li>➤ Hemorrhage of various types (ISTH standard).</li><li>➤ All adverse events (AEs), serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs).</li></ul>

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	<p>Of particular focus are the following events:</p> <ul style="list-style-type: none"><li>➤ All-cause deaths within 7 days and 90 days after treatment;</li><li>➤ Symptomatic intracranial hemorrhage (SITS-MOST and ECASS III standards).</li><li>➤ Massive hemorrhage events after treatment (ISTH standard).</li><li>➤ Alanine transaminase (ALT) <math>\geq 3 \times \text{ULN}</math> and total bilirubin (TBIL) <math>\geq 2 \times \text{ULN}</math> in the liver function test within 7 days after treatment; creatinine (CREA) <math>\geq 3</math> times the baseline value or <math>\geq 4 \text{ mg/dL}</math> (<math>353.6 \text{ }\mu\text{mol/L}</math>) in the kidney function test within 7 days after treatment.</li></ul>
<b>Statistical Hypothesis/ Sample Size Estimation</b>	<p>The primary efficacy endpoint, the proportion of patients with mRS score of 0-1 at 90 days after treatment, will be evaluated using the non-inferiority test method. Based on historical trial data for the positive control drug alteplase<sup>[5][6]</sup>, 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. 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 (<math>\alpha</math>) of 0.025, test power (<math>1-\beta</math>) 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<sup>[7]</sup>, the estimated incidence of symptomatic intracranial hemorrhage is approximately 1%. Referring to NOR-TEST study<sup>[8]</sup>, 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.</p>
<b>Statistical Analysis</b>	<p>All data processing, summarization and analyses will be conducted using the SAS® system (SAS Institute Inc., Cary, NC) Version 9.4 or above. In general, continuous variables will be summarized by number of patients with available data (n), mean, standard deviation (SD), median, minimum, and maximum values. Categorical and</p>

	<p>ordinal variables will be summarized by the number (n) and percentage of patients in each category or grade,. Missing values will not be included in the percentage calculation unless otherwise specified.</p> <p>Unless otherwise specified, all statistical tests will use a bilateral test with <math>\alpha =0.05</math> to calculate a bilateral 95% confidence interval.</p> <p><b>Population for Statistical Analysis:</b></p> <ul style="list-style-type: none"><li>➤ <b>Intention-to-treat (ITT):</b> Including all participants who are randomized, receive study drug., meet the basic inclusion criteria.</li><li>➤ <b>Safety analysis set (SS):</b> 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)</li></ul> <p><b>Demographic and Other Baseline Characteristics:</b></p> <p>Descriptive statistics will be used to summarize the demographic and other baseline characteristics (including disease characteristics, medical history, medication history, etc.).</p> <p><b>Efficacy Analysis:</b></p> <p><b>Primary Estimand Analysis</b></p> <p>For subjects with intercurrent events, mRS scores will be collected continually at day 90 after treatment based on the treatment policy strategy. Multiple imputation method will be used for patients with 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,</p>
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	<p>then superiority is confirmed.</p> <p>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.</p> <p><b>Analysis of Other Efficacy endpoints</b></p> <p>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.</p> <p><b>Safety Analysis</b></p> <p>Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).</p> <p>Adverse events will be analyzed based on Treatment-emergent adverse events (TEAEs). All TEAEs, TEAEs related to study drug, serious adverse events (SAEs), adverse events of special interest (AESIs), etc. will be summarized.</p> <p>TEAEs will also be grouped by system organ class (SOC) and preferred term (PT) and summarized by group. The summary tables will present the number and percentage of total patients, by SOC and by PT for each group.</p>
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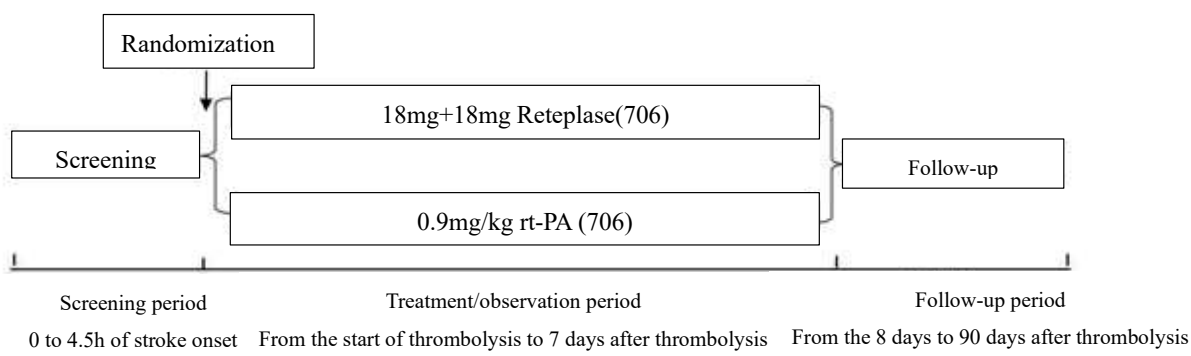
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	<p>The incidence and the differences between two groups will be performed for each adverse event.</p> <p>The Kaplan Meier method will be used to evaluate the survival situation up to day 90, and the median survival time and corresponding 95% confidence interval will be evaluated.</p> <p>Descriptive statistics will be used to summarize vital signs, physical examinations, electrocardiogram parameters, and laboratory tests, as well as their changes relative to baseline. shift tables will be used to describe the changesfrom baseline for variables judged by clinical significance.</p>
<b>Clinical Trial Progress</b>	It is expected to be carried out from October 2021 to March 2025.

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Trial Flow Chart



Trial Flow Chart

	Screening Period	Treatment/Observation Period				Follow-up Period <sup>a</sup>	
Visit	V1	V2	V3	V4	V5	V6	V7
Time Point	D1(-4.5h to 0h)	D1 (0h)	D2 (24h±2h)	D4 (72h±6h)	D8±1d	D31±3d	D91±7d
Signing Informed Consent Form <sup>a</sup>	X						
Demographic Data <sup>b</sup>	X						
Weight <sup>c</sup>	X						
Medical History, Treatment History, and Allergy History <sup>d</sup>	X						
Inclusion/Exclusion Criteria Determination	X						
Vital Signs <sup>e</sup>	X		X	X	X	X	X
Physical Examination <sup>f</sup>	X				X		
Cranial CT/MRI <sup>g</sup>	X		X				
Pregnancy Test (Women of Childbearing Age) <sup>h</sup>	X						
Blood Routine	X <sup>i</sup>		X		X		
Urine Routine <sup>j</sup>			X		X		
Stool Routine +Occult Blood <sup>k</sup>			X				
Blood Biochemistry	X <sup>l</sup>		X		X		
Cogulation Function Test	X <sup>l</sup>		X	X			
Finger Blood Glucose <sup>m</sup>	X						
12-lead ECG <sup>n</sup>	X		X		X		
NIHSS Score	X		X		X		
mRS Score	X (Pre-stroke)					X <sup>o</sup>	X <sup>o</sup>
Barthel Index Score						X <sup>o</sup>	X <sup>o</sup>
Randomization	X						
Administration <sup>p</sup>		X					



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	Screening Period	Treatment/Observation Period				Follow-up Period <sup>a</sup>	
Visit	V1	V2	V3	V4	V5	V6	V7
Time Point	D1(-4.5h to 0h)	D1 (0h)	D2 (24h±2h)	D4 (72h±6h)	D8±1d	D31±3d	D91±7d
Combined Medication	X						
Adverse Event	X						

- Note:**
- a)

There is no need for patients to repeat the examination after signing the informed consent, if the subjects have undergone laboratory examination, imaging examinationand 12-lead electrocardiogram examination (to ensure traceability) in the study center after the onset of this stroke (-4.5h~0h) and before signing the informed consent for this study. The pre-informed test data can be used as screening period data.
- b)

Demographic information includes birth date, gender, ethnicity, etc.
- c)

The weight can be weighed or reported by the patient himself/her family.
- d)

Medical history includes a history of past serious diseases and a current medical history.  
  
Current medical history includes disease information and diagnosis of this AIS, as well as present accompanying disease (or vital signs and symptoms, if diagnosis cannot be determined). For disease information and diagnosis of this AIS, the name and corresponding basis of the "diagnosis" need to be recorded, including but not limited to: the earliest occurrence of stroke symptoms, neurological impairment (NIHSS evaluation), CT/MRI examination results, non vascular diseases excluded ort not, and other information. For accompanying diseases, other diseases of the subjects except this acute ischemic stroke should be collected, e.g. hypertension, coronary heart disease, diabetes, and the current treatment of these diseases (drug/non-drug treatment) should be also collected. See section 8.3.2 of this protocol for the remaining inquiries during the screening period.
- e)

Vital signs include body temperature, heart rate, respiration, and blood pressure. Visits are conducted during the screening period, at 24h, 72h, 7 days, 30 days, and 90 days after the start of thrombolysis. Continuous monitoring shall be conducted within 24 hours after the start of thrombolysis. If clinically significant abnormalities occur, the investigators shall record and report them as AEs. If the visit at 30 or 90 days after the start of thrombolysis is conducted via a phone call or video call, then this examination is not necessary.
- f)

Physical examinations mainly include items such as skin, mucosa, lymph nodes, ear, nose, throat, head, neck, chest, abdomen, spine/limbs, nervous system, etc. Visits will be conducted during the screening period and at 7 days after the start of thrombolysis.
- g)

Cranial CT or MRI examination is conducted during the screening period to exclude hemorrhagic stroke, and CT reports of other hospitals CT reports are acceptable

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after stroke onset. CT is preferred for cranial imaging examination at 24h to 36h after the start of 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. It is also acceptable for the investigators to determine the need for direct cranial MRI based on the patient's condition.

- h) Pregnancy test is only limited to women of childbearing age, including blood or urine pregnancy tests.
- i) Blood routine: A blood routine test report from an external hospital is acceptable after the onset of this stroke. If the patient has no history of thrombocytopenia, intravenous thrombolysis can be performed before platelet count is obtained; once the blood routine test result during thrombolysis shows platelet count  $< 100 \times 10^9/L$ , intravenous thrombolysis should be discontinued.
- j) Urinary routine: Urinary routine tests are performed at  $24h \pm 12h$  and at 7 days  $\pm 1$  day after the start of thrombolysis.
- k) Stool routine + occult blood: The first collected stool samples are tested within 24h to 7 days after the start of thrombolysis. In case of clinically significant abnormalities, continuous collection will be conducted in the later stage.
- l) During the screening period, blood biochemistry and coagulation function do not require a return for the test reports after collecting samples. If the laboratory results show abnormal indicators during the thrombolysis, the subjects who the investigator believes are not eligible for thrombolysis treatment can discontinue the medication and should be closely observed for their safety.
- m) The finger blood glucose results can be used as a reference for inclusion criteria during the screening period. If it is not possible to determine whether a patient should be enrolled based on this result, the investigators will decide whether to start enrollment after blood biochemical glucose test results are issued.
- n) ECG indicators mainly include heart rate, PR interval, QRS time, QT interval and QTc. Visits will be conducted during the screening period and at 24h-36h and 7 days after the start of thrombolysis.
- o) During the follow-up period, mRS score and Barthel index score are evaluated in a blind state.
- p) Administration: It is necessary to strictly follow the time window  $\leq 4.5h$  from the onset of acute ischemic stroke symptoms to the start of the investigational drug administration. The time of symptom onset is defined as the last known time when patients were functioning normally. The beginning of administration is counted as 0h. The investigational drug reteplase<sup>®</sup> is injected intravenously twice, with the second intravenous injection performed 30 minutes  $\pm 5$  minutes after the completion of the first injection, at least 2 minutes for each injection.
- q) Follow-up visits can be conducted through phone calls or video calls.

# Protocol

## 1. Study Background

### 1.1. Introduction to Disease Background

Acute ischemic stroke (AIS) is a disorder of blood supply in the local brain tissue region caused by various reasons, which leads to cerebral ischemia, hypoxic lesion necrosis, thereby producing the corresponding clinical manifestations of nerve function loss. AIS is featured by high incidence, high disability rate, high mortality and high recurrence rate. The global disease burden data shows that the incidence of AIS was 156/100,000 and the prevalence rate was 1981/100,000 for the middle-aged in China in 2017 <sup>[9]</sup>. Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition<sup>[1]</sup>, the mortality rate within one month after the onset of AIS requiring admission is about 2.3% -3.2% and at three months is 9% -9.6%, and the mortality/disability rate is 34.5% -37.1% in China. AIS has caused serious burden to patients, their relatives and society.

Early diagnosis, early treatment, early rehabilitation and early prevention of recurrence are emphasized for the treatment of AIS. At present, the main treatments for AIS include intravenous thrombolysis, mechanical thrombectomy, etc. In recent years, interventional thrombectomy has developed rapidly, but it is only suitable for patients with large artery occlusion. Due to the difficulties in surgery, it is hard to make it popularize. Intravenous thrombolysis is currently regarded as the main treatment for super early ischemic stroke in China for easy operation and better popularization.

### 1.2. Research and Development Progress of Related Drugs

Due to limited types of thrombolytic drugs for AIS that have been listed and used in China, urokinase and alteplase are the main thrombolytic drugs currently used in China.

Streptokinase (SK) and urokinase (UK), early thrombolytic drugs, are first-generation thrombolytic drugs with non-specific fibrinolytic effect which often cause systemic hemorrhage (including some important organs). Recombinant human tissue plasminogen activator (rt-PA), as a second-generation thrombolytic drug, is considered as the first choice for intravenous thrombolysis for its certain thrombolytic specificity according to the Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition <sup>[1]</sup>.

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There is still a great demand for new thrombolytic drugs with better fibrin specificity, higher recanalization rate, lower hemorrhage rate, lower recurrence rate, convenient use, no antigenicity and higher cost performance.

### 1.3.Introduction to the Investigational Drug

Recombinant human tissue-type plasminogen activator derivative for injection with its trade name Reteplase® is a third-generation thrombolytic drug, which is derived from the first- and second- generation thrombolytic drugs modified structurally by using genetic engineering technology and protein technology. It is featured by the advantages including better fibrin specificity, lower hemorrhage rate, relatively loose combination with thrombus, faster thrombolysis, significantly prolonged plasma half-life (about 11-16min), direct administration by intravenous injection instead of intravenous infusion, more convenience for clinical use, etc.

Reteplase®, successfully listed in 2007 with the approval number of Guo Yao Zhun Zi S20070023, is used for thrombolytic therapy of acute myocardial infarction caused by coronary artery infarction in adults. The post-marketing data shows that the drug has good safety and efficacy in the treatment of acute myocardial infarction. According to the Measures for the Administration of Drug Registration, the sponsor has applied for the new indication of AIS for thrombolysis provided by the drug. In 2017, CFDA approved the clinical study of reteplase for thrombolysis of AIS, with clinical approval number 2017L00263.

A phase II clinical study on intravenous thrombolysis for the treatment of ischemic stroke has been completed for the product, which adopted a multicenter, randomized, open-label, parallel controlled, and blinded evaluation design. In the study, a total of 180 patients with AIS within 4.5h of onset were enrolled in the study group, 67:61:52 cases for the high-dose reteplase group (18mg+18mg), low-dose reteplase group (12mg+12mg), and alteplase control group (0.9mg/kg), respectively, who were observed for the improvement of NIHSS score at 72h and 14 days after thrombolysis, of mRS score and Barthel index score at 30 and 90 days after the start of thrombolysis. During the course of the trial, all adverse events patients experienced, especially symptomatic intracranial hemorrhage, adverse events leading to death and other serious adverse events, were observed and treated.

The efficacy results of the phase II clinical study demonstrated that based on the full

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analysis set (FAS), the proportion of subjects with mRS score of 0-1 at 90 days after treatment was 73.4%, 66.7%, and 66.0% for the high-dose reteplase<sup>®</sup> group, low-dose reteplase<sup>®</sup> group, and alteplase group, respectively; the proportion of subjects with NIHSS score of  $\leq 1$  point or decreasing  $\geq 4$  points from baseline at 72h after treatment was 62.9%, 64.8%, and 62.0%, respectively; the proportion of subjects with Barthel index score  $\geq 95$  points at 90 days after treatment was 83.6%, 74.5%, and 77.1%, respectively.

The safety results of the phase II clinical study showed that during the trial, the incidence of adverse events related to the investigational drug was 77.3%, 55.0%, and 38.0% for the high-dose reteplase<sup>®</sup> group, low-dose reteplase<sup>®</sup> group, and alteplase group respectively; the incidence of serious adverse event related to the investigational drug was 4.5%, 6.7% and 4.0%, respectively; the incidence of symptomatic intracranial hemorrhage (NINDS standard) was 4.5%, 6.7%, and 2.0%, respectively, and the all-cause mortality rate within 90 days was 4.5%, 5.0%, and 4.0%, respectively.

The results of the phase II clinical study indicated that both high-dose and low-dose reteplase<sup>®</sup> could promote functional recovery, alleviate symptoms of neurological deficits, and improve quality of life of patients. Compared with the alteplase control group, there was no significant difference in various efficacy indicators; the proportion of subjects with 90 day mRS score of 0-1 at 90 days in the high-dose reteplase<sup>®</sup> group was higher than that in the low-dose group and control group. The safety results showed that there was no significant difference in important safety indicators between the high-dose and low-dose reteplase<sup>®</sup> groups and the alteplase control group. The high-dose reteplase<sup>®</sup> group did not show higher risks in all-cause mortality, the incidence of serious adverse events (SAE) related to the investigational drug, symptomatic intracranial hemorrhage and other important safety indicators after treatment. Considering the efficacy and safety results, the high-dose reteplase<sup>®</sup> group (18mg+18mg) was selected for the phase III confirmatory study.

## 1.4. Risk and Benefit Assessment

### 1.4.1. Risk Assessment

The most serious adverse reaction of thrombolysis for AIS is intracranial hemorrhage with an incidence of about 10% to 48%, higher than that of spontaneous hemorrhage transformation

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(7% to 29%), of which the incidence of symptomatic intracranial hemorrhage is about 2% to 7% [10]. In the phase II clinical study completed for the investigational drug, the incidence of intracranial hemorrhage after treatment was 6.7% to 10.6%, and of symptomatic intracranial hemorrhage (NINDS standard) was 4.5% to 6.7%.

In the phase II clinical study, the incidence of hemorrhage events related to the investigational drug in other site was 23.3% to 37.9%, mainly manifested as gingival bleeding.

In clinical trials of similar products, allergic reactions were reported in patients treated with reteplase, with an incidence rate of approximately 0.03% [11].

#### 1.4.2. Benefit Assessment

AIS, featured by high incidence, high disability rate, high mortality and high recurrence rate, has caused increasing disease burden. Due to limited types of thrombolytic drugs for AIS that have been listed and used in China, alteplase, as a second-generation thrombolytic drug, is considered as the first choice for intravenous thrombolysis. There is still a great demand for new thrombolytic drugs with better fibrin specificity, higher recanalization rate, lower bleeding rate, lower recurrence rate, convenient use, no antigenicity and higher cost performance.

Reteplase®, a third-generation thrombolytic drug, is featured by the advantages including better fibrin specificity, lower hemorrhage rate, relatively loose combination with thrombus, faster thrombolysis, significantly prolonged plasma half-life (about 11-16min), direct administration by intravenous injection instead of intravenous infusion, more convenience for clinical use, saving thrombolysis time and striving for more opportunities for patients' subsequent treatment. It has been indicated for acute myocardial infarction and is well used in the market. It is expected to provide definite clinical benefits for patients with AIS.

#### 1.4.3. Potential Risk and Benefit Assessment

Due to acute and severe attack of AIS, the study doctors should fully weigh the benefits and risks of patients and strictly screen patients according to the provisions of the protocol. This study adopts the “head to head” design with alteplase in which it is assumed that the reteplase has non-inferior efficacy to alteplase, better safety and is easier to use. If the results of this phase III clinical trial prove the hypothesis to be valid, more thrombolytic drug choices can be provided for AIS patients and clinical doctors.

2. Objectives

2.1.Primary Objective

To evaluate the effectiveness of recombinant human tissue-type plasminogen activator derivative for injection versus alteplase in the treatment of patients with acute ischemic stroke within 4.5h of onset.

2.2.Secondary Objective

To evaluate the safety of recombinant human tissue-type plasminogen activator derivative for injection versus alteplase in the treatment of patients with acute ischemic stroke within 4.5h of onset.

3. Estimand

3.1.Primary Estimand

**The primary clinical question:** whether the clinical thrombolytic effect of recombinant human tissue-type plasminogen activator derivative for injection is non-inferior to alteplase in the treatment of patients with acute ischemic stroke.

3.1.1. Definition of Primary Estimand

**Target population:** All randomized patients with AIS who have received at least one dose of the test drugs and meet the basic inclusion criteria.

**Target variable:** The proportion of patients 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 event and corresponding treatment strategy:

Intercurrent Event	Treatment Strategy	Note
Use of other thrombolytic and defibrase drugs	Composite strategy	Treated as no response

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Use of antiplatelet and anticoagulant drugs (within 24 hours of thrombolysis):	Treatment policy strategy	Clinical practice reflecting reality. The mRS score will continue to be collected after the occurrence of the intercurrent events. Regardless of whether or not such events occur, the actual observed values of mRS scores will be used for analysis.
Intracranial endovascular treatment performed during the trial for treating AIS*	Composite strategy	Treated as no response
Failure to complete treatment per protocol requirements (including uncompleted two injections of recombinant human tissue-type plasminogen activator derivative or uncompleted infusion of planned dosage of alteplase, treatment beyond the specified window, inconsistency between actual treatment drug and planned treatment drug, non-compliance of treatment dosage, etc.)	Treatment policy strategy	Clinical practice reflecting reality. The mRS score will continue to be collected after the occurrence of the intercurrent events. Regardless of whether or not such events occur, the actual observed values of mRS scores will be used for analysis.

**Note:** \*Intracranial endovascular treatment for this acute ischemic stroke is performed during the trial, including the routine use of antiplatelet and anticoagulant drugs within 24 hours after thrombolysis for the treatment of this acute ischemic stroke.

**Population-level summary:** relative ratio (RR) of efficacy rate and its bilateral 95% confidence interval.



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**3.1.2. Selection Basis for Intercurrent Events and Corresponding Treatment Strategy:**

## 1) Use of other thrombolytic and defibrase drugs: composite strategy

Basis: The use of other thrombolytic and defibrase drugs is considered as having poor thrombolytic efficacy or even a failure of thrombolysis for the test drugs previously used, so the complex strategy is used in which it is treated as no response.

## 2) Use of antiplatelet and anticoagulant drugs (within 24h of thrombolysis): treatment policy strategy

Basis: This intercurrent event is comply with clinical practice and is also related to the treatment, so as a part of the treatment, it conforms to the ITT principle in ICH E9. Therefore, the intercurrent event is treated using the treatment policy strategy.

## 3) Intracranial endovascular treatment performed during the trial for treating AIS: composite strategy

Basis: Intracranial endovascular treatment performed during the trial for treating AIS is considered as having poor thrombolytic efficacy or even a failure of thrombolysis for test drugs previously used, so the composite strategy is used in which it is treated as no response.

## 4) Failure to complete treatment per protocol requirements (including uncompleted two injections of recombinant human tissue-type plasminogen activator derivative or uncompleted infusion of planned dosage of alteplase, treatment beyond the specified window, inconsistency between actual treatment drug and planned treatment drug, non-compliance of treatment dosage, etc.)

Basis: Failure to complete treatment per protocol requirements that may occur in both the investigational drug group and the control drug group conforms to clinical practices. After such event occurs, the subjects will be followed up, from whom the collected data can still reflect the efficacy of the test drugs in the corresponding group and comply with the ITT principle in ICH E9.

Note: Considering that this study uses the block randomization, no inter-group bias can be found in the incidence of the aforementioned intercurrent events, nor can any inter-group differences between efficacy evaluation and actual situation caused by strategy selection be found.

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### 3.2. Secondary Estimand

See Statistical Analysis Plan for details.

## 4. Study Design

### 4.1. Overall Design

This is a multicenter, randomized, blind endpoint and positive drug parallel controlled phase III study of recombinant human tissue-type plasminogen activator derivative for injection compared with alteplase in the treatment of acute ischemic stroke (AIS) within 4.5h of onset. Non-inferiority hypothesis is adopted to compare the difference in the primary efficacy indicator, the proportion of subjects with a mRS score of 0-1 at 90 days after thrombolysis in the investigational drug group and the positive drug alteplase group.

In this study conducted only in Chinese population with multicenter's participation, 1412 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. After receiving thrombolysis, the subjects need to undergo a series of safety and efficacy tests and make mRS score and Barthel index score visits at 90 days ( $\pm 7$  days) after the start of thrombolysis. Following the visits, the subjects complete the study.

In this study, an independent blind endpoint evaluator is set up to make blinded assessment on the mRS score at 30 and 90 days after the start of thrombolysis.

### 4.2. Randomization

A random number will be assigned, and patients will be allocated to treatment using the randomization and trial Drug management system IWRS. The random number will be generated by an independent statistician independent of this study using SAS 9.4 or higher version software, changeable block randomization will be performed by 1:1 ratio for two groups. The investigator will log in the IWRS and assign a random number for a patient after screened successfully.

Patients who are randomized but withdraw from the study for any reason, their random number will be retained and cannot be replaced whether or not the study drug is used, and patients withdraw from study will not be able to re-participate in the trial.

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### 4.3. Population Selection and Basis

In this study, patients with AIS within 4.5hs of stroke onset are selected as the study population.

According to the Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition<sup>[1]</sup>, patients with ischemic stroke within 3h (Grade I recommendation, Grade A evidence) and 3-4. 5h (Grade I recommendation, Grade B evidence) of onset should be strictly screened for indications, contraindications, and relative contraindications, and given intravenous thrombolysis with alteplase as soon as possible. Based on Guidelines for Clinical Trials of Drugs for the Treatment of Acute Ischemic Stroke released by CDE in 2018<sup>[2]</sup>, it is recommended to select subjects with an onset of less than 4.5h for intravenous thrombolysis drugs. Therefore, this study enrolls patients with AIS within 4.5h of stroke onset.

Based on the recommendations in the Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition<sup>[1]</sup> on relative contraindications of intravenous thrombolysis with rt-PA within 3h to 4.5h (severe stroke, i.e. NIHSS score>25 points), and in Technical Guidelines for Clinical Trials of Drugs for Acute Ischemic Stroke Treatment<sup>[2]</sup> on the severity of cerebral stroke in the trial (the inclusion criteria can be limited to patients with moderate impairment at baseline level), the enrolled patients in this study are required to have  $4 \leq \text{NIHSS score} \leq 25$  prior to thrombolysis treatment.

### 4.4. Dose Selection and Basis of the Investigational Drug

In this study, the dosage of the investigational drug is selected mainly based on the results of phase II clinical trial, as detailed in section 1.3.

Meanwhile, in the clinical trial of alteplase treatment of AIS within 4.5h of onset, the significant safety data shows that the all-cause mortality rate at 90 days is 5% -17%, and the incidence rate of symptomatic intracranial hemorrhage is about 7% according to the most stringent NINDS standard in the alteplase treatment group. Due to the large span of time for clinical trials conducted, the continuous development of basic medical level, and slightly different NIHSS range of the population baseline, the following safety indicators for alteplase are only for reference under different trial systems. In the phase II trial of the investigational drug reteplase, the all-cause mortality rate at 90 days and symptomatic intracranial hemorrhage

rate (NINDS, ECASS II, SITS – MOST) in the high-dose group were 4.5%, 4.5%, 1.5% and 1.5% respectively, comparable to that of the positive control group alteplase and not higher than the historical similar data of alteplase.

Therefore, based on the efficacy and safety results, the high-dose reteplase group (18mg+18mg) in the phase II study of reteplase is selected for the Phase III confirmatory study.

Table 1 Significant Safety Data of the Clinical Trial of Alteplase within 4.5h of Onset							
Test	Onset Time	Intracranial Hemorrhage Rate	Symptomatic Intracranial Hemorrhage Rate				All-cause Mortality Rate at 90 Days
			NINDS	ECASS II	ECASS III	SITS-MOST	
NINDS	<3h	10.9%	6.4%	-	-	-	17%
SITS-MOST	<3h	-	7.3%	4.6%	-	1.7%	11.3%
ECASS III	3-4.5h	27%	7.9%	5.3%	2.4%	1.9%	7.7%
NOR-TEST	<4.5h	9%	-	-	2.4%	-	5%
Alteplase Group in Phase II Reteplase®	<4.5h	10%	2%	2%	-	2%	4%

4.5. Selection of Control Drug

Alteplase is selected as a positive control drug. According to the the recommendations in Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 Edition<sup>[1]</sup>, patients with ischemic stroke within 3h (Level I recommendation, Level A evidence) and 3-4.5h (Level I recommendation, Level B evidence) of of onset should be strictly screened for indications, contraindications, and relative contraindications, and receive intravenous thrombolysis with alteplase as soon as possible.

4.6. Selection of Efficacy Endpoint Indicators

With reference to the recommendations in Technical Guidelines for Clinical Trials of Drugs for Acute Ischemic Stroke Treatment<sup>[2]</sup>, the primary efficacy endpoint of this study is mRS score at 90 days, with mRS score at 30 days after the start of thrombolysis, NIHSS score at 24h and 7 days, and Barthel index at 90 days as the secondary efficacy indicators.

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#### **4.7. Blind Endpoint**

Due to the different routes of administration for the investigational drug and control drug, and the limited treatment time window for emergency patients, blind design cannot be carried out at the drug and clinical treatment levels. However, in order to make the evaluation of the primary endpoint indicator more objective and minimize human bias, independent blind endpoint evaluators are set up in each study site to evaluate the mRS score and Barthel index score at 30 and 90 days after the start of thrombolysis in a blind manner.

#### **4.8. Independent Data Monitoring Committee**

In this study, an IDMC will be established, whose responsibilities include conducting safety assessments of cumulative data from the ongoing clinical trial to ensure the safety of subjects.

The IDMC is composed of clinical experts and statistical experts in this field. The composition, operating procedures, and operating frequency of the IDMC will be specifically described in the relevant charter.

#### **4.9. Independent Clinical Event Committee**

A CEC, established in this study, is composed of clinical experts in the field independent of the project, who will rule on important clinical events case by case in a blind manner to ensure the scientific and reasonable judgment of events. The composition, responsibilities, operating procedures, and operating cycle of the CEC will be specifically described in the relevant charter.

#### **4.10. Trial Completion and Early Termination**

##### **4.10.1. Trial Completion**

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 end of the last visit of the last subject is considered as the completion of the clinical trial. The last visit includes additional unplanned visit due to adverse events.

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#### 4.10.2. Early Termination

Early termination of a trial is defined as the cessation of the entire trial or a portion of the trial (such as a site) in the course of a clinical trial in which studies on all subjects has not yet been completed as per the protocol. Early termination aims to protect the rights and interests of the subjects, ensure the quality of the trial, and avoid unnecessary economic losses.

Generally, the trial will not be terminated prematurely. However, if any of the following cases occur, the entire trial (or a certain site) can be terminated in advance:

- 1) The total sample size for competitive enrollment has met the trial requirements, but the site has not completed the planned enrollment under the contract and/or all subjects in the site have completed the study;
- 2) The investigators at the center cannot follow the protocol, GCP, etc;
- 3) New information obtained leads to unfavorable risk benefit evaluations of the investigational drug, including sufficient evidence indicating lack of efficacy or unacceptable safety;
- 4) During the trial, significant errors found in the design of the clinical trial protocol make it difficult to evaluate the drug, or significant deviations occurring during the implementation of the protocol affect the final evaluation of the drug;
- 5) For medical, ethical or commercial reasons, the sponsor believes that it is inappropriate to continue the clinical trial;
- 6) Relatively slow enrollment of the subjects makes it impossible to complete the study within an acceptable time frame;
- 7) The National Medical Products Administration or an ethics committee orders to terminate the trial for some reason.

All parties involved in the study (including the sponsor, investigators, ethics committees, clinical trial institutions, and administrative departmentd) should be notified of early termination of the clinical trial in writing in a timely manner.

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## 5. Population Selection

### 5.1. Inclusion Criteria

**Patients who meet all of the following criteria may be considered for enrollment:**

- 1) Aged  $\geq 18$  and  $\leq 80$  at the time of signing the informed consent form, either males or females;
- 2) Within 4.5 hours after the onset of symptoms of neurological impairment due to acute ischemic stroke according to the diagnosis criteria for stroke issued by the World Health Organization (WHO)<sup>[3]</sup>, Onset time refers to the time the patient was last known to be well.
- 3)  $4 \leq \text{NIHSS score} \leq 25$  before thrombolysis.
- 4) Fertile men and women of childbearing age who have no childbearing plan from the date of enrollment to 3 months after thrombolysis administration and are willing to take effective contraceptive measures.
- 5) Understand and follow the procedures of clinical trial, participate voluntarily, and sign the informed consent (which can be signed voluntarily by the person or guardian).

### 5.2. Exclusion Criteria

**Patients who meet any of the following criteria may not be enrolled:**

- 1) Patients are known to be allergic to investigational drugs (recombinant human tissue-type plasminogen activator derivative for injection, alteplase) or similar components, or materials used for imaging examinations.
- 2) Body weight  $> 120\text{kg}$  or  $< 45\text{kg}$ ;
- 3) The onset of stroke symptoms cannot be ascertained.;
- 4) mRS score  $\geq 2$  before the onset of the current stroke;
- 5) 1a (level of consciousness) of NIHSS score  $\geq 2$  at screening;
- 6) Intracranial hemorrhage history (including parenchymal / intraventricular / subarachnoid hemorrhage, subdural / external hematoma, etc.);
- 7) CT/MRI imaging shows signs of intracranial hemorrhage or subarachnoid hemorrhage is suspected despite normal CT/MRI;
- 8) Severe head trauma, clinically symptomatic stroke history, or other severe trauma in

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the last 3 months.

- 9) Patients with intracranial tumor, arteriovenous malformation and aneurysm found before enrollment;
- 10) Intracranial surgery, intraspinal surgery or other major surgeries within 3 months before enrollment(based on the assessment of the investigators);
- 11) Gastrointestinal or urinary system hemorrhage within the past 3 weeks;
- 12) Patients with active visceral hemorrhage;
- 13) Aortic arch dissection confirmed by pre-study examination or medical history;
- 14) Arterial puncture at the site that is not easily compressed to stop bleeding within the last week;
- 15) Acute hemorrhage tendency, including but not limited to the following: 1) Platelet count less than  $100 \times 10^9/L$ ; 2) patients received low molecular heparin within 24h before onset; 3) use of thrombin inhibitors or factor Xa inhibitor within 48 hours before onset; 4) taking oral anticoagulant drugs with an INR > 1.7 or PT>15s;
- 16) Actively treated but uncontrolled hypertension, defined as systolic blood pressure >185 mmHg and/or diastolic blood pressure >110 mmHg;
- 17) Blood glucose <50 mg/dl (equivalent to 2.78mmol/L) or >400 mg/dl (equivalent to 22.2mmol/L) during screening;
- 18) Large cerebral infarction on CT or MRI;
- 19) Severe liver impairment, including liver failure, cirrhosis, portal hypertension (esophageal varices), and active hepatitis;
- 20) Patients with bacterial endocarditis, pericarditis or acute pancreatitis at enrollment;
- 21) History of gastrointestinal ulcers, esophageal varices, aneurysms, or arterial / venous malformations within 3 months before enrollment;
- 22) Unable or unwilling to cooperate due to epileptic seizures during stroke episodes, or other mental illnesses;
- 23) Planned or received endovascular treatment after the onset of the current stroke;
- 24) Patients have to take or desire to continue to take the restrictive drugs specified in the protocol or any drug that may interfere with the test results;
- 25) With an expected survival time less than 1 year due to other diseases;



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- 26) Have participated in other clinical trials within 30 days prior to randomization or are participating in other clinical trials;
- 27) Females are in pregnancy or lactation, or have a positive pregnancy test result;
- 28) Considered by the investigator to have other conditions that might affect compliance or preclude participation in this study.

### **5.3. Subjects' Withdrawal from the Study**

#### **5.3.1. Voluntary Withdrawal**

- 1) Subjects withdraw their consent;
- 2) Subjects are lost to follow-up and cannot be contacted by at least three attempts.

#### **5.3.2. Withdrawal Determined by the Investigators**

- 1) Subjects become pregnant or are suspected to be pregnant;
- 2) Subjects are found not to be eligible as patients with AIS after randomization;
- 3) 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.

If a patient experiences AEs that may discontinue the trial and the investigators determine that he/she needs to withdraw from the trial, AEs must be followed up as per the protocol until recovery, improvement, stable condition (continuous, without signs of deterioration), or loss of follow-up (including the patient or his/her guardian explicitly stating any follow-up will no longer be received), in order to determine the patient's withdrawal. The follow-up process should be recorded and entered in eCRF.

Following the withdrawal of the subjects, the investigators must fill in the reason for withdrawal in the medical record, complete the evaluation items as much as possible, and fill in the last visit record in the medical record. The data of the withdrawing subjects should be entered into eCRF. Th withdrawing subjects who undergo screening without obtaining random numbers will not be considered as withdrawal cases and will not be replaced by other patients.

### **5.4. Provisions for Screening Failure**

Screening failure is defined as failure to participate in a study for subjects agreeing to

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participate in the clinical trial. 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 adverse events, and be entered into eCRF.

### 5.5. Subject Allocation and Numbering

After signing the informed consent form and before undergoing the relevant study examinations, the subject will be assigned a unique screening number composed of capital letter "S"+5 Arabic numerals: the first two digits are "center number", and the last three digits are "screening serial number". For example, the screening number of the second subject screened in 01 center is "S01002".

In the trial, the random number of each subject is generated by SAS9.4 or higher version software used by an independent statistician and can be assigned to the investigational drug group or control drug group in a 1:1 ratio by variable block randomization. After each subject passes the screening, the investigators log into the randomization and investigational drug management system IWRS and obtains a random number.

Since the randomization process is reproducible, the set seed parameters of the initial value of the random number need to be saved.

If a subject withdraws from this study, his/her screening number/random number cannot be reused, and he/she cannot participate in this study again.

## 6. Test Drugs

### 6.1. Basic Information

#### Investigational Drug<sup>[9]</sup>:

- **Name:** Recombinant Human Tissue-type Plasminogen Activator Derivative for Injection
- **Trade Name:** Reteplase;
- **Specification:** 18mg/10ml/vial;
- **Character:** White or almost white freeze-dried powder injection;
- **Route of Administration:** It is injected intravenously twice, with the first dose of 18mg (mix into 10mL and take 10mL) and the second dose of 18mg 30 minutes later

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(mix into 10mL and take 10mL), for at least 2 minutes each time;

- **Storage Condition:** Keep it sealed and away from light at 2-8 °C for storage and transportation. Do not freeze;
- **Expiry Date:** As indicated by the actual batch;
- **Excipient Ingredients:** L-arginine, phosphate, and Tween 80;
- **Packaging:** butyl rubber stopper, glass vial, 1 vial/box;
- **Manufacturer:** China Resources Angde Biotech Pharma Co., Ltd;
- **Supplier:** China Resources Angde Biotech Pharma Co., Ltd.

#### Control Drug<sup>[12]</sup>:

- **Name:** Alteplase for Injection;
- **Trade Name:** Actilyse;
- **Specification:** 20mg/vial, 50mg/vial;
- **Route of Administration:** 0.9mg/kg (the maximum dose of 90mg); 10% of the total dose is administered intravenously within the first 1 minute and the remaining dose is continuously administered intravenously for 60 minutes;
- **Storage conditions:** keep it in the original packaging, away from light, at 25°C below. Following solution preparation, it is recommended to use it immediately. The prepared solution has been proven to remain stable for 24h at 2-8°C. Do not freeze;
- **Expiry Date:** As indicated by the actual batch;
- **Excipient Ingredients:** L-arginine, phosphate, poloxamer 188, and water for injection;
- **Packaging:** Colorless glass vial, 1 vial/box (including diluent);
- **Manufacturer:** Boehringer Ingelheim Shanghai Pharmaceuticals Co., Ltd.
- **Supplier:** China Resources Angde Biotech Pharma Co., Ltd.

## 6.2. Packaging and Labeling

According to the requirements of GCP and national regulations, China Resources Angde Biotech Pharma Co., Ltd. is responsible for labeling on the packaging boxes of the test drugs. All subjects' investigational drug is packaged uniformly.

The label of the investigational drug indicates the name of the sponsor, package specification, batch number, dosage form, route of administration, quantity, drug number, trial

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code, subject identification code, usage and dosage, drug storage conditions, validity period, etc. The specific packaging shall be based on the actual product.

### **6.3. Management of the Test Drugs**

The sponsor is responsible for providing test drugs to the investigators and clinical trial institutions.

The sponsor is not allowed to provide test drugs to investigators and clinical trial institutions before obtaining the approval of the ethics committees and the approval or filing of the drug regulatory authorities for clinical trials.

The sponsor shall provide a written explanation of the test drugs to the investigators and clinical trial institutions, indicating the use, storage, and relevant records of the test drugs. The sponsor shall establish regulations for the supply and management of the test drugs, including the receipt, storage, distribution, use, and recovery of the test drugs. The recovered test drugs from the subjects and those not used by the investigators should be returned to the sponsor, or destroyed by clinical trial institutions with the sponsor's authorization.

The sponsor shall ensure the timely delivery of the test drugs to the investigators and clinical trial institutions for subjects to use them timely; keep records of the transportation, receipt, distribution, recovery, and destruction of the test drugs; establish a management system for the recovery of the test drugs to ensure the recall of defective products, post-trial recovery, recovery after expiration; establish a destruction system for unused test drugs. The management process of all test drugs should be recorded in writing, with accurate count.

The sponsor shall take measures to ensure the stability of the test drugs during the trial. The retained samples of the test drugs shall be stored until the end of clinical trial data analysis or the time limit required by relevant regulations within the storage period of the test drugs. For inconsistency between two time limits, the longer time limit shall prevail.

### **6.4. Medication Compliance**

The investigators authentically records the number, date, actual dosage, starting and ending time of administration of drugs taken by subjects, and determine medication compliance based on the records.

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## 6.5. Combined Medication and Treatment

Except for using the investigational drug specified in the protocol for thrombolysis, patients receiving thrombolysis for AIS in this trial are not allowed to use other thrombolytic and defibrase drugs, including urokinase, defibrase, batroxobin, anklokinase lumbrokinase, and agkistrodon acutus enzyme.

The use of antiplatelet and anticoagulant drugs is prohibited within 24h after the start of thrombolysis and is allowed after 24h at the investigators' discretion based on the condition of the subjects.

Starting from the screening of subjects, the use of other drugs and treatments other than the investigational drug for any reason should be recorded in detail on the concomitant/non-drug treatment page of eCRF, indicating the reason, method, dosage, frequency, starting and ending time of medication.

The investigators should promptly contact with CRA for any issues with the combination therapy.

## 7. Trial Procedures

### 7.1. Screening Period (-4.5h to 0h before Thrombolysis on D1)

- Explain the disease condition, diagnosis, and treatment suggestions to the patient and his/her family members, and the patient or his/her guardian agrees and signs the informed consent form;
- Collect demographic information;
- Collect medical history, treatment history, allergy history, etc.;
- Measure weight (or reported by the patient/ his/her family members);
- Vital signs;
- Physical examinations;
- Inquire and evaluate the pre-stroke mRS score and NIHSS score;
- Cranial CT or MRI examinations;
- Laboratory tests: finger blood glucose, blood routine test, blood biochemistry, coagulation function, blood/urine pregnancy test for women of childbearing age;
- 12-lead electrocardiograms;

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- Check inclusion and exclusion criteria;
- Randomization;
- Record combined treatments and adverse events.

Note:

- 1) If the subject has undergone laboratory tests, imaging examinations (such as emergency examinations), and 12-lead electrocardiograms (to ensure traceability) related to this study at the study site after the onset of this stroke (-4.5h to 0h) and before signing the informed consent form, there is no need to repeat the examinations after signing the informed consent form. The examination data prior to the informed consent can be used as the data during the screening period.
- 2) The finger blood glucose results can be used as a reference for inclusion criteria during the screening period. If patients' enrollment failed to be determined/enrolled based on this result, the investigators will decide whether to complete the enrollment after the blood glucose test results are issued.
- 3) During the screening period, the test reports of blood biochemistry and coagulation function are not required after collecting samples. In case of abnormal indicators for laboratory results during the thrombolysis process, based on which the investigators determine that the subject is no longer eligible for thrombolysis, the drug can be discontinued and the safety is closely observed.
- 4) CT result and blood routine test result performed in other hospitals after the onset of this stroke are acceptable. For patients who have no history of thrombocytopenia, intravenous thrombolysis can be initiated before platelet count is obtained; once the blood routine test result shows platelet count  $<100 \times 10^9/L$  during thrombolysis, intravenous thrombolysis should be discontinued.
- 5) Pregnancy test: either blood pregnancy test or urine pregnancy test.

## 7.2. Treatment Period (D1-D8)

### 7.2.1. D1 (Thrombolysis, 0h)

- Thrombolysis:

**Trial group (reteplase):** It is injected intravenously twice, with the first dose of 18mg

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(mix into 10mL and take 10mL) and the second dose of 18mg 30 minutes later (mix into 10mL and take 10mL), for at least 2 minutes each time;

**Control group (alteplase):** alteplase is dissolved at a concentration of 1mg/ml in water for injection packaged and administered at the total dose of 0.9mg/kg (the maximum dose of 90mg); 10% of the total dose is administered intravenously within the first 1 minute, and the remaining dose is continuously administered intravenously for 60 minutes.

- It is necessary to strictly follow the time window of  $\leq 4.5$ h from the onset of AIS symptoms to the administration of the investigational drug. The time of symptom onset is defined as the time of known last normal function. The beginning of administration is counted as 0h. The investigational drug reteplase is injected intravenously twice, with the second intravenous injection performed 30 minutes  $\pm$  5 minutes after the completion of the first injection, at least 2 minutes for each injection.
- Within 24h after the start of thrombolysis, electrocardiogram, blood pressure, respiration, blood oxygen, body temperature, etc. are monitored according to the requirements of each study hospital; If clinically significant abnormalities occur, the investigators shall record and report them as AEs.
- During and after thrombolysis, cranial hemorrhage and skin, conjunctiva, respiratory, digestive, and urinary system hemorrhage should be closely observed.
- In the process of thrombolysis, when patients suffer from severe headache, hypertension, nausea or vomiting, or worsened neurological symptoms and signs, which the investigators believe are clinically significant so that thrombolysis cannot continue, the thrombolysis treatment should be discontinued immediately, and the cranial CT examination or other necessary examinations should be performed.
- If the above symptoms and signs appear after thrombolysis, the investigators can add CT examination or other necessary examinations at any time.
- Under no special circumstances, cranial CT is re-performed 24h to 36h after the start of thrombolysis.
- Record combined treatments and adverse events.

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**7.2.2. D2 (24h  $\pm$  2h after the start of Thrombolysis)**

- Cranial CT examination;
- NIHSS score;
- Vital signs;
- Laboratory tests: blood routine, urine routine (24h and 12h after the start of thrombolysis), stool routine+occult blood (collect the first stool sample within 24h and 7 days after the start of thrombolysis, and continue to collect the sample if clinically significant abnormalities occur), blood biochemistry, and coagulation function;
- 12-lead electrocardiogram (24h to 36h after thrombolysis);
- Record combined treatments and adverse events.

Note: CT is preferred for cranial imaging examination 24h to 36h after the start of thrombolysis; If the investigators believe that further examinations are necessary after CT examination (in case of hemorrhage or other conditions), an cranial MRI examination can be performed. It is also acceptable for the investigators to determine to perform cranial MRI directly based on the patient's condition.

**7.2.3. D4 (72h  $\pm$  6h after the Start of Thrombolysis)**

- Vital signs;
- Coagulation function;
- Record combined treatments and adverse events.

**7.2.4. D8 (7 Days  $\pm$  1 Day after the Start of Thrombolysis)**

- Vital signs;
- Physical examination;
- NIHSS score;
- Laboratory tests: blood routine, urine routine, stool routine+occult blood (collect the first stool sample within 24h to 7 days after administration, and continue to collect the sample if clinically significant abnormalities occur), and blood biochemistry;
- 12-lead electrocardiogram;
- Record combined treatments and adverse events.



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### 7.3. Follow-up Period (D9-D91)

#### 7.3.1. D31 (30 Days $\pm$ 3 Days after the Start of Thrombolysis)

- Vital signs;
- mRS score;
- Barthel Index score;
- Record combined treatments and adverse events.

Note: If a visit is made through a phone call or video call, there is no need for vital signs examination.

#### 7.3.2. D91 (90 Days $\pm$ 7 Days after the Start of Thrombolysis)

- Vital signs;
- mRS score;
- Barthel index score;
- Record combined treatments and adverse events.

Note: If a visit is made through a phone call or video call, there is no need for vital signs examination.

### 7.4. Unscheduled visits

Considering the safety of the subjects, the investigators may request the subjects to undergo additional visits or examinations. The results of unscheduled visits or examinations must be recorded in the electronic case report form (eCRF).

## 8. Trial Evaluation

### 8.1. Efficacy Evaluation Indicators

- **Primary efficacy evaluation indicator:** the proportion of subjects with mRS scores of 0 to 1 point at 90 days after treatment;
- **Secondary efficacy evaluation indicators:**
  - The proportion of subjects with NIHSS scores  $\leq 1$  or decreasing  $\geq 4$  points from baseline at 24h and 7 days after treatment;
  - The difference in NIHSS scores from baseline at 24h and 7 days after treatment;

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- The proportion of subjects with mRS scores of 0 to 2 points at 90 days after treatment;
- Continuous changes in mRS scores at 30 and 90 days after treatment;
- The proportion of subjects with Barthel index scores  $\geq 95$  points at 90 days after treatment.

## 8.2. Safety Evaluation Indicators

- Vital signs, physical examinations, laboratory tests, 12-lead electrocardiograms;
  - Hemorrhage events of various types (ISTH standard);
  - All AEs, SAEs, and SUSARs;
- Of particular concern are the following events:
- All-cause deaths within 7 days and 90 days after treatment;
  - Symptomatic intracranial hemorrhage (SITS-MOST and ECASS III standards);
  - Massive hemorrhage events after treatment (ISTH standard);
  - Alanine transaminase (ALT)  $\geq 3 \times \text{ULN}$  and total bilirubin (TBIL)  $\geq 2 \times \text{ULN}$  in the liver function test within 7 days after treatment; creatinine (CREA)  $\geq 3$  times the baseline value or  $\geq 4$  mg/dL (353.6  $\mu\text{mol/L}$ ) in the kidney function test within 7 days after treatment.

## 8.3. Detailed Indicator Requirements

### 8.3.1. Demographic Data

Demographic data of the subjects is obtained before randomization, including birth date, gender, nationality, etc.

### 8.3.2. Medical History, Treatment History, and Allergy History

- Medical history includes past serious disease history and current medical history:

1) Past medical history refers to the previous serious diseases developed before signing the informed consent form. Treatments (drug treatment/non-drug treatment) for previous serious diseases are collected.

2) Current medical history includes disease information and diagnosis of this acute ischemic stroke, as well as accompanying disease conditions (or vital signs and symptoms, if diagnosis cannot be determined). The medical history should be recorded in the original records

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and eCRF during the screening period.

①Disease information and diagnosis of this acute ischemic stroke: If the patient has been diagnosed clearly in the emergency/outpatient of the hospital, the diagnosis and corresponding basis of the diagnosis should be recorded, including but not limited to: the earliest occurrence of stroke symptoms, neurological impairment (NIHSS evaluation), CT/MRI examination results, whether non-vascular diseases have been ruled out, etc.

② Accompanying diseases information should be collected from patients with other diseases except this acute ischemic stroke, such as hypertension, coronary heart disease, diabetes, and the current treatment of these diseases (drug treatment/non-drug treatment).

➤ Allergy history:

Information about patients' allergy, specific allergic substances (if available), and allergy to study drugs (recombinant human tissue-type plasminogen activator derivative for injection and alteplase) or similar components, or to materials used for imaging examination.

➤ During the screening period, it is necessary to inquire and collect the following information:

- 1) Intracranial hemorrhage, intracranial tumor, intracranial arteriovenous malformation or aneurysm, and aortic arch dissection that have been diagnosed in the past;
- 2) Any serious head injury, history of stroke with clinical symptoms, or other serious injuries in the past 3 months;
- 3) Intracranial or spinal surgery or other major surgeries performed within the past 3 months;
- 4) Gastrointestinal or urinary system hemorrhage in the last 3 weeks, or visceral hemorrhage at present;
- 5) Arterial puncture in the past week;
- 6) Low molecular heparin within the past 24 hours; thrombin inhibitor or Xa factor inhibitor used within the past 48 hours; or anticoagulant taken orally at present;
- 7) Previously diagnosed or currently combined: liver failure, cirrhosis, portal hypertension (esophageal varices), active hepatitis, bacterial endocarditis or pericarditis, acute pancreatitis;
- 8) A history of gastrointestinal ulcers, esophageal varices, aneurysms, or arterial/venous

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malformations within the past 3 months;

- 9) A history of epilepsy and seizure.

### 8.3.3. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and body temperature, will be measured at visits during the screening period, 24h, 72h, 7 days, 30 days and 90 days after the start of thrombolysis. Within 24h after the start of thrombolysis, monitoring is performed according to the requirements of each study site. In case of clinically significant abnormalities, the investigators shall record and report AE. If visits are made by telephone or video within 30 or 90 days after the start of thrombolysis, this examination is not necessary.

### 8.3.4. Physical Examination

Physical examination, mainly including items such as skin, mucosa, lymph nodes, ear, nose, throat, head, neck, chest, abdomen, spine/limbs, nervous system, etc., will be conducted during the screening period and at visits 7 days after the start of thrombolysis.

### 8.3.5. 12-lead ECG Examination

The 12-lead ECG examination, mainly including indicators of heart rate, PR interval, QRS duration, QT interval and QTc interval, will be conducted during the screening period and at visits 24h to 36h and 7 days after the start of thrombolysis.

During the treatment and follow-up period, the results of the 12-lead ECG will be referred to comprehensively determine whether the subjects have experienced adverse events, which will be recorded after being determined by the investigators.

### 8.3.6. Cranial CT or MRI Examination

Cranial CT or MRI examination will be conducted during the screening period to exclude hemorrhagic stroke. 24h to 36h after the start of thrombolysis, CT should be adopted for cranial detection as much as possible in order to find post-thrombolysis intracranial hemorrhage in time.

### 8.3.7. mRS Score, NIHSS Score, Barthel Index Score

See attachments for the specific details of mRS score, NIHSS score, and Barthel index

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score.

- MRS score: it is conducted during the screening period and at visits 30 days and 90 days after the start of thrombolysis;
- NIHSS score: it is conducted during the screening period and at visits 24h and 7 days after the start of thrombolysis. If intracranial hemorrhage is found in unplanned CT, additional NIHSS score shall be made in time after rescue.
- Barthel index score: it is conducted at visits 30 and 90 days after the start of thrombolysis.

8.3.8. Laboratory Tests

Laboratory tests include blood routine, urine routine, stool routine+occult blood, blood biochemistry, coagulation function, finger blood glucose, and pregnancy test (for women of childbearing age). The specific test time points are shown in the flowchart, and the test items specified in the protocol need to be entered into eCRF.

The biological samples collected in this study, including blood, urine, and feces, will be analyzed in the laboratories of clinical trial sites. The remaining biological samples will be disposed of by each clinical trial site in accordance with the relevant regulations for medical waste at the site. All biological samples will not be used for any tests unrelated to the trial protocol agreed upon by the ethics committees.

Table 2 List of Laboratory Test Items

Blood Biochemistry Test		Blood Routine
Alanine aminotransferase (ALT)	Urea (UREA)	White blood cell count (WBC)
Aspartate aminotransferase (AST)	Creatinine (CREA)	Red blood cell count (RBC)
Total bilirubin (TBIL)	Glucose (GLU)	Hemoglobin (HGB)
Direct bilirubin (DBIL)		Platelet count (PLT)
Total cholesterol (TC)		Absolute neutrophil (NEUT#)
Triglyceride (TG)		Absolute lymphocytes (LY#)
Blood urea nitrogen (BUN)		
Note: Either urea or blood urea nitrogen is collected in blood biochemistry test.		
Urine Routine	Stool Routine	Coagulation
Urinary red blood cell (U-RBC)	Red blood cell (RBC)	Activated partial prothrombin time (APTT)

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Urinary white blood cell (U-WBC)	White blood cell (WBC)	Thrombin time (TT)
Urinary protein (U-PRO)	Occult blood test (OBT)	Prothrombin time (PT)
Urinary glucose (U-GLU)		International normalized ratio (INR)
Urine ketone (U-KET)		Fibrinogen (FIB)
Finger blood glucose		
Pregnancy test: $\beta$ - human chorionic gonadotropin ( $\beta$ - HCG (blood pregnancy, urine pregnancy)		

9. Adverse Event

9.1. Definition of Adverse Event

An adverse event is defined as the adverse medical event that occurs in a subject who receives the test drugs in the clinical trial, which manifests as symptoms, vital signs, diseases, or laboratory abnormalities, but may not necessarily have a causal relationship with the test drugs<sup>[4]</sup>.

The existing symptoms/signs of the subjects during the screening period which do not worsen in the course of the trial will not be reported as adverse events. However, they should be recorded as adverse events in case of deterioration.

Note: Pre-medication adverse events refer to adverse events that occur after signing of the informed consent form by the subject and before administering test drugs, or the worsened medical conditions that pre-exist after signing the informed consent form and before administering test drugs. This type of adverse event can be recorded and entered into eCRF, but not be included in the safety set and not be calculated.

9.2. Monitoring of Adverse Events

During the trial, the subjects should be closely monitored for any adverse events. The monitoring period of adverse events/serious adverse event is defined as the period from the enrollment of the subjects in the study (the signing of the informed consent form) to the end of follow-up.

The sources of adverse events include:

- Subjects' answers to their health status questions (non-directive question such as "How do you feel since the last visit?" raised during each visit);

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- Symptoms spontaneously reported by the subjects;
- Symptoms, vital signs, test abnormalities, or disease diagnoses that the investigators believes are clinically significant;
- Other information related to the health of the subjects (such as hospitalization) known by the investigators.

### 9.3. Record of Adverse Event

All adverse events are encoded and described using Medical Dictionary for Regulatory Activities (MedDRA). During the trial, an adverse event record form should be authentically filled in, in which the name, starting/ending time, duration, severity of the adverse event, causal relationship with the investigational drug, medical treatment, measures taken on the investigational drug (no measures taken, termination of administration, reduction of dosage, recovery after drug suspension, non applicable), outcome (recovery, sequelae after recovery, improvement, duration, death, unknown) and SAE or not should be recorded.

If possible, an adverse event should be recorded based on accurate diagnosis. If it cannot be recorded as an accurate diagnosis, separate physical signs and symptoms should be recorded; When the later diagnosis is made clear, the records should be updated to replace the previous symptoms/signs with diagnosis.

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 (judged by the investigators to be the progression of previous adverse event or intermittent 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 there is no correlation, they will be recorded as separate adverse event in the medical record and the original record should indicate that the subject has had similar adverse events recently as much as possible, so that the sponsor can determine whether to merge the reports when processing them.

If the severity of adverse events of the same type increases, an AE will be recorded according to the highest severity level. If the aggravation of AE leads to another disease/symptom/sign (such as intracranial hemorrhage leading to brain hernia), it is recommended to re-record an AE.

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Note:

- 1) The investigators will determine the outcome of AE.
- 2) The measures taken are not adverse events, while the reasons for the measures taken are adverse events. Hospitalization is not an adverse event, while the reasons for hospitalization are adverse events. Death is not an adverse event, while the causes of death are adverse events (except for sudden death of unknown cause).
- 3) The start date of an adverse event is the date when the first sign or symptom is first observed. If the adverse event is a clinically significant abnormal laboratory test or examination result, the sampling date is regarded as the start time.
- 4) If the symptoms/signs of the subjects during the screening period do not worsen after participating in the trial, they will not be reported as adverse events after medication. However, in case of deterioration during the trial, they should be recorded as post-medication adverse events.

#### 9.4. Abnormal Laboratory Test Results

Whether an objective abnormal examination result should be reported as an adverse event should be determined based on the following criteria:

- 1) The examination result is related to accompanying symptoms;
- 2) The examination result requires further diagnostic tests, drug or non-drug treatment;
- 3) The examination result leads to a change in the dosage of the investigational drug of the subject or discontinuation of the trial;
- 4) The investigators or the sponsor believes that the examination result should be reported as an adverse event.

The result of the examination that is made only for the purpose of checking certain abnormality and does not meet any of the above conditions will not constitute an adverse event. Any abnormal examination results that are judged as system errors, sampling operation errors, etc., are not required to be reported as adverse events after being judged by the investigators.

#### 9.5. Outcomes of Adverse Event

The outcomes of adverse events can be described as follows:

- Recovered/resolved without any sequelae: "termination date of AE" should be



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indicated;

- Recovered/resolved with sequelae: only when the subject has long-term or lifelong sequelae, such as blindness caused by diabetes. "Termination date of AE" should be indicated;
- Remitted/improved: The event has returned to baseline or the subject is in remission/improvement;
- 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 determine that there are no signs of deterioration.
- Fatality: AE leads to death; Unknown: lost to follow-up and unable to determine the outcome of adverse events.

## 9.6. Severity of Adverse Event

The investigators will develop 5-grade determination criteria with reference to NCI CTCAE V5.0 (or updated version), including:

- 1) Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- 2) Grade 2: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living\*;
- 3) Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living\*\*;
- 4) Grade 4: Life-threatening consequences; urgent intervention indicated;
- 5) Grade 5: Death related to AE.

\* Instrumental activity of daily living includes cooking, shopping, using telephone, managing money, et.;

\*\* Self care activity of daily living includes taking a shower, dressing and undressing, eating, washing, taking medication, etc., not bedridden.

## 9.7. Causal Determination Criteria for Adverse Events

All AEs that occur during the clinical trial need to be judged for their correlation with the investigational drug. The causal relationship between AE and the investigational drug is

evaluated as the five results, including certainly related, probably related, possibly related, possibly unrelated, and certainly unrelated, among which certainly related, probably related and possibly related are classified as related, and possibly unrelated and certainly unrelated as unrelated. The analysis of the correlation between AE and the investigational drug needs to analyzed comprehensively based on the following factors:

- A. A reasonable time sequence between the occurrence of AEs and the time when test drugs take effect or not;
- B. Clinical symptoms/signs or imaging manifestations of adverse events are consistent with the pharmacology and toxicology of the known test drugs or not;
- C. Adverse events can be explained by the subjects’ clinical status, psychological factors, concomitant medications or treatments, or other environmental factors or not;
- D. Adverse events disappear or remit or not after discontinuation or reduced dosage of the test drugs;
- E. Adverse events recur or worsen (if feasible) following re-administration of the test drugs,

Table 3 Correlation Determination between Adverse Events and the Drug

	A	B	C	D	E
Certainly related	+	+	-	+	+
Probably related	+	+	-	+	?
Possibly related	+	+	±	±	?
Possibly unrelated	+	-	±	±	?
Certainly unrelated	-	-	+	-	-

Note: + represents Yes; - represents No; ± represents Yes or No; ? represents unknown.

9.8. Follow-up of Adverse Event

Before the end of the follow-up period, the investigators must follow up each adverse event until it recovers, improves, stabilizes (sustains without signs of deterioration), or is lost to follow-up.

After the end of the follow-up period, the investigators must follow up the serious adverse events or adverse events that may have a causal relationship with the investigational drug during the study period until they recover, improve, stabilize (sustain without signs of deterioration) or are lost to follow-up. All relevant follow-up information must be reported to the sponsor.

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### 9.9. Unexpected Adverse Event

Unexpected adverse events refer to events that are not mentioned in the investigator's brochure, or whose nature and severity are inconsistent with that described in the investigator's brochure.

### 9.10. Serious Adverse Event

SAE refers to the occurrence of any of the following adverse medical events after the subject receiving the test drugs that :

- 1) result in death;
- 2) are life-threatening;
- 3) are congenital abnormalities and birth defects;
- 4) result in persistent or significant human disability or damage to organ function
- 5) require inpatient hospitalization or prolongation of existing hospitalization;

The following cases will not be reported as SAE for not considering hospitalization or due to hospitalization: observations in emergency room; stay-in observation within 24h; hospitalization for routine diagnosis and treatment, with a length of stay less than 24h; hospitalization for social reasons (such as hospitalization due to lack of care); hospitalization due to surgery scheduled before the study; planned hospitalization and/or surgical treatment performed before the trial when the subject has already contracted a disease before participating in the trial, which does not worsen during the trial period.

- 6) Other important medical events, such as those listed above that may occur without treatment.

### 9.11. Suspected and Unexpected Serious Adverse Reactions

According to the definition in GCP, suspicious and unexpected serious adverse reactions refer to the serious adverse reactions whose nature and severity of clinical manifestations are not consistent with existing information in the investigator's brochure of the investigational drug, the instructions of marketed drugs, or product characteristic summary.

### 9.12. Report of Serious Adverse Events

The investigators shall immediately report all serious adverse events in writing to the

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sponsor, and then provide a detailed and written follow-up report in a timely manner. Serious adverse event reports and follow-up reports should indicate the identification code of the subjects in the clinical trial, instead of the subjects' real name, citizenship number, address and other identity information. The adverse events and laboratory abnormalities specified in the protocol that are significant for safety evaluation should be reported to the sponsor according to the requirements and time limit of the protocol.

For reports involving death events, the investigators should provide other necessary information to the sponsor and ethics committees, such as autopsy report and final medical report.

Reports of suspicious and unexpected serious adverse reactions judged will be reported by the sponsor or contract research organization (CRO) to all investigators' participating in the clinical trial, clinical trial institutions, ethics committees, drug regulatory authorities and health authorities within the prescribed time limit.

After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigators should promptly sign and read it, consider that whether to make corresponding adjustments to the treatment of the subjects, communicate with the subjects as soon as necessary, and report suspicious and unexpected serious adverse reactions provided by the sponsor to the ethics committees.

### 9.13. Adverse Events of Special Concern

- 1) Symptomatic intracranial hemorrhage (SITS-MOST and ECASS III standards);
- 2) Massive hemorrhage events after treatment (ISTH standard);
- 3) ALT  $\geq 3 \times$ ULN and TBIL  $\geq 2 \times$ ULN in the liver function test within 7 days after treatment;
- 4) Creatinine (CREA)  $\geq 3$  times the baseline value or  $\geq 4$  mg/dL (353.6  $\mu$ mol/L) in the kidney function test within 7 days after treatment.

Adverse events of special concern should be reported as SAEs and counted separately according to the SAE process.

9.13.1. Definition of Symptomatic Intracranial Hemorrhage and Collection Requirements

The symptomatic intracranial hemorrhage in this study is defined and collected separately according to SITS-MOST<sup>[7]</sup> and ECASS III<sup>[5]</sup> standards.

- 1) SITS-MOST: It is defined as a hemorrhage event that results in local or remote parenchymal hematoma type 2 on the imaging scan obtained within 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
- 2) ECASS III: It is defined as any intracranial hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days after thrombolysis. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.

9.13.2. Definition of Hemorrhage Events and Collection Requirements

Hemorrhage in this study is defined based on the International Society of Thrombosis and Hemostasis (ISTH) standard<sup>[13]</sup> and collected at different levels.

Among them, **massive hemorrhage** is an adverse event of special concern.

	Level	Definition
ISTH	Massive hemorrhage	<div><div>➤ Hemoglobin decrease ≥ 2g/dL</div><div>➤ Blood transfusion volume ≥ 2U compensatory red blood cells</div><div>➤ Symptomatic hemorrhage in a critical area or organ</div><div>➤ Fatal hemorrhage*</div></div>
	Clinically related non-massive hemorrhage	<div><div>➤ Hospitalization or prolonged hospitalization</div><div>➤ Laboratory tests, imaging examinations, compression hemostasis, surgery, or discontinuation of the study drug</div><div>➤ Change accompanying treatment</div></div>
	Mild bleeding	<div><div>➤ Visible bleeding** that does not meet the criteria for massive hemorrhage or clinically relevant non-major hemorrhage</div></div>

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Note:

\*Fatal hemorrhage: refers to a hemorrhage event that directly leads to death within 7 days. Fatal hemorrhage events include intracranial hemorrhage leading to brain hernia and death within 24 hours, as well as massive gastrointestinal and other organ hemorrhages leading to shock, hemodynamic disorders and death. If a hemorrhage event is considered fatal, the death must be caused by intracranial or non-intracranial hemorrhage.

\*\*Visible bleeding: refers to bleeding that is observable in the naked eyes or can be detected by imaging examinations, as determined by on-site investigators.

#### 9.14. Pregnancy Report

Pregnancy is not considered an adverse event unless it is suspected that the test drugs being tested may affect the effectiveness of the contraceptive pill. Congenital malformations/birth defects and spontaneous abortions should be reported and treated as SAEs. Selective abortions without complications shall not be treated as AEs. All pregnancy outcomes (spontaneous abortions, elective abortions, ectopic pregnancies, normal deliveries or congenital abnormalities) should be followed up and recorded, even if the subjects have withdrawn from the trial.

Once a pregnancy event occurs to the subject (or the subject's sexual partner) during the trial, the investigators shall decide whether to suspend his/her participation in the clinical trial as soon as possible according to the specific situation. The investigators shall scientifically and carefully communicate with the subject according to the medication information, inform him/her of the possible effects and risks of the investigational drug on pregnant women and fetuses, and the subject shall decide whether to terminate pregnancy or continue pregnancy at his/her own discretion.

If the subject (or the subject's sexual partner) decides to terminate the pregnancy, the investigators shall complete the corresponding part of pregnancy report form and report to the sponsor within 24 hours after being informed of the termination of pregnancy, and to the ethics committees if necessary.

If the subject (or the subject's sexual partner) decides to continue pregnancy, it is required to follow up the pregnancy every 3 months until the subject (or the subject's sexual partner) gives birth with known pregnancy outcome. The investigators shall complete the tracking report

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of the pregnancy report form within 24h of each follow-up, and report it to the sponsor, and to the ethics committees if necessary.

## 10. Risk Control and Management

The preliminary clinical trials of the investigational drug and clinical research information of related product, show that the most common adverse reaction among the subjects in this trial is hemorrhage, including visceral hemorrhage and superficial hemorrhage. In the phase II clinical study completed for the investigational drug, the incidence of intracranial hemorrhage after treatment was 6.7% to 10.6%, of symptomatic intracranial hemorrhage (NINDS standard) 4.5% to 6.7% and of other bleeding events related to the investigational drug 23.3% to 37.9%, mainly gingival bleeding.

In addition to hemorrhage, previous trials of similar products reported that subjects had allergic reactions during treatment, manifesting as dyspnea and hypotension, but the incidence was very low, about 0.03%.

During the use of reteplase in patients with myocardial infarction, many symptoms that are also present in myocardial infarction may be reported during treatment. It remains unclear whether the symptoms are caused by reteplase. These events include: cardiogenic shock, arrhythmia, pulmonary edema, heart failure, cardiac arrest, recurrent angina pectoris, reinfarction, cardiac perforation, mitral regurgitation, pericardial effusion, pericarditis, acute cardiac tamponade, venous thrombosis, embolism and electromechanical separation. Some complications that are extremely dangerous can lead to death.

Other adverse reactions have also been reported, such as nausea, vomiting, fever and hypotension.

Based on the above information, subjects who participate in this study may have one or more risks, including but not limited to the aforementioned adverse events. In this study, any adverse drug reactions the subjects have should be intervened in a timely manner upon the requirements of the protocol and in accordance with the clinical routine treatment measures and risk management plan. If necessary, the drug can be discontinued by the judgment of the investigators.

The study sites must be equipped with necessary medical rescue equipment, first aid drugs,

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and work out emergency measures. If necessary, an emergency medical team shall be established to treat emergency medical events and accidental injuries in accordance with relevant standard operating procedures. Close observation of potential AEs, especially unexpected AEs, timely analysis and communication, and detailed recording of AEs shall be conducted. Communication procedures with the hospital's intensive care unit for subject transfer and care shall be established. Communication mechanisms between the investigators and the laboratory as well as between the the investigators and the sponsor shall be established in order to ensure timely communication and treatment of potential AEs.

In the inclusion/exclusion criteria of this trial, attention is paid to whether there is a history of hemorrhagic diseases (including gastrointestinal hemorrhage and intracranial hemorrhage), platelet count, coagulation function, and whether there are combined oral anticoagulants. During the trial, attention should be paid to subjects for blood pressure levels and puncture site conditions to avoid abnormalities. During the administration, a regular safety examination will be conducted, mainly including vital signs, physical examination, blood routine, blood biochemistry (liver function, kidney function, etc.), etc. At the end of the dosing period, vital signs, physical examination, blood routine, blood biochemistry, urine routine, etc. are performed. The above examinations and the observation of the investigators allow early detection of adverse events for which necessary intervention and treatment should be given. During the follow-up period, if the subject experiences any adverse event or uses any concomitant medication or treatment method, it is necessary to report to the investigators in a timely manner, and if necessary, visit the hospital for necessary intervention. If the drug is discontinued due to an adverse event related to the test drugs, follow-up is required until the adverse event is recovered, improved or stabilized (sustained without signs of deterioration) or follow-up is lost.

## 11. Statistical Analysis

All data processing, summarization and analyses will be conducted using the SAS® system (SAS Institute Inc., Cary, NC) Version 9.4 or above. In general, continuous variables will be summarized by number of patients with available data (n), mean, standard deviation (SD), median, minimum, and maximum values. Categorical and ordinal variables will be



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summarized by the number (n) and percentage of patients in each category or grade,. Missing values will not be included in the percentage calculation unless otherwise specified.

Unless otherwise specified, all statistical tests will use a bilateral test with  $\alpha = 0.05$  to calculate a bilateral 95% confidence interval.

### 11.1. Statistical Hypothesis and Sample Size Estimation

The primary efficacy endpoint, the proportion of patients with mRS score of 0-1 at 90 days after treatment, will be evaluated using the non-inferiority test method. Based on historical trial data for the positive control drug alteplase<sup>[5][6]</sup>, 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  $\alpha$  as 0.5, the non-inferiority boundary for RR is 0.93 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 ( $\alpha$ ) of 0.025, test power ( $1-\beta$ ) 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<sup>[7]</sup>, the estimated incidence of symptomatic intracranial hemorrhage is approximately 1%. Referring to NOR-TEST study<sup>[8]</sup>, 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.

### 11.2. Statistical Analysis of Population

#### 11.2.1. Intention-To-Treat (ITT)

Including all participants who are randomized, receive study drug, meet the basic inclusion criteria.

#### 11.2.2. 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'

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(i.e. according to the drug the patient received, rather than the drug to which the patient may have been randomized)

### 11.2.3. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize the demographic and other baseline characteristics (including disease characteristics, medical history, medication history, etc.).

## 11.3. Statistical Analysis Method

### 11.3.1. Efficacy Analysis

#### Primary Estimand Analysis

For subjects with intercurrent events, mRS scores will be collected continually at day 90 after treatment based on the treatment policy strategy. Multiple imputation method will be used for patients with 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 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.

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

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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.

### **11.3.2. Safety Analysis**

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be analyzed based on Treatment-emergent adverse events (TEAEs). All TEAEs, TEAEs related to study drug, serious adverse events (SAEs), adverse events of special interest (AESIs), etc. will be summarized.

TEAEs will also be grouped by system organ class (SOC) and preferred term (PT) and summarized by group. The summary tables will present the number and percentage of total patients, by SOC and by PT for each group.

The incidence and the differences between two groups will be performed for each adverse event.

The Kaplan Meier method will be used to evaluate the survival situation up to day 90, and the median survival time and corresponding 95% confidence interval will be evaluated.

Descriptive statistics will be used to summarize vital signs, physical examinations, electrocardiogram parameters, and laboratory tests, as well as their changes relative to baseline. shift tables will be used to describe the changes from baseline for variables judged by clinical significance.

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## 12. Data Management

### 12.1. Source Data and Source Files

#### Source Data

Source data refers to all information recorded on the original records or certified copies of clinical trials, including clinical findings, observation results, and other relevant activity records required for reconstruction and evaluation of clinical trials.

#### Source Files

Source files refer to the original records, files, and data generated in clinical trials, including medical records, medical images, laboratory records, memorandums, subject diaries or evaluation forms, drug distribution records, data automatically recorded by devices, microfilms, photographic negatives, magnetic media, X-rays, subject files, and clinical trial related documents and records kept by pharmacies, laboratories, and medical technology departments, and certified copies. The source files include source data that presents in paper or electronic form.

### 12.2. Database Creation

After a CRF, designed by the data administrator on the trial protocol and statistical analysis requirements, is reviewed by the project team and the sponsor, the database designer will establish a data input interface for the database in EDC. The input interface being fully tested in the testing environment can only be put into use after being approved by the sponsor and the project team.

### 12.3. Data Collection and Input

The data input in this study is directly entered into the Electronic Data Collection (EDC) system. The investigators or CRC fills in the subject information accurately, timely, completely, and normatively through the EDC system based on the subject's original information.

The major responsibility of the investigators is to ensure that the data reported in the electronic case report form or other forms is accurate, complete and timely, and that the data on the electronic case report form are derived from the original data of the subjects, and must

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be explained for any differences.

CRA should monitor whether the clinical trial follows the trial protocol, conduct source document verification (SDV), and confirm that all electronic case report forms (eCRF) are filled in as consistent with the original data. For errors or differences, the investigators should be notified and corresponding doubts should be recorded to ensure that all data records and reports are correct and complete.

#### **12.4. Data Verification and Challenge Management**

Clinical trial data administrator conducts data verification according to the data verification plan, mainly including manual verification and logical verification of computer system. Queries arising from verification must be answered by the data entry personnel. If a query is answered, the data administrator will close the query. If not answered, it will be raised again. This process continues until the completion of data cleaning.

#### **12.5. Data Review Meeting**

Prior to the locking of the database and following the completion of the basic data cleaning, the project manager organizes a data review meeting to discuss the data table/list and the final deviation from the protocol, and generates corresponding meeting minutes. The database can not be locked until all doubts that need to be verified are resolved and the data is completely cleaned during the data review meeting.

#### **12.6. Database Locking**

According to the procedures for database locking, once all steps are completed prior to locking, a written approval for database locking should be given, and data editing permission of the database should be revoked for database locking. If any issues are found after the database is locked and need to be modified, the data should be strictly modified as per the procedures for unlocking and relocking.

#### **12.7. Storage of Materials**

The necessary documents for the sponsor refer to documents that can be used individually or collectively to evaluate the implementation process of clinical trials and the quality of trial

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data, which are used to prove that the investigators, the sponsor, and CRA have complied with GCP and legal and regulatory requirements of related drug clinical trials during the clinical trial process.

The necessary documents are considered important for the sponsor's auditing and the drug regulatory department's inspection of the clinical trial, and serve as the basis for confirming the authenticity of the clinical trial implementation and the integrity of the collected data.

The sponsor, the investigators, and clinical trial institutions should confirm places and conditions for storing necessary documents for clinical trials. The conditions for storing documents should include keeping away from direct light, waterproof, and fireproof, which are conducive to the long-term storage of documents. Standard operating procedures for document management should be established. The saved documents need to be easy to identify, search for, retrieve, and return. The media used to store clinical trial materials should ensure that the source data or its certified copies are kept intact and readable during the retention period, and reading ability should be regularly tested or checked to avoid intentional or unintentional changes or losses.

If some documents generated during the implementation of the clinical trial are not listed in the necessary document management directory of clinical trials, the sponsor, investigators, and clinical trial institutions can also include them in their respective necessary document archives for preservation based on necessity and relevance.

The necessary documents for clinical trials should be kept for 5 years after the approval of the investigational drug for marketing or 5 years after the termination of the clinical trial. All materials of this clinical study are proprietary to China Resources Angde Biotech Pharma Co., Ltd. Unless required by the National Health Commission, investigators shall not provide them to any third party in any form without the written consent of the sponsor.

The sponsor should ensure that investigators can always access, input and correct data in the case report form reported to the sponsor during the trial process, and the data should not be solely controlled by the sponsor.

The sponsor should ensure that investigators can retain the data in the case report forms that have been submitted to the sponsor. The copies used as source documents should meet the requirements for certified copies.

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At the beginning of a clinical trial, investigators and clinical trial institutions, as well as the sponsor should establish a file management system for necessary documents. At the end of the clinical trial, CRA should review and confirm the necessary documents of the investigators, clinical trial institution and the sponsor, which should be properly stored in their respective clinical trial archives.

### 13. Clinical Monitoring

In order to guarantee the rights and well-being of subjects in the trial, to ensure the accuracy and integrity of the trial record and the reported trial data, and to ensure the compliance of the trial with the approved protocol, GCP, and the applicable regulatory requirements, the sponsor should assign qualified CRA who should be appropriately trained, and have sufficient scientific and/or clinical knowledge required for monitoring the trial. The responsibilities of a CRA mainly include:

- 1) CRA should be thoroughly familiar with the information of the test drugs, the protocol, the informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirements.
- 2) CRA should conscientiously perform monitoring in accordance with the requirements of the sponsor to ensure that the clinical trial is properly implemented and documented as per the clinical trial protocol.
- 3) CRA serves as the main contact person between the sponsor and the investigators. Prior to the clinical trial, CRA should confirm that the investigators have adequate qualifications and resources to complete the trial and the study sites have appropriate conditions to complete the trial, including personnel allocation and training, complete and well-operated laboratory equipment and various inspection conditions related to the trial.
- 4) CRA should verify that the investigational drug is within validity period under acceptable storage conditions and in sufficient supply during the clinical trial; the test drugs are provided only to subjects who are eligible to receive them at the specified doses in the protocol; subjects are provided with the instructions on proper use, disposition, storage, and return of the test drugs; the reception, use, and return of the

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test drugs at the study sites are properly controlled and documented; the disposition of the unused test drugs conducted by the study sites complies with applicable regulatory requirements and the sponsor's requirements.

- 5) CRA should verify the investigator's implementation of the trial protocol during the clinical trial implementation; confirm that all subjects or their guardians have signed informed consent forms before the trial; ensure that the investigators receive the latest version of the investigator's brochure, all trial-related documents, and necessary trial supplies, which are implemented in accordance with relevant laws and regulations; ensure that the investigator has full knowledge of the clinical trial.
- 6) CRA should verify whether the investigators have fulfilled the responsibilities specified in the trial protocol and contract, and whether these responsibilities have been delegated to unauthorized personnel; confirm the eligibility of enrolled subjects and report the enrollment rate and progress of the clinical trial; confirm that the records and the data are correct and complete, and that the trial records and files are updated in real time and well kept; verify that all medical reports, records, and documents provided by the investigators are traceable, clear, synchronously recorded, original, accurate, complete, and dated.
- 7) CRA should verify the accuracy and completeness of the entered information of the CRFs and compares it with the source document. CRA should pay attention to checking that the data specified in the trial protocol is accurately recorded in the CRFs and consistent with the source document; confirm that the dose changes, treatment changes, adverse events, concomitant medication, complications, lost visits, and missed examinations of the subjects are recorded in the CRFs; confirm that follow-up visits, trials, examinations that are not conducted by the investigators and corrections that have been made to errors or omissions are recorded in the CRFs; verify that the withdrawal and loss of follow-up of the enrolled subjects have been recorded and explained in the CRFs.
- 8) CRA should inform the investigators of wrong information, omission, or illegibility in the CRFs; ensure that appropriate corrections, additions, or deletions are made by the investigators or the authorized personnel and are signed and dated by the reviser.



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If necessary, the reasons for the revisions shall be explained.

- 9) CRA confirms whether all adverse events (AEs) are appropriately reported within the time period according to the requirements of the applicable laws and regulations, the trial protocol, ethics committees, and the sponsor.
- 10) CRA confirms whether the investigators keep the essential documents as required in GCP.
- 11) CRA should communicate any deviations from the protocol, SOPs, and the applicable laws and regulations with the investigators and take appropriate actions to prevent recurrence of the deviations. CRA should submit a written report to the sponsor after each monitoring visit. The report should include date, site, the name of the CRA and the name of the investigators or other personnel contacted; the report include a summary of monitoring, issues and facts found in the clinical trial, deviations from the trial protocol and deficiencies and monitoring conclusions; the report should illustrate actions taken or to be taken for the issues as well as suggestions to ensure compliance of the trial with the protocol; the report should provide sufficient details to review compliance with the monitoring plan. Centralized monitoring reports and on-site monitoring reports can be submitted separately. The sponsor should review and follow up the issues in the monitoring reports, and form a document for preservation.

#### 14. Quality Control and Assurance

- 1) The investigators participating in the clinical trial must possess professional expertise, qualifications and competencies for clinical trials. Researchers participating in clinical trials must possess the professional expertise, qualifications, and abilities of the clinical trial. After qualification review, the personnel requirements are relatively fixed.
- 2) The trial participants are trained on the trial protocol, the current GCP and the current SOP of the study prior to the initiation of the trial, so that the study personnel have full understanding and knowledge of the clinical trial protocol and the specific connotations of the indicators.

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- 3) To ensure the quality of the clinical trial and the rights and interests of the subjects, the clinical units set up special subject members and the sponsor appoints at least one CRA to monitor the progress of the trial.

## 15. Protocol Compliance and Deviations

The investigators should conduct the trial in compliance with the protocol agreed by the ethic committee. Without the consent of the sponsor and tethics committees, the investigators shall not make changes to or deviate from the protocol, except for changes only in clinical trial management to eliminate emergency risks to the subjects, or to replace CRA and phone number. The investigators or the study personnel designated by the investigators should document any deviations from the protocol and make explanations. In order to eliminate emergency risks to the subjects, without the consent of the ethics committees, any changes to or deviations from the trial protocol made by the investigators should be promptly reported to the ethics committees and the sponsor with the reasons indicated, and to the drug regulatory authority if necessary.

The investigators should take measures to avoid concomitant medications that are prohibited in the trial protocol. The study sites and the principle investigator should take measures to strengthen the training of the investigators and indicate the clinical trials participated on the subjects' paper and electronic medical records; Necessary restrictions on prohibited drugs specified in the protocol should also be made through the information system to remind caution in medication. At the same time, the subjects should inform their participation in the clinical trial, especially the medication, of the physicians when visiting other hospitals during the trial period.

CRA should promptly communicate with the investigators about deviations from the trial protocol, SOP, and applicable laws and regulations, and take appropriate measures to prevent their recurrence.

The sponsor is responsible for formulating, implementing, and timely updating the SOP regarding the quality assurance and quality control system of the clinical trial in order to ensure that the implementation of the clinical trial as well as the generation, recording and reporting of data comply with the requirements of the trial protocol, GCP, and relevant laws and

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regulations. For noncompliance with the trial protocol, SOP, GCP, or relevant laws and regulations by the investigators, study sites or the personnel from the sponsor in the clinical trial that may have significant impacts on the safety and rights of the subjects or on the reliability of the clinical trial data, the sponsor shall promptly conduct a root cause analysis and take appropriate corrective and preventive measures. In case of serious violations of the trial protocol or GCP, the sponsor can hold the relevant personnel responsible and report to the drug regulatory authority.

## 16. Report and Publication

### 16.1. Clinical Trial Report

For the data and information collected during this trial, a clinical report is drafted by China Resources Angde Biotech Pharma Co., Ltd. or the authorized party and submitted to the undersigned investigators for review.

### 16.2. Confidentiality and Ownership of the Trial Data

Any confidential information related to the investigational drug or this trial, including any data and results derived from this trial, is the sole property of China Resources Angde Biotech Pharma Co., Ltd. The investigators and any other personnel participating in this trial shall protect the confidentiality of such proprietary information of China Resources Angde Biotech Pharma Co., Ltd.

The investigators and other staff of the study sites shall keep confidential all information provided by China Resources Angde Biotech Pharma Co., Ltd and all data generated in the course of the study (except medical records of the subjects). The investigators or other staff of the study sites shall not use the information, data or records for any other purposes other than for this study. The restrictions are not applicable to: (1) the data that has been published not due to errors by the investigators or the staff of the study sites; (2) the information that must be disclosed for the purpose of gaining the trust of an academic or ethics committees to evaluate the study; (3) the information that must be disclosed in order to provide appropriate medical care to the subjects participating in the study.

Any summary, submission, and publication of the study sites must be reviewed by the sponsor and the principle investigator of the leading unit for the clinical study.

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## **17. Ethical Norms, Informed Consent and Additional Protection Measures for Vulnerable Groups**

### **17.1. Review and Approval of the Ethics Committees**

The trial will be implemented in accordance with the trial protocol, GCP and relevant laws and regulations. The sponsor shall not conduct the clinical trial until obtaining the consent of the ethics committees. The sponsor shall obtain from the investigators and study sites the name and address of the ethics committees, the list of ethics committee members involved in the review of the project, the review statement in compliance with GCP and relevant laws and regulations, documents and other relevant information approved in the ethics committee review.

Documents that the ethics committees should review include: the trial protocol and its revised edition, the informed consent form and its updates, the method and information for recruiting subjects, other written information provided to subjects, the investigator's brochure, available safety information, documents containing information on compensations to subjects, documentation of the investigator's qualifications, and other documents required by the ethics committees to perform their duties. The ethics committees should ensure that the informed consent form and other written information provided to subjects describe the compensations to subjects, including the mode, amount and plan for compensations.

The review comments of the ethics committees include: approval, approval upon necessary modifications, disapproval, termination or suspension of the approved study. The review comment should explain the requested modifications or the reason for denial.

If the review comment of the ethics committees is "approval upon necessary modifications", such as modifications of the protocol, informed consent form, and/or other relevant documents provided to the subjects, the sponsor should consult with the investigators and study sites to modify relevant documents and submit them to the ethics committees. If the review comment of the ethics committees is "disapproval", the sponsor and the investigators shall modify the issues related to the clinical trial and submit to the ethics committees for re-review.

### **17.2. Informed Consent of Subjects**

The informed consent should be conducted by the investigators in compliance with the ethical principles of the Declaration of Helsinki and the following requirements:

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- 1) The investigators should use the latest version of the informed consent form approved by the ethics committees and other information provided to the subjects. If necessary, the subjects should sign the informed consent form again during the clinical trial.
- 2) During the informed consent of the subjects, the investigators must comply with the regulatory requirements of the drug regulatory authority and adhere to the ethical principles of Declaration of Helsinki and meet the GCP requirements.
- 3) In the course of the clinical trial, when the investigators obtain new information that may affect the subject's continued participation in the trial, he/she should promptly inform the subject or his/her guardian and make corresponding records.
- 4) The study personnel shall not use improper methods such as coercion or inducement to influence subjects to participate in or continue the clinical trial.
- 5) The investigators or designated study personnel should fully inform subjects of all relevant matters concerning the clinical trial, including written information and the approval comment of the ethics committees.
- 6) Both oral and written information provided to the subjects, including informed consent form, should be expressed in an easy-to-understand way so that the subjects or their guardians or witnesses can easily understand.
- 7) The final text of the informed consent form should contain the following information: the purpose of the trial, the procedures and duration of the trial, the examination operations, the expected possible benefits and risks to the subject, informing the subject of the possible assignment to different groups of the trial; the treatment and corresponding compensation available to the subject in case of trial-related damages, the principle of confidentiality for the subject's personal data, etc.
- 8) Before signing the informed consent form, the investigators or the designated study personnel should give the subject or his/her guardian sufficient time and opportunities to understand the details of the trial and exhaustively answer all trial-related questions raised by the subject or his/her guardian.
- 9) The subject or his/her guardian, and the investigators performing the informed consent should sign and date the informed consent form separately, and if it is not signed by the subject personally, the relationship with the subject should be indicated.
- 10) If the subject or his/her guardian lacks the ability to read, an impartial witness should witness the entire informed consent process. The investigators should explain the content of the informed consent form and other written materials to the subject or his/her guardian or witness in detail. If the subject or his/her guardian verbally agrees

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to participate in the trial and is capable of signing the informed consent form, it should be signed as much as possible. The witness should also sign and date the informed consent form to certify that the subject or his/her guardian has received an accurate explanation of the informed consent form and other written information from the investigators, understood the content and agreed to participate in the clinical trial.

- 11) The subject or his/her guardian shall be provided with the original or a copy of the signed and dated informed consent form and other written information provided to the subjects, including the original or a copy of the updated informed consent form and the revised version of other written information provided to the subjects.
- 12) If the subject is a person with no legal capacity, an written informed consent should be obtained from his/her guardian; if the subject is a person with limited civil capacity, an written informed consent should be obtained from the subject himself/herself and his/her guardian. When the guardian gives informed consent on behalf of the subject, he/she should inform the subject of relevant information about the clinical trial in a way the subject can understand, and try to have the subject personally sign the informed consent form and indicate date.
- 13) In case of emergency, if the informed consent from the subject cannot be obtained prior to participation in the clinical trial, his/her guardian may give informed consent on behalf of the subject. If the guardian is also not present, the enrollment mode of the subject should be clearly expressed in the trial protocol and other documents, and the written consent of the ethics committees should be obtained; at the same time, the informed consent for continuing to participate in the clinical trial should be obtained from the subject or his/her guardian.
- 14) The exact time of subject providing informed consent and the person who conducts the informed consent discussion should be documented in the medical records.

### 17.3. Additional Protection Measures for Vulnerable Groups

Among the patients included in this study are emergency patients and patients with critical diseases. For vulnerable groups, the sponsor will take the following additional protection measures:

- 1) All the participating sites screened for the project are qualified to conduct neurology clinical trials and are confirmed by the Office of Cerebral Stroke Screening and Prevention Engineering Committee of National Health Commission as stroke centers with all medical equipment and drugs required for emergency and intensive care, so

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that they can provide patients with appropriate and active treatment promptly.

- 2) The clinical trial procedures will be aligned with the routine clinical treatment procedures which will greatly reduce the delay in treatment time caused by the clinical trial procedures.
- 3) According to the Article 23 of GCP 2020 Edition, in case of emergency, if the informed consent from the subject cannot be obtained prior to participation in the clinical trial, his/her guardian may give informed consent on behalf of the subject; at the same time, the informed consent for continuing to participate in the clinical trial should be obtained from the subject or his/her guardian.
- 4) In this project, informed consent discussion and the signing of informed consent form will be conducted in strict accordance with the requirements for informed consent in the latest version of GCP.
- 5) The sponsor will purchase adequate medical insurance for the study and establish a smooth claims process to ensure that the subjects will get the relevant insurance payments in the first time in the event of a claim during the clinical trial.

## 18. Liability and Insurance

### 18.1. GCP Liability

China Resources Angde Biotech Pharma Co., Ltd., CRA, and the investigators have liabilities that are consistent in the provisions of GCP, related guidelines, and relevant regulatory requirements in China. The investigators are responsible for taking on the investigators' responsibilities set forth in GCP and for distributing the test drugs according to the trial protocol agreed to by the ethics committees or a signed revision of the protocol. The sponsor should ensure timely delivery of the test drugs to the investigators and the clinical trial sites as well as safe storage and disposal of the test drugs throughout the trial period.

### 18.2. Subjects' Benefits

Subjects' participation in this trial is free of charge for all examinations or other operations related to the trial. Subjects enrolled in this trial will be reimbursed for travel to the hospital for each visit. Travel reimbursement will be issued to subjects based on their progress toward completion of the trial.

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### **18.3. Liability and Insurance**

In order to protect the subjects from any damage related to the investigational drug or participation in the trial, China Resources Angde Biotech Pharma Co., Ltd. has purchased insurance for the subjects in accordance with the relevant laws of China. The cost of treatment for adverse events related to the investigational drug will be provided by the sponsor/insurance company.

### **18.4. Archiving**

#### **18.4.1. Investigator's Documents**

The investigators and study sites should properly retain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The storage period, cost, and the disposition of essential documents (upon expiration of the contract) should be specified in a contract between the sponsor and the investigators/institutions.

The investigators are responsible for completing and retaining the confidential subject identification code list, which refers to the unique code assigned to a subject in a clinical trial to identify him/her. The investigators use this code in place of the subject's name to protect his/her privacy when reporting adverse events and other data related to the trial.

Trial documents shall not be destroyed without the written authorization of China Resources Angde Biotech Pharma Co., Ltd. and the investigators. If the investigators retire or the institutions are unable to continue to maintain the trial documents, the trial documents may be transferred to a qualified third party for storage.

#### **18.4.2. Core Trial Documents**

China Resources Angde Biotech Pharma Co., Ltd. will archive core trial documents in accordance with GCP and applicable regulatory requirements.

### **18.5. The Responsibilities Assumed by Each Party and Other Relevant Provisions**

#### **1) Sponsor**

According to the provisions of GCPs, the sponsor should carefully perform the following duties:



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- The sponsor should be responsible for initiating, managing and providing funds for clinical trials.
- The sponsor should take the protection of the subjects' rights and safety and the reliability and credibility of the clinical trial results as the basic considerations of the clinical trial.
- The sponsor should select clinical trial institutions and investigators and recognize their qualifications and conditions to ensure the completion of the trial.
- Before the parties involved participate in the clinical trial, the sponsor should clarify and indicate their responsibilities in the signed contract.
- The contract between the sponsor and the investigators/institutions should indicate the responsibilities, rights and interests of the parties involved in the trial, as well as possible conflicts of interests that should be avoided by all parties. The funds indicated in the contract should be reasonable and conform to market rules. The sponsor, investigators and clinical trial institutions should sign a contract for confirmation.
- When designing the clinical trial, the sponsor should ensure that sufficient safety and efficacy data are available to support human exposure by the route, at the dosages, for the duration. The sponsor should update the investigator's brochure as significant new information is available.
- Prior to the clinical trial, the sponsor should submit relevant clinical trial information to the drug regulatory authority and obtain permission for the clinical trial or complete filing. The submitted documents should indicate version number and version date.
- The sponsor should obtain from the investigators and the clinical trial institutions the name and address of the EC, the list of EC members involved in the study review, a review statement indicating that it is organized and operates according to GCP and the applicable laws and regulations, the documents and other related materials reviewed and approved by the EC.
- The sponsor should select qualified biostatisticians, clinical pharmacologists and clinicians to participate in the trial, including designing the trial protocol and CRF, developing a statistical analysis plan, analyzing data, and writing clinical trial summary reports.
- The sponsor should provide the investigators with the investigational drugs that are easily identifiable, correctly coded and specially labeled, and guarantee quality conformance. The test drugs should be properly packaged and stored as required in the protocol. The sponsor should establish a management system and record system

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for the test drugs.

- The sponsor is responsible for the safety assessment of the test drugs during the trial. The sponsor should timely notify the investigators, clinical trial institutions and the drug regulatory authorities of any issues found in the clinical trial that may affect the safety of the subjects and the implementation of the clinical trial, and may change the approval comment of the ethics committees.
- The sponsor should appoint qualified CRA who are acceptable to the investigators.
- The sponsor should establish a quality control and assurance system for clinical trials and may organize audits of clinical trials to ensure quality.
- The sponsor should clarify the access to trial records. The sponsor should specify in the trial protocol or contract that investigators and clinical trial institutions provide direct access to source data and source documents related to the clinical trial for CRA, auditors, EC reviewers and regulatory inspectors. The sponsor should confirm that each subject has given his/her consent to the direct access of the above mentioned personnel to the original medical records related to the clinical trial in a written form.
- The sponsor should designate competent medical experts for timely consultation on medical issues related to the clinical trial.
- The sponsor should report adverse drug reactions in accordance with the requirements and within a specified period of time.
- The sponsor shall immediately inform the investigators, clinical trial institutions and drug regulatory authorities of, and explain the reasons for the early termination or suspension of the clinical trial.
- The sponsor should take appropriate measures to ensure that compensations or indemnities can be provided to the subjects and the investigators. The sponsor should provide investigators and clinical trial institutions with legal and financial insurance or guarantee related to the clinical trial and make them appropriate to the nature and degree of risks of the clinical trial. However it does not cover the injury caused by the negligence of the investigators and clinical trial institutions. The sponsor shall bear the cost of medical treatment for injury or death related to the clinical trial, as well as the corresponding compensation. The sponsor and the investigators should timely provide the compensation and indemnity to the subjects. The method and manner of providing compensation to the subjects by the sponsor should comply with applicable regulatory requirements. The sponsor should provide the test drugs to the subjects free of charge and pay for the cost of the clinical trial related medical examinations.

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- The sponsor should ensure the compliance of the clinical trial. If it is found that investigators and clinical trial institutions have serious or dissuaded non-compliance issues, the sponsor should terminate the participation of the investigators and clinical trial institutions in the clinical trial, and submit a written report to drug regulatory authorities in a timely manner. Meanwhile, the sponsor and investigators should take appropriate emergency safety measures to protect the safety and rights of the subjects.
- If the clinical trial is completed or terminated prematurely, the sponsor should submit a clinical trial report that reflects the outcomes of the clinical trial comprehensively, completely and accurately to the drug regulatory authority in accordance with relevant laws and regulation. The safety data and efficacy data therein should be consistent with the clinical trial source data.

## 2) Clinical Trial Institutions and Investigators

According to the provisions of GCP, the investigators should carefully perform the following duties:

- Investigators and clinical trial institutions should have the qualifications required in GCP.
- Investigators and clinical trial institutions should have the necessary conditions required to complete clinical trials.
- Investigators should give the subjects appropriate medical treatment.
- Investigators should communicate with EC.
- Investigators should comply with the trial protocol.
- Investigators and clinical trial institutions have responsibilities for the management of the test drugs provided by the sponsor.
- Investigators should comply with the randomization procedures for clinical trials.
- During the informed consent of the subjects, investigators must comply with the ethical principles of the Declaration of Helsinki and meet GCP requirements for providing informed consent forms and other information.
- The recording and reporting of the clinical trial should comply with GCP requirements.
- The safety report prepared by the investigators should comply with GCP requirements.
- In case of early termination or suspension of the clinical trial, investigators should promptly notify the subjects and give them appropriate treatment and follow-up. In addition, other requirements specified in GCP should be met.
- Investigators should provide clinical trial progress reports.

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### 3) Biostatistical Analysis (Data Management/Statistical Unit)

According to the provisions of GCP, the data management personnel and statisticians should carefully perform the duties, that is, at the end of the trial, they are responsible for managing data, making statistics as per the statistical protocol developed and issuing a statistical analysis report.

#### 18.6. Study Units and Trial Participants

##### 18.6.1. Sponsor

Sponsor: China Resources Angde Biotech Pharma Co., Ltd

Address: No. 78, Ejiao Street, DongE County, Shandong Province.

##### 18.6.2. Major Study Unit

Majors study unit: Beijing Tiantan Hospital, Capital Medical University

Principle Investigator: Yongjun Wang

Address: No. 119, Nansihuan West Road, Fengtai District, Beijing.

##### 18.6.3. Data Management and Statistics Unit

Company name: Nanjing CR Medicon Technology Co., Ltd.

Address: No.18, Zhilan Road, Science Park, Jiangning District, Nanjing.

##### 18.6.4. Clinical Monitoring Unit

Company name: Nanjing CR Medicon Technology Co., Ltd.

Address: No.18, Zhilan Road, Science Park, Jiangning District, Nanjing.

Company name: Beijing Highthink Pharmaceutical Technology Co., Ltd.

Address: Room 03, Floor 9, 101 inside Building 1, Floor 1 to 11, No. 186 Nansihuan West Road, Fengtai District, Beijing;

Company name: Beijing Borrun Technology Co., Ltd.

Address: Room 402, Building 2, No.3 Yard, East Binhe Road, Andingmen, Dongcheng District, Beijing.

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## 20. Appendixes

### Appendix 1: Contraceptive Measures, Definition of Women of Childbearing Age, and Contraceptive Requirements

#### 1. Definition of Women of Childbearing Age:

Women aged  $>52$  with a history of menstrual cessation for  $\geq 12$  months or women who have undergone hysterectomy, bilateral oophorectomy, or have medically confirmed ovarian failure, regardless of age, are considered non-childbearing.

Women aged  $\leq 52$  who have not undergone hysterectomy and bilateral oophorectomy, and have no medically confirmed ovarian failure (including those with any duration of amenorrhea) are considered women of childbearing age.

#### 2. Contraceptive Requirements:

During the screening period, female subjects of childbearing age must have a negative serum pregnancy test at screening and a negative urine pregnancy test at Day -1 visit.

From the screening period to the end of the trial (at 90 days after thrombolysis), subjects must agree to one of the following options:

- 1) Complete abstinence. Periodic abstinence methods (including calendar method, ovulation method, symptothermal method, or post-ovulation method) are not allowed.
- 2) Or correct use of condoms by the male partner.
- 3) Or correct use of one of the following contraceptive measures:
  - Intrauterine device with an annual failure rate of  $<1\%$ ;
  - Female barrier method: Cervical cap or pessary with spermicide;
  - Tubal sterilization;
- 4) Vasectomy performed on the male partner.

#### 4. Procedures to be Followed in Case of Pregnancy:

If a subject becomes pregnant within 90 days after thrombolysis (or if the partner of a male subject becomes pregnant within 90 days after thrombolysis), the subject should notify the investigators as instructed.

Appendix 2: Modified Rankin Scale (mRS)

mRS is used to measure the functional recovery outcomes of patients after a stroke. The formal definitions for each level are indicated in bold, while additional guidance is provided in *italics* to reduce potential discrepancies between different observers, although there is no requirement for face-to-face interviews. It is important to note that only symptoms occurring after the stroke should be considered. If a patient is able to walk independently with the assistance of certain devices, he/she should be considered capable of independent ambulation.

In cases where two levels seem equally applicable to a patient and further questioning is not feasible for making an absolutely correct choice, the more severe level should be selected.

Patient Status	Scoring Criteria
No symptom	0
No significant disability despite symptoms: able to perform all usual duties and activities	1
Slight disability: unable to perform all previous activities, but able to look after personal affairs without assistance	2
Moderate disability: requiring help, but able to walk without assistance	3
Moderately severe disability: unable to walk and take care of physical needs without assistance	4
Severe disability: bedridden, incontinent and requiring constant nursing care and attention	5
Death	6

Interpretation:

0-No symptom

*Despite mild symptoms, the patient has not noticed any new functional limitations or symptoms since the stroke.*

1-No significant disability despite symptoms: able to perform all usual duties and activities

*The patient has some symptoms caused by the stroke, either physical or cognitive (e.g., affecting speech, reading, or writing; or body movement; or sensation; or vision; or swallowing; or emotion), but can continue to work and carry out social, and leisure activities that are performed prior to the stroke. The key questions used to differentiate level 1 and level 2 (see below) can be: "Are there things you used to do, but you couldn't do anymore after the stroke?" . Activities done more frequently than once a month are considered "regular"*

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2-Slight disability: unable to perform all previous activities, but able to look after personal affairs without assistance

*For certain activities that could be done before the stroke (such as driving, dancing, reading, or working), the patient is no longer able to do after the stroke, but is still able to care for himself or herself on a daily basis without assistance. The patient is able to dress, walk, eat, go to the bathroom, prepare simple foods, shop, and travel locally without assistance. The patient lives without supervision. It is envisioned that patients at this level can live alone in their homes for a week or more without care.*

3-Moderate disability: requiring help, but able to walk without assistance

*At this level, the patient is able to walk independently (with a walking aid) and can dress, go to the bathroom, eat, etc., but more complex tasks need to be completed with the assistance of others. For example, someone else is required to do the shopping, cooking or cleaning, and to visit the patient more than once a week to ensure that the above activities are completed. Assistance is needed not only to take care of the body, but also to give advice: for example, patients at this level will need supervision or encouragement to handle finances.*

4-Moderately severe disability; unable to walk and attend to bodily needs without assistance

*The patient needs others to help with activities of daily living, whether it is walking, dressing, going to the bathroom or eating. The patient requires care at least once a day, usually twice or more, or must live in close proximity to the caregiver. To distinguish levels 4 and 5 (see below), whether the patient is able to routinely live alone for an appropriate amount of time during the day should be considered..*

5-Severe disability; bedridden, incontinent and requiring constant nursing care and attention

*Although trained nurses are not required, someone is needed to look after the patient several times throughout the day and night.*

6-Death



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**Appendix 3: National Institutes of Health Stroke Scale (NIHSS)**

It should be noted that during each NIHSS score, the actual assessment time should be recorded and scoring should be done according to the provided table. Do not alter the score. The score reflects what a patient does, not what doctors believe the patient can do. A quick examination is conducted and the results are recorded simultaneously. Unless necessary for guidance, do not coach the patient (e.g., repeatedly asking the patient to make certain efforts). Any items that are not assessed should be explained in detail in the form.

	Examination	Scoring	Score
<b>1a</b>	Level of Consciousness (LOC): Examiner must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages etc. A3 is only scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimuli.	0= Alert, keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer or respond. 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.	_____
<b>1b</b>	LOC Questions: The patient is asked the month and his/her age. The answer must be correct. There is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak due to endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer should be graded and that the examiner should not help the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	_____
<b>1c</b>	LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand.. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completes due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her. (pantomime) and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	_____

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	Examination	Scoring	Score
2	<p><b>Best Gaze</b></p> <p>Only horizontal movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be tested, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (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 disorder 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.</p>	<p>0=Normal</p> <p>1=Partial gaze palsy: gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.</p> <p>2=Forced deviation or total gaze paresis not overcome by the oculocephalic maneuver.</p>	_____
3	<p><b>Visual Fields:</b></p> <p>Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. 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.</p>	<p>0=No visual loss</p> <p>1=Partial hemianopia</p> <p>2= Complete hemianopia</p> <p>3=Bilateral hemianopia (blind including cortical blindness)</p>	_____
4	<p><b>Facial Palsy:</b></p> <p>Ask or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0=Normal symmetrical movements.</p> <p>1=Minor paralysis (flattened nasolabial fold, asymmetry on smiling).</p> <p>2=Partial paralysis (total or near-total paralysis of lower face).</p> <p>3=Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>	_____
5	<p><b>Motor Arm:</b></p> <p>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 if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and</p>	<p>0=No drift; limb holds 90 (or 45) degrees for full 10 seconds.</p> <p>1=Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>2= Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.</p> <p>3=No effort against gravity; limb falls.</p> <p>4=No movement.</p> <p>UN = Amputation or joint fusion, explain:</p>	_____

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	Examination	Scoring	Score
	clearly write the explanation for this choice.	_____ 5a. Left Arm 5b. Right Arm	
6	<b>Motor Leg:</b> The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0=No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2=Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3=No effort against gravity; leg falls to bed immediately. 4=No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	_____
7	<b>Limb Ataxia:</b> This item is aimed at finding evidence of a unilateral 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. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	_____
8	<b>Sensory:</b> Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9	<b>Best Language:</b> A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes	

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	Examination	Scoring	Score
	and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____
10	Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain: _____	_____
11	Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0= No abnormality. 1=Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	_____
Total score			_____

Some items that are not rated should be detailed in the form. Items that are not rated should be studied retrospectively through surveillance video and discussed with the examiner.

Attached: 1. Test Figures for Items 9 and 10

Figure 1 for Reading Test

Figure 2 for Reading Test

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Figure 3 for Reading Test

Please read the  
following sentences:  
You know how.  
Down to earth.  
I got home from work.  
Near the table in the  
dining room  
They heard him  
speak on the radio last  
night

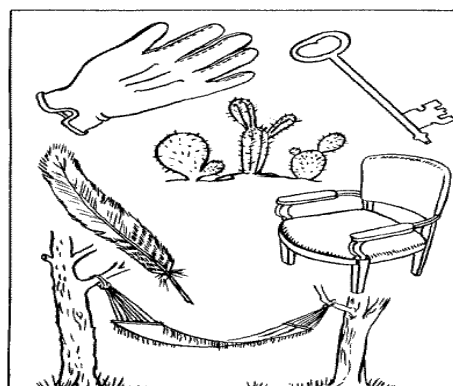


Figure 4 for Reading Test

Please read the  
following words:  
MAMA  
TIP-TOP  
FIFTY-FIFTY  
THANKS  
HUCKLEBERRY  
BASEBALL PLAYER

## 2. How to evaluate NIHSS score for special situations?

### ➤ NIHSS score for uncooperative patients:

➤ If a patient is uncooperative for one item, it should be clearly documented. All unassessed items should be reviewed by CRA and discussed with the examiner when necessary.

### ➤ NIHSS score for coma patients:

For Item 1a with a score less than 3, each component should be assessed individually.

➤ Only when the patient shows no response to any noxious stimuli (e.g., sternal rub, supraorbital pressure) and only reflex activity is present, a score of 3 should be assigned to Item 1a.

If Item 1a is scored as 3, the other items should be assessed as follows:

- Item 1b: LOC questions - 2 points
- Item 1c: LOC commands - 2 points
- Item 2: Best gaze - assessed based on oculoccephalic reflex. If the patient's conjugate eye deviation can be overcome by reflexive activity, score 1 point; otherwise, score 2 points.

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- Item 3: Visual fields - assessed based on visual threat. If the patient can correctly look toward the side with finger movement, it is considered normal.

- Item 4: Facial palsy - 3 points

- Item 5: Motor arm-5a = 4, 5b = 4

- Item 6: Motor leg-6a = 4, 6b = 4

- Item 7: Limb ataxia - 0 points. A score can only be given if there is ataxia present. If the patient has decreased muscle strength and cannot perform the finger-nose or heel-shin tests, a score of 0 should be assigned.

- Item 8: Sensory - 2 points

- Item 9: Best language - 3 points

- Item 10: Dysarthria - 2 points

- Item 11: Extinction and inattention - Coma implies a complete loss of cognitive capacity, so a score of 2 is assigned.

- NIHSS score for aphasic patients:

- 1b-LOC Questions: For aphasic patients who cannot understand questions, a score of 2 is given. The score is based solely on the initial response and should never be recorded as "unable to assess."

- 1c-LOC Commands: If the patient does not respond to commands, the examiner should provide a demonstration (e.g., using gestures), and then score based on the result (i.e., compliance with 0, 1, or 2 commands). Only the first attempt should be scored, and the question should only be asked once.

- 2-Best Gaze: Gaze can be examined in all aphasic patients. Establishing eye contact and having the patient walk around the bed can be helpful. This item is an exception to the "observe the first response and cannot train" principle. If the patient cannot gaze voluntarily, methods such as head and eye movements, eye fixation, and tracking by the examiner can be used to provide stronger examination stimuli.

- 3-Visual Fields: Not limited by aphasia.

- 4-Facial Palsy: For aphasic patients, score based on the symmetry of facial expressions during noxious stimulation.

- 5-Motor Arm: Guide aphasic patients using voice or gestures, without using noxious stimuli. If testing the non-paretic side of the limbs first, aphasic patients may understand what you are trying to test.

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● 6-Motor Leg: Guide aphasic patients using voice or gestures, without using noxious stimuli. If testing the non-paretic side of the limbs first, aphasic patients may understand what you are trying to test.

● 7-Limb Ataxia: If the patient cannot understand, score as 0. If the limbs are initially moved passively by the examiner, aphasic patients often perform the examination correctly.

● 8-Sensory: Examine aphasic patients for evasive responses to noxious stimuli. Score 2 only when severe or complete sensory loss is clearly confirmed. Therefore, aphasic patients may also be scored as 1 or 0.

● 9-Best Language: Have the patient describe pictures, name objects on cards, and read sentences from a language list. Mild aphasia scores 1 point. Use all available materials to determine whether to score 1 or 2. Score 2 if it is estimated that the patient has missed more than two-thirds of the named objects and sentences or performed very few and simple one-step commands.

● 10-Dysarthria: Score aphasic patients based on their spontaneous speech and having them repeat words spoken loudly by the examiner. If there is severe aphasia, score based on the clarity of pronunciation in spontaneous speech.

● 11-Extinction and Inattention: If aphasic but does show bilateral attention, score as normal. Because only abnormal performance is recorded, this item must be measurable.

### 3. How to calculate the total score of NIHSS?

When calculating the total score, the following items should not be counted in the total score:

- "UN = amputation or joint fusion" in items 5 and 6 - Motor arm/leg.
- "UN = amputation or joint fusion" in item 7 - Limb Ataxia.
- "UN = tracheal intubation or other physical impairment" in item 10 - Dysarthria.



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Appendix 4: Barthel Index for Activities of Daily Living (Barthel Index)

Item	Score Standard	Score
Feeding	0 Dependent	_____
	5 Help required	
	10 Independent	
Bathing	0 Dependent	_____
	5 Independent	
Grooming (Washing face, combing hair, brushing teeth and shaving)	0 Dependent	_____
	5 Independent	
Dressing (unbuttoning, zipping, putting on shoes, etc.)	0 Dependent	_____
	5 Partial help required	
	10 Independent	
Defecate	0 Incontinent (or enemas required)	_____
	5 Occasional incontinence	
	10 Continent	
Urinate	0 Incontinent or enemas required and independent	_____
	5 Occasional incontinence	
	10 Controlled	
Toilet use (including wiping, tidying clothes and flushing)	0 Dependent	_____
	5 Partial help required	
	10 Independent	
Transfers (from bed to chair and from chair to bed)	0 Totally dependent and unable to sit	_____
	5 Lots of help required (1-2 persons) and able to sit	
	10 Less help required(1 person) or guidance required	
	15 Independent	
Movement on the ground	0 Unable to move or move <50m	_____
	5 Operate the wheelchair independently, including turning>50m	
	10 Walk >50m with the help of one person (verbal or physical)	
	15 Walk >45m independently (auxiliary devices available)	
Going upstairs	0 Unable	_____
	5 Help required (verbal, physical, auxiliary devices)	
	10 Independent	
Total score	The total score of the table is 100 points.	



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## Appendix 5: Post-thrombolysis Adverse Reaction Emergency Response Plan for Reference

Bleeding is the most common adverse reaction for thrombolytic drugs; other adverse reactions include allergy, hypotension, etc. The emergency response plan is formulated to minimize the harm caused by bleeding and allergy that may be caused by the study drug to the subjects participating in this clinical trial and to protect the safety and rights of the subjects to the maximum extent. Specific responses are as follows:

### 1. Response Procedures:

In the event of an emergency, investigators should provide appropriate clinical interventions to the subjects and provide real-time observation and guidance on the necessary measures according to this emergency response plan and the actual situation. When guidance or intervention from relevant departments is required, timely consultation with the on-duty physicians of relevant departments should be made to observe the subjects and provide guidance on necessary measures. At the same time, the responsible neurologist 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.

### 2. The following conditions will lead to discontinuation of infusion of the investigational drug during the trial:

2.1 Allergic reactions: they manifest as significant hypotension and lingual swelling.

2.2 Neurological deterioration: it manifests as decreased level of consciousness and worsening of disease condition.

2.3 Sustained blood pressure  $> 185/110$  mmHg.

2.4 Severe hemorrhage: It includes intracranial hemorrhage and/or gastrointestinal hemorrhage and/or intraperitoneal hemorrhage and/or genitourinary hemorrhage and/or respiratory hemorrhage.

### 3. Response to Hemorrhage:

3.1 Drug administration may be suspended for subjects with mild bleeding (nasal bleeding, gingival bleeding, skin mucosal bleeding spots, petechiae, and excessive menstruation) as judged by the investigators in order to examine the site and extent of bleeding, closely monitor

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the patients' blood pressure, pulse changes, and mental status in real time, and give transfusions if blood pressure is significantly lowered.

3.2 Plasma substitute or whole blood transfusion will be given along with hemostatic drugs for subjects with severe hemorrhage (carnal hematuria, gastrointestinal hemorrhage) until the patients' blood pressure, pulse, and mental status recover to normal.

### 3.2.1 Upper Gastrointestinal Hemorrhage:

Acute upper gastrointestinal hemorrhage refers to hemorrhage caused by lesions in the gastrointestinal tract above the flexural ligament, including esophagus, stomach, duodenum, bile duct and pancreatic duct. Typical clinical manifestations are vomiting blood, black stools or bloody stools, accompanied by hemorrhagic peripheral circulatory failure. Lower gastrointestinal hemorrhage refers to hemorrhage from the gastrointestinal tract below the flexural ligament, including jejunum, ileum, cecum, colon and rectum, which occurs less frequently in the thrombolytic treatment of acute ischemic stroke. It should be treated in the same principles as for upper gastrointestinal hemorrhage.

Identification: Acute upper gastrointestinal hemorrhage refers to hemorrhage caused by lesions in the gastrointestinal tract above the flexural ligament, including esophagus, stomach, duodenum, bile duct and pancreatic duct. Typical clinical manifestations are vomiting blood, black stools or bloody stools, accompanied by hemorrhagic peripheral circulatory failure.

Treatment: ① If thrombolysis can be suspended as judged by the investigators for upper gastrointestinal hemorrhage occurring during thrombolysis, generally, the administration of anticoagulants, antiplatelet aggregation drugs and blood-stasis activating drugs need to be discontinued. Individual cases are considered specifically according to the condition and the opinion of the investigators; ② Closely monitor hemorrhage signs; ③ Monitor electrocardiogram, blood pressure and oxygen saturation; ④ Consult gastroenterology and hematology departments; ⑤ Reserve blood and establish venous channels. Establish central venous channel to facilitate rapid rehydration and transfusion for patients with massive hemorrhage and to avoid acute pulmonary edema caused by excessive transfusion for patients of advanced age and with cardiopulmonary and renal diseases. Perform central venous pressure monitoring as much as possible to guide the amount of fluid input for patients with acute massive hemorrhage; ⑥ Rapid rehydration and blood transfusion to correct shock; ⑦ ⑦

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Drug treatment: a combination of empirical use of PPI + growth inhibitor + antibacterial drugs (+ vasoactive drugs) is recommended; ⑧emergency endoscopy when necessary.

Disease assessment: It mainly includes the assessment of the severity of the patient's condition, the presence of active bleeding and the prognosis of bleeding. The severity of the disease is positively correlated with the amount of blood loss. Because vomiting and black stools are mixed with gastric contents and feces, and some blood is retained in the gastrointestinal tract and not discharged, it is difficult to accurately determine the amount of blood loss based on the amount of vomiting or black stools. The amount of blood loss is judged based on the changes in peripheral circulation caused by the decrease in blood volume, and the shock index (heart rate/systolic blood pressure) is regarded as an important index to determine the amount of blood loss; clinically, active bleeding is considered in the following cases: ① Increased number of vomiting blood or black stools, with bright red vomitus or dark red blood stools discharged, or accompanied by active bowel sounds; ②No significant improvement in the manifestation of peripheral circulation failure after rapid blood transfusion; or despite temporary improvement, it worsens again and central venous pressure still fluctuates, slightly stable and then decreasing again; ③Red blood cell count, hemoglobin measurement and Hct continue to decline and reticulocyte count continues to increase; ④ The blood urea nitrogen continues or increases again when rehydration and volume of urine are sufficient; ⑤ There are more fresh blood in the gastric tube extract.

### 3.2.2 Hemoptysis:

The respiratory tract is divided into upper and lower parts: the nose, pharynx, and larynx are collectively referred to as the upper respiratory tract, and the trachea, bronchi, and lung organs are collectively referred to as the lower respiratory tract.

Identification: Hemoptysis refers to bleeding from any part of the respiratory tract below the larynx discharged through the oral cavity. First of all, it is determined to be hemoptysis, neither oral or nasal bleeding nor upper digestive hemorrhage (vomiting blood).

Treatment: ① If thrombolysis can be suspended as judged by the investigators for respiratory hemorrhage occurring during thrombolysis, generally, the administration of anticoagulants, antiplatelet aggregation drugs and blood-stasis activating drugs need to be discontinued. Individual cases are considered specifically according to the condition and the

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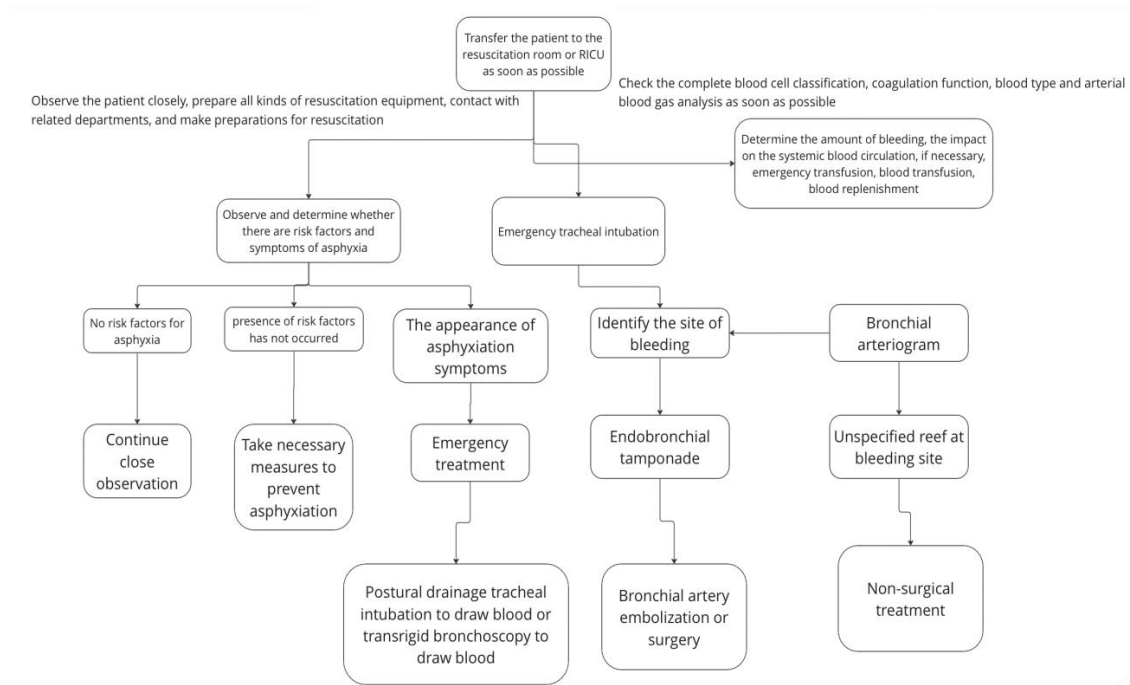
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opinion of the investigators; ② Closely monitor hemorrhage signs; ③ Monitor electrocardiogram, blood pressure and oxygen saturation; ④Consult respiratory medicine and haematology department; ⑤Perform chest CT, bronchoscopy and other examinations if necessary. ⑥In view of the fact that clinical hemoptysis is mostly caused by rupture of a bronchial artery or pulmonary artery, drugs for hemoptysis are posterior pituitary hormone, oxytocin and vasodilators as major choices, and other hemostatic drugs can only be used as adjunctive treatment measures. The application of hemostatic drugs should be individualized. The mechanism of hemoptysis and the complications of the patients should be noted in particular. ⑦ Non-drug treatment: (1) bronchial artery embolization: bronchial artery embolization for hemoptysis is mainly applied to ①patients with acute massive hemoptysis occurring for any reason, the cause of which cannot be removed at the moment, when a surgery is planned to alleviate the conditions; ② patients who are not suitable for surgery, or refuse surgery, with ineffective internal and surgical treatment; ③patients with recurrent hemoptysis in small amounts. (2) Transbronchoscopic treatment: In spite of a risk of aggravating hemoptysis when the bronchoscopic operation is performed for hemoptysis, it is still an effective diagnostic and therapeutic measure when necessary. Prior to the bronchoscopic operation, adequate preparations for treatment should be made, and the airway should be ensured to be unobstructed, preferably by establishing a reliable artificial airway. Coughs caused by the operation should be reduced as much as possible. (3) Surgical treatment: For recurrent hemoptysis that is ineffective with active conservative treatment, an emergency surgery can be considered to stop the haemorrhage for patients with hemoptysis  $>1500$  mL in 24h, or hemoptysis  $>500$  mL at one time, with a precursor of asphyxia and a clear site of hemorrhage and no contraindication to surgery; ⑧Prevention and treatment of complications: Complications of hemoptysis mainly include asphyxia, hemorrhagic shock, aspiration pneumonia and pulmonary atelectasis, etc. Attention should be paid to keeping the airway unobstructed, dilation, anti infection, etc.

Disease assessment: There are different definitions for the estimated amount of hemoptysis, usually stipulating that: ① hemoptysis  $>500$  mL (or  $>100$  mL in one time) within 24h is considered massive hemoptysis; ②100-500mL is considered moderate hemoptysis; ③  $<$

100mL is considered small amount of hemoptysis. It is sometimes difficult to accurately estimate the amount of hemoptysis clinically. On one hand, blood may be mixed with sputum or saliva during hemoptysis. On the other hand, the amount of hemoptysis does not necessarily equal the real amount of hemorrhage in the patient's lungs. It should be noted that the severity of the disease do not exactly coincide with the amount of hemoptysis sometimes. In addition to the amount of hemoptysis, the estimation of the amount of hemoptysis should take into account its duration, frequency and the condition of the body, thereby comprehensively evaluating prognosis and risk of hemoptysis. If asphyxia attacks after hemoptysis, the patient can die suddenly within a few minutes if he is not detected and rescued in time. Fatal hemoptysis means that frequent hemoptysis may cause asphyxia or asphyxia has already occurred. The rescue procedures for fatal hemoptysis is shown in the following diagram:



3.2.3 Cerebral Hemorrhage

The majority of subjects should be treated primarily with internal medical therapy. Post-thrombolysis hemorrhage for ischemic stroke is treated in the general principles that are similar to those for treating spontaneous cerebral hemorrhage.

If the hemorrhagic transformation is judged to be caused by the study drug, the study drug should be discontinued first. Immediate cardiovascular and respiratory support, blood pressure

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management, glucose management, drug therapy, etiologic treatment, and complication treatment (e.g., increased intracranial pressure, seizures, and deep vein thrombosis and pulmonary embolism), neurologic monitoring, prevention of hematoma expansion, and treatment of increased intracranial pressure and other complications (e.g., epilepsy) resulting from the hemorrhage should be given. Fibrinogen levels are tested using reversal agents (e.g., cold precipitation) to reverse the coagulation dysfunction caused by the study drug; platelet levels are also tested, and platelet transfusions may be performed; antifibrinolytic agents (e.g., aminocaproic acid and tranexamic acid) may also be used to neutralize the effects of the study drug. When the benefits of a surgery can be assessed to outweigh the risk of bleeding complications due to study drug related coagulation dysfunction, or cannot be determined, the surgeon should be contacted immediately for treatment.

#### 3.2.3.1 Cerebral Parenchymal Hemorrhage:

In most patients with primary cerebral hemorrhage, the effectiveness of surgical treatment is not sufficiently verified. Therefore, the indiscriminate and routine use of surgical or minimally invasive procedures (Level II recommendation, Level B evidence) is not advocated.

The choice of surgical treatment or minimally invasive surgical treatment may be considered on an individualized basis in the following clinical situations:

(1) Patients with cerebellar hemorrhage accompanied by neurological deterioration or brainstem compression should undergo surgical removal of the hematoma as soon as possible regardless of the presence or absence of hydrocephalus caused by ventricular obstruction (Level II recommendation, Level B evidence); ventricular drainage alone without hematoma removal is not recommended (Level II recommendation, Level C evidence).

(2) For patients with lobar hemorrhage  $> 30$  ml and within 1 cm from the cortical surface, standard craniotomy for the removal of supratentorial hematoma (Level II recommendation, Level B evidence) or minimally invasive surgery for hematoma removal (Level II recommendation, Level D evidence) may be considered.

(3) For patients with supratentorial hypertensive cerebral hemorrhage, hematoma volume of 20–40 ml, and GCS  $\geq 9$  points within 72h of onset, minimally invasive surgery combined with liquefied drainage of thrombolytic drugs or not can be adopted after rigorous selection in

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hospitals where available (Level II recommendation, Level B evidence).

(4) Minimally invasive surgery for removal of hematoma can be considered for patients with severe cerebral hemorrhage  $>40$  ml who have deterioration of consciousness due to the dominant effect of hematoma (Level II recommendation, Level D evidence).

(5) Patients with cerebral hemorrhage of undetermined cause should undergo vascular-related examinations before performing minimally invasive surgery to exclude vascular lesions and to avoid and reduce the risk of re-hemorrhage (Level II recommendation, Level D evidence).

### 3.2.3.2 Ventricular Hemorrhage:

There is a lack of sufficient evidence-based medical evidence to recommend surgical treatment for intraventricular hemorrhage. The effectiveness of rt-PA therapeutic approach in ventricle needs further exploration (Level II recommendation, Level B evidence).

### 3.2.4 Symptomatic Intracranial Hemorrhage 24h after Thrombolysis:

Thrombolytic drugs should be discontinued and tests should be conducted for whole blood count, prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen level, blood type and crossmatch. Emergency CT examination is performed. Cryoprecipitation (including coagulation factor VIII) is infused with 10U within 10-30 min (1h of onset, 12h of peak); in case of fibrinogen level  $<2$ g/L, an additional dose is given with tranexamic acid 1000 mg IV over 10 min or  $\epsilon$ -aminocaproic acid 4-5 g IV over 1 h, followed by additional 1g until bleeding is controlled (3h of peak); supportive therapies are given, including management of blood pressure, intracranial pressure, cerebral perfusion pressure, mean arterial pressure, temperature and blood glucose.

## 4. Response Measures for Allergic Reactions:

When allergic symptoms such as shortness of breath and rash occur in the subjects, the drug administration should be stopped immediately and the subjects are given appropriate treatment according to the condition of the allergic reactions. For mild cases, transfusion and diuretics are given to promote drug excretion; antihistamines and vitamin C, 10% calcium gluconate or 10% sodium thiosulfate are administered, with topical application of glyburide lotion, oscillating lotion or puff powder containing camphor or menthol; for slightly severe cases (more extensive rash accompanied by fever), they should rest in bed, apply the above



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topical drugs, and take prednisone; for severe cases (including severe erythema multiforme, bullous epidermal necrolysis and generalized exfoliative dermatitis rash), and the following measures should be taken immediately: (1) corticosteroids: hydrocortisone 300~500mg, vitamin C 3g, and 10% potassium chloride 20~30ml are infused slowly with 5~10% glucose solution 1000~2000ml added. When the body temperature returns to normal, most of rash subsides and the blood picture is normal, the hormone dosage can be gradually reduced until the equivalent amount of prednisone or dexamethasone taken orally instead. If the rash subsides and the systemic condition further improves, the amount of hormone taken orally is reduced gradually. (2) Antihistamines: two kinds of drugs are chosen to be taken orally at the same time. (3) Fresh blood or plasma transfusion is given. (4) Appropriate antibiotics is selected to prevent infection. (5) Local treatment: In patients with severe drug rash, in the, arge amounts of puff powder or glutamate lotion can be used in skin lesions in the early acute stage to protect the skin and alleviate inflammation and swelling. If there is an exudate, physiological saline or 3% boric acid solution is used for wet dressing. After drying, 0.5% neomycin and 3% sugar distillation oil paste are used. The conjunctiva and cornea often involved must be treated with saline or 3% boric acid to flush and remove secretions in a timely manner. De-inflammatory pine acetate or hydrocortisone eye drops and boric acid or hydrocortisone eye ointment rubbed every night can prevent corneal exfoliation leading to blindness and conjunctival adhesions. Mucosal damage to the mouth and lips that often prevents food intake can be treated with compound borax solution and with mucosal ulcer cream or pearl yellow powder, tin powder, etc applied topically. For those who cannot feed, nasal feeding can be used. (6) Accompanied heart, lung, liver, kidney, brain and other organ damage and hematopoietic dysfunction, etc. need to be treated in a timely manner. (7) Close attention should be paid to the balance of water and electrolytes; adenosine triphosphate, coenzyme A, inosine and vitamin B6 should be given as appropriate. Life care should also be strengthened.

#### Response to Angioedema of the Mouth and Tongue:

(1) Keep the airway unobstructed (tracheal intubation may not be required if the edema is limited to the anterior part of the tongue and lips). If the edema involves the larynx, palate, floor of the mouth, or oropharynx and progresses rapidly (within 30 min), fiberoptic intubation

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should be performed while the subject is awake;

(2) Discontinue the administration of thrombolytic drugs and ACEI analogs. Intravenously injection methylprednisolone 125mg, diphenhydramine 50mg, ranitidine 50mg or famotidine 20 mg;

(3) Give subcutaneous epinephrine (0.1%) 0.3ml or 0.5ml, nebulized inhalation of etiprant, selective bradykinin B2 receptor antagonist, subcutaneous abdominal injection of 3ml (30mg) if angioedema continues to progress; give another 30mg at a 6-hour interval, with no more than 3 total injections in 24h; Plasma C1 esterase inhibitor (20 IU/kg) for hereditary angioedema and ACEI-related angioedema are effective;

(4) Supportive therapy.