Supplement 1

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1	Protocol	1.0	August 03, 2018
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3	Detail of Protocol Change	-	-

PROTOCOL

Version 1.0 of August 03, 2018

Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS): a prospective, randomized, open-label, blinded-endpoint, multi-centre trial

Principal Investigator:

Prof Hui-Sheng Chen

Department of Neurology

General Hospital of Shenyang Military Region

83 Wenhua Rd

Shenyang, China

Tel: 86-13352452086

Fax: 86-024-28897495

E-mail: chszh@aliyun.com

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Abstract

Title	Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS): a prospective, randomized, open-label, blinded-endpoint, multi-centre trial
Principle Centre	General Hospital of Shenyang Military Region
Sponsor	Cerebrovascular Disease Collaboration Innovation Alliance (CDCIA) – Liaoning
Objective	To explore the efficacy and safety of dual antiplatelet vs intravenous alteplase for nondisabling acute minor ischemic stroke
Efficacy Outcome	**Primary outcome：** 1. Proportion of modified Rankin Score (mRS, 0–1) at 90±7 days after randomization. **Secondary outcome：** 1. Proportion of mRS (0–2) at 90±7 days after randomization; 2. Change in National Institute of Health Stroke Scale (NIHSS) score compared with baseline at 24 hours; 3. Incidence of early neurological improvement, defined as more than or equal to 2 NIHSS scores decrease, compared with baseline at 24 hours; 4. Incidence of early neurological deterioration, defined as more than or equal to 2 NIHSS scores increase, but not result of cerebral hemorrhage, compared with baseline at 24 hours; 5. Occurrence of stroke or other vascular events at 90±7 days; 6. Occurrence of all-cause mortality at 90±7 days.
Safety Outcome	1. Proportion of symptomatic intracranial hemorrhage at 90±7 days; 2. Occurrence of any bleeding events at 90±7 days.
Trial Design	This is a prospective, randomized, open-label, blinded-endpoint, multi-centre trial. Subjects included are randomly and divided into two groups: the experiment group and the control group. Follow-up was to be performed at baseline, 24 hours, 7±1 days, 12±2 days, and 90±7 days after

	randomization. All the outcome assessors were masked to the allocation assignment and follow-up.
Trial Population	Patients with nondisabling acute minor ischemic stroke
Sample Size	760
Inclusion criteria	1. Patient age≥18 years; 2. Acute ischemic stroke receiving intravenous thrombolysis within 4.5 hours; 3. NIHSS scores ≤ 5, with ≤ 1 on the NIHSS score in single item scores such as vision, language, neglect and single limb and no score in consciousness item; 4. Ischemic stroke confirmed by head CT or MRI; 5. Signed informed consent.
Exclusion criteria	1. Serve neurological deficit before stroke onset (premorbid mRS ≥ 2); 2. Obvious head injuries or strokes within 3 months; 3. Subarachnoid hemorrhage; 4. History of intracranial hemorrhage; 5. Intracranial tumor, arteriovenous malformation or aneurysm; 6. Intracranial or spinal cord surgery within 3 months; 7. Arterial puncture at a noncompressible site within the previous 7 days; 8. Gastrointestinal or urinary tract hemorrhage within the previous 21 days; 9. Major surgery within 1 month; 10. Uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg after drug treatment); 11. Blood glucose < 50 mg/dl (2.7 mmol/L); 12. Heparin therapy or oral anticoagulation therapy within 48 hours; 13. Platelet count of < 100,000/mm^3 (This does not need to be verified prior to randomization if clinical abnormality is not suspected); 14. Oral warfarin is being taken and INR > 1.6; 15. Abnormal APTT;

	16. Pregnancy; 17. Neurological deficit after epileptic seizures; 18. Myocardial infarction within 3 months; 19. Cerebral infarction with definite anticoagulation indications, such as cerebral infarction caused by cardiogenic embolism; 20. Oral administration is not allowed due to dysphagia; 21. Allergy to test drugs; 22. Other serious illness that would confound the clinical outcome at 90 days; 23. Participating in other clinical trials within 3 months; 24. Patients not suitable for this trial considered by investigators.
Trial Cycle	All included patients were given dual antiplatelet or intravenous alteplase on the guideline-based therapy and were followed up at baseline, 24 hours, 7 ± 1 days, 12 ± 2 days, and 90 ± 7 days after randomization, respectively.
Treatment Regimens	Patients with nondisabling acute minor ischemic stroke within 4.5 hours of onset were randomly divided into the experimental group and the control group in a ratio of 1:1. The patients in the experimental group will receive dual antiplatelet (orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily) for 10–14 days; The patients in the control group will receive intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, followed by guideline-based antithrombotic treatment 24 hours after thrombolysis.
Procedure	**Screening period:** On day 0 (baseline period), it is necessary to complete enrolment screening, and collect demographic characteristics, medical history (including history of hypertension, diabetes and drug treatment history), brain imaging (computer tomography, computed tomography angiography or magnetic resonance imaging), neurological measurements (NIHSS score, mRS score), haematological examination (blood routine, blood glucose, hepatic and renal function, coagulation routine, urine routine, electrocardiogram, etc) and other information. **Treatment period:** After randomization, the patients were given orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days

	and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days (experimental group) or intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg (control group), and then patients were given standard guideline-based antithrombotic treatment. **Follow-up period:** NIHSS score was assessed at 24 hours, 7 ± 1 days, and 12 ± 2 days after randomization. The mRS score was assessed at 90 ± 7 days after randomization. All concomitant medications, adverse events, stroke recurrence and other vascular events of each visit were recorded since the last visit. All the adverse events of included subjects should be recorded and tracked until properly resolved. All the serious adverse events of included subjects should be recorded and tracked, even if the subjects have finished the trial, until the events were resolved, or stabilization judged by the investigator.
Concomitant Treatment	Guideline-based treatment
Statistical Analysis	Intention-to-treat analysis will be used to compare the treatment effect between two groups and all the data will be analyzed with Software Statistical Product and Service Solutions. The mean standard deviation will be used if the continuous data were normally distributed, and the median and interquartile range will be used if the continuous data were non-normally distributed. Categorical data will be expressed as number (percentage). When comparing the data of two groups, t test or Mann–Whitney test was used for continuous data, and chi-square test was used for categorical data. The proportion of mRS 0-1 at 90 days, mRS 0-2 at 90 days, early neurological improvement within 24 hours, early neurological deterioration within 24 hours, symptomatic intracranial haemorrhage at 90 days, any bleeding events at 90 days, and all-cause mortality within 90 days between two groups will be compared through binary logistic analysis with calculated risk difference and 95% confidence interval. The occurrence of time-to-events of stroke and other vascular events will be compared through cox logistic analysis with calculated hazard ratio and 95% confidence interval. The change in NIHSS at 24 hours compared baseline will be

	compared through generalized liner model. Statistical tests were considered significant when the two-sided *P* value was less than 0.05.
Sites Number	20
Duration	18 months

Abbreviation

Abbreviation	Full title
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
Cr	Creatinine
CT	Computed Tomography
CTA	Computed Tomography Angiography
CRF	Case Report Form
DBIL	Direct Bilirubin
ECG	Electrocardiogram
FAS	Full Analysis Set
FIB	Human Fibrinogen
GCP	Good Clinical Practice
GLU	Glucose
HGB	Hemoglobin
HDL	High Density Lipoprotein
ID	Identification
ITT	Intention to Treat
IQR	Inter-Quartile Range
LDL	Low Density Lipoprotein
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NRBC	Urine Red Blood Cell
NWBC	Urine White Blood Cell
NIHSS	National Institute of Health Stroke Scale
PT	Prothrombin Time
PRO	Urine Protein

PPS	Per Protocol Set
PLT	Platelets
RBC	Red Blood Cell
RIC	Remote Ischemic Conditioning
SCr	Serum Creatinine
SAE	Serious Adverse Event
SD	Standard Deviation
SS	Safety Set
TBIL	Total Bilirubin
TC	Total Cholesterol
TG	Triglyceride
TOAST	Trial of Org 10 172 in acute stroke treatment
TT	Thrombin Time
WBC	White Blood Cell

1.Background and current state of knowledge

Acute ischemic stroke (AIS) is one of common diseases with significant morbidity, mortality, and disability. A wide array of studies have confirmed that intravenous thrombolytic therapy with alteplase can effectively improve the functional prognosis in AIS,[1] thus all guidelines recommended the intravenous thrombolytic therapy with alteplase for AIS within 4.5 hours from stroke onset.[2]

Minor stroke is usually defined as NIHSS score ≤ 3 or 5, that accounts for 1/2-2/3 of AIS,[3-4] but the evidence of intravenous thrombolysis of those without clearly disabling deficits is still insufficient.[5-6] A study from Canada shows that 28.5% of patients with minor stroke and without receiving alteplase therapy were unable to walk independently when discharged.[7] The PRISMS study is designed to further compare the efficacy and safety of intravenous alteplase vs. aspirin alone in patients with minor stroke (NIHSS ≤ 5) and without clearly disabling deficits.[8] Unfortunately, the study has been prematurely terminated due to the sponsorship reason in 2018, with only 313 cases enrolled. The preliminary results show that there is no significant difference of the 90-day neurological function between the two groups, while the treatment group with alteplase has a higher rate of symptomatic intracranial hemorrhage than the control group with aspirin alone. Furthermore, the guidelines recommend that once the patients received thrombolysis, antithrombotic therapy cannot be given within 24 hours after thrombolysis. The recommendation makes clinical doctors puzzled to treat the early neurological deterioration, especially in minor stroke patients.

The CHANCE trial in 2013 shows that the efficacy of the combination of aspirin with clopidogrel is superior to aspirin alone with minor stroke (NIHSS ≤ 3) or TIA (ABCD2 ≤ 4).[9] The post hoc analysis of the CHANCE trial in 2017 indicates that bleeding risk outweighs benefit after the 10th day.[10] The POINT study in 2018 further confirmed the efficacy and safety of intensive antiplatelet therapy in minor stroke within 12 hours of onset.[11]

2.Objectives of the trial

2.1 Hypothesis tested

This study intends to demonstrate that dual antiplatelet have similar effect with alteplase on 90-day functional outcome in nondisabling mild stroke population, and have more less symptomatic intracranial hemorrhage.

2.2 Primary objective

To test the hypothesis that dual antiplatelet have similar effect with alteplase on 90-day excellent functional outcome in nondisabling mild stroke population.

2.3 Secondary objectives

1. To determine the proportion of favorable functional outcome at 90 days by treatment group.
2. To determine change in neurological function at 24 hours by treatment group.
3. To determine occurrence of early neurological improvement at 24 hours by treatment group.
4. To determine occurrence of early neurological deterioration at 24 hours by treatment group.
5. To determine occurrence of stroke or other vascular events at 90 days by treatment group.
6. To determine all-cause mortality at 90 days by treatment group.

3. Design and selection of patients

3.1 Trial plan

This is a prospective, randomized, open-label, blinded-endpoint, multi-centre trial.

The patients were randomly divided into the two groups:

Experimental group: orally administered with 300 mg clopidogrel and 100 mg

aspirin after randomization, followed by 75 mg clopidogrel and 100 mg aspirin for 10-14 days;

Control group: intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg after randomization;

Both groups of patients were given standard guideline-based treatment until to 90 days.

Follow-up was performed at baseline, 24 hours, 7 ± 1 days, 12 ± 2 days, and 90 ± 7 days after randomization, respectively.

3.2 Selection criteria:

Inclusion criteria: in order to be eligible, the patients must meet all of the following criteria:

1. Patient age≥18 years;
2. Acute ischemic stroke receiving intravenous thrombolysis within 4.5 hours;
3. NIHSS scores ≤ 5, with ≤ 1 on the NIHSS score in single item scores such as vision, language, neglect and single limb and no score in consciousness item;
4. Ischemic stroke confirmed by head CT or MRI;
5. Signed informed consent.

Exclusion criteria: in order to be included the patients must not have any of the following criteria:

1. Serve neurological deficit before stroke onset (premorbid mRS ≥ 2);
2. Obvious head injuries or strokes within 3 months;
3. Subarachnoid hemorrhage;
4. History of intracranial hemorrhage;;
5. Intracranial tumor, arteriovenous malformation or aneurysm
6. Intracranial or spinal cord surgery within 3 months;
7. Arterial puncture at a noncompressible site within the previous 7 days;
8. Gastrointestinal or urinary tract hemorrhage within the previous 21 days;
9. Major surgery within 1 month;

10. Uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg after drug treatment);
11. Blood glucose < 50 mg/dl (2.7 mmol/L);
12. Heparin therapy or oral anticoagulation therapy within 48 hours;
13. Platelet count of < 100,000/mm^3 (This does not need to be verified prior to randomization if clinical abnormality is not suspected);
14. Oral warfarin is being taken and INR > 1.6;
15. Abnormal APTT;
16. Pregnancy;
17. Neurological deficit after epileptic seizures;
18. Myocardial infarction within 3 months;
19. Cerebral infarction with definite anticoagulation indications, such as cerebral infarction caused by cardiogenic embolism;
20. Oral administration is not allowed due to dysphagia;
21. Allergy to test drugs;
22. Other serious illness that would confound the clinical outcome at 90 days;
23. Participating in other clinical trials within 3 months;
24. Patients not suitable for this trial considered by investigators.

Suspension Criteria:

Trial suspension means that the clinical trial has not finished as planned, and all trials are stopped in the middle period. The purpose of trial suspension is to protect the rights and interests of subjects, ensure the quality of the trial, and avoid unnecessary economic losses:

1. The proportion of serious adverse events during the trial is higher than 10%, and Data Monitoring Committee (DMC) has the right to terminate the study unconditionally.

2. Trial should be discontinued when one treatment is found to be significantly better than the other.

3.3 Duration of participation for each subject:

Each subject will be followed up in the trial for 3 months.

3.4 Randomization and measures to reduce bias:

In the trial, included patients were randomly assigned into the experiment group or control group using a simple randomization (1:1) method through a computer-generated random sequence that was centrally administrated via a password-protected, web-based program at http://aramis.medsci.cn (Shanghai Meisi Medical Technology Co., Ltd). The number of randomized patients planned for this study is approximately 760.

Final follow-up was done at 90 days, in person or by telephone, by one or two trained and certified assessors in each site who were unaware of the randomized allocation assignment. Central adjudication of clinical and safety outcomes was also done by assessors who were unaware of the randomized allocation assignment or clinical details.

4 Plan and conduct of the trial

4.1 Clinical trial flow chart

Item \ Period	Screening	Treatment	Follow-up		
Visit	1	2	3	4	5
Time	0 day[1]	24 hours after randomization	7 ± 1 days after randomization	12 ± 2 days after randomization	90 ± 7 days after randomization
Inclusion/Exclusion Criteria	x				
Sign informed consent	x				
Randomization	x				
Demographic characteristics[2]	x				
Medical history	x				
Physical examination	x	x	x	x	x
Brain CT/MRI	x	x			
TOAST classification				x	
ECG（12 lead）	x			x	
24h ambulatory ECG[3]				x[3]	
Blood routine[4]	x			x	
Urine routine[5]	x				
Blood biochemistry[6]	x			x	
Coagulation routine[7]	x	x	x	x	
NIHSS score	x	x	x	x	
mRS score	x				x
Concomitant medication		x	x	x	x
Adverse events		x	x	x	x
Stroke recurrence and other		x	x	x	x

vascular events [8]					

1. Day 0: limited to the period from the onset of stroke to the time before randomization;
2. Demographic characteristics: The age of the subjects is calculated based on the identification (ID) card information;
3. 24h ambulatory electrocardiogram: required to be completed within 7 days of admission;
4. Blood routine: including total number of red blood cells (RBC), total number of white blood cells (WBC), platelet count (PLT), hemoglobin (HGB). The results are measured within 24 hours before screening;
5. Urine routine: including urine red blood cells (NRBC), urine white blood cells (NWBC), urine protein (PRO), and urine sugar (GLU). The results are measured within 24 hours before screening;
6. Blood biochemistry: Hepatic function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL); Renal function tests: serum urea nitrogen (BUN), Creatinine (Cr); Blood Glucose (GLU); Lipid, including total cholesterol (TC), triglycerides (TG), high density cholesterol (HDL), low density cholesterol (LDL). The results are measured within 24 hours before screening;
7. Coagulation examination: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT). The results are measured within 24 hours before screening;
8. Stroke recurrence and other vascular events: occurrence of stroke recurrence and other vascular events within 90 days from randomization.

4.2 Study completion

The study is considered to be finished when the last visit of the last subject in the trial is completed.

4.3 Study termination

The sponsor reserves the right to close the study centre or suspend the study at any time. The study centre should be closed after the study is completed. The centre is considered closed after all required documentation and study supplies have been collected and a centre closure visit has been conducted.

Investigators can also request to suspend the study, but they must give reasonable reasons in advance.

Reasons for the sponsor or investigator to close the centre in advance may include, but are not limited to:

1. Investigator fails to comply with the requirements of the study protocol, IEC/IRB or local regulatory authorities, sponsor's operating procedures or GCP guidelines;
2. Security considerations;
3. Investigators are not recruiting enough subjects.

5. Study medications

5.1 Identification of study drugs

Alteplase (specification: 20 mg/ampoule or 50 mg/ ampoule, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer: Boehringer Ingelheim Co., Ltd)

Clopidogrel tablet (specification: 75 mg/tablet, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer: Shenzhen Salubris Pharmaceutical Co., Ltd)

Aspirin enteric-coated tablet (specification: 100 mg/tablet, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer:

ORIGINAL PHARMACOLABO Corporation)

5.2 Responsibilities of study drugs administration

The investigator of the clinical trial is responsible for ensuring that the study drugs received by the study centre are counted and recorded during the whole process of the study, and the distribution and recovery of the drug must be recorded in the Drug Dispensing and Recycling Record Form. The original packaging of the study drug must be returned, whether there is any remaining study drug in it. Returned study drugs should be kept at the site designated by the study centre and separate from unused study drugs. Do not destroy or mix medicines in different packages until inspectors have counted them. The use of the study drug must strictly follow the instructions in the protocol and the package label. The sponsor monitor must be allowed to count and reconcile unused and returned study drugs at each monitoring. Unused or returned study drugs to be destroyed must be recorded on the Drug Recycling Record Form and returned to the medication destruction centre.

6. Treatment administered to included subjects

6.1 Description of the treatment required to conduct the study

The experimental group were administrated orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days. Patients were then given standard guideline-based antithrombotic therapy from 14 days to 90 days.

The control group were administrated intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg, followed by guideline-based antithrombotic therapy from 24 hours after intravenous thrombolysis to 90 days.

6.2 Permitted and prohibited medical drugs and treatments in the study

There are no specific medical treatments for this study.

7. Outcome measurements

7.1 Primary efficacy outcome

Proportion of mRS (0−1) at 90±7 days after randomization.

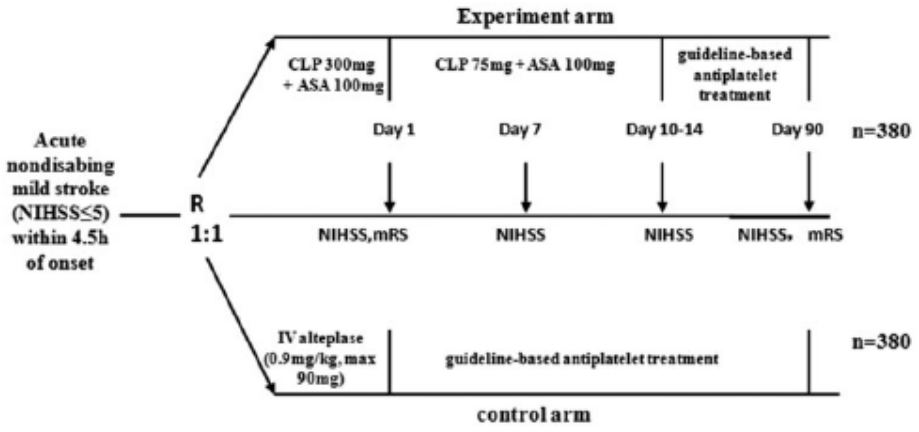
7.2 Secondary efficacy outcomes

1. Proportion of mRS (0−2) at 90±7 days after randomization;
2. Change in National Institute of Health Stroke Scale (NIHSS) score compared with baseline at 24 hours;
3. Incidence of early neurological improvement, defined as more than or equal to 2 NIHSS scores decrease, compared with baseline at 24 hours;
4. Incidence of early neurological deterioration, defined as more than or equal to 2 NIHSS scores increase, but not result of cerebral hemorrhage, compared with baseline at 24 hours;
5. Occurrence of stroke or other vascular events at 90±7 days;
6. Occurrence of all-cause mortality at 90±7 days.

7.3 Safety outcomes

1. Proportion of symptomatic intracranial hemorrhage at 90±7 days;
2. Occurrence of any bleeding events at 90±7 days.

7.4 Study procedure



7.5 Study periods

Screening period: On day 0 (baseline period), it is necessary to complete enrolment screening, and collect demographic characteristics, medical history (including history of hypertension, diabetes and drug treatment history), brain imaging (computer tomography, computed tomography angiography or magnetic resonance imaging), neurological measurements (NIHSS score, mRS score), hematological examination (blood routine, blood glucose, hepatic and renal function, coagulation routine, urine routine, electrocardiogram, etc.) and other information.

Treatment period: After randomization, the two groups were given orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days (experimental group) or intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg (control group), and then patients were given standard guideline-based treatment.

Follow-up period: NIHSS score was assessed at 24 hours, 7 ± 1 days, and 12 ± 2 days after randomization. The mRS score was assessed at 90 ± 7 days after randomization. All concomitant medications, adverse events, stroke recurrence and other vascular events of each visit were recorded since the last visit.

All the adverse events of included subjects should be recorded and tracked until properly resolved.

All the serious adverse events of included subjects should be recorded and tracked, even if the subjects have finished the trial, until the events were resolved, or stabilization judged by the investigator.

8. Description of safety assessment parameters

8.1 Evaluate clinical safety:

Physical examinations, including neurological assessments, imaging studies, were performed at baseline, Hour 24, Day 7 ± 1, Day 12 ± 2, and Day 90 ± 7 after

randomization; adverse event of each visit was collected after baseline visit.

Adverse events monitoring

All information on adverse events, whether mentioned by subjects, discovered by investigators, or discovered through physical examination, laboratory tests, and other methods, should be recorded on the adverse events page of the case report form and handled in accordance with appropriate regulations and report.

Adverse Event (AE)

The adverse event (AE) is any adverse medical event that occurs in a study subject during a study that is not necessarily related to this treatment. Thus, the adverse event (AE) can be any unfavorable and unexpected sign (including abnormal laboratory findings), symptom or disease temporally related to the use of study drugs, regardless of whether it is related to the study drugs or not.

It is included that any events that are new or that have worsened in severity and frequency from baseline, including abnormal results from diagnostic methods such as laboratory tests.

Note: Adverse event collection begins with signed informed consent.

Serious Adverse Event (SAE)

Serious adverse event (SAE) is any adverse medical event at any dose that meets one or more of the following criteria:

- cause death (note: death is a consequence, not an event);
- Life-threatening (Note: "Life-threatening" means that the subject is in immediate danger of death at the time of the event, not the assumption that death would have occurred if the event is more severe);
- cause significant or permanent disability or impairment of organ function;
- Teratogenic and birth defects;

- Causing or prolonging hospitalization;
- Significant medical event or need for intervention (occur without treatment)’

Note: Any event requiring hospitalization (or prolonged hospitalization) that occurs during the subject's participation in the study must be reported as a serious adverse event. The following circumstances leading to hospitalization are not considered serious adverse events:

- Hospitalization for social reasons other than adverse events
- Hospitalization for a scheduled surgery or other treatment or examination prior to study entry (must be recorded on the case report form)
- Hospitalization for elective surgery or treatment or examination due to anticipated disease progression

8.2 Safety assessment

For all adverse events in clinical studies, the following factors must be evaluated for safety:

- Severity criteria for SAE
- The causal relationship between the event and the investigational drug
- Severity of incident
- Anticipation of events

Causal relationship between events and the study drugs

Regardless of serious adverse events or non-serious adverse events, the investigator must evaluate the relevance of the event to the use of the study drugs according to the following criteria:

Evaluating association between adverse events and study treatments Criteria

5-level classification	Judgment criteria
Definitely related	The time of initiation of use is reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event reduce or disappear after study treatment dose reduction or discontinuation; similar adverse events (non-essential) can occur with re-use of study treatment.
Probably related	The time of initiation of use is reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; it is not sure whether similar adverse events (non-essential) can occur with re-use of study treatment.
Probably unrelated	The time of initiation of use is not reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse

5-level classification	Judgment criteria
	event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; it is not sure whether similar adverse events (non-essential) can occur with re-use of study treatment.
Definitely unrelated	The time of initiation of use is not reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; similar adverse events (non-essential) cannot occur with re-use of study treatment.
Unjudged	The judgment cannot be made due to incomplete, contradictory information or the fact that the information cannot be supplemented and verified.

Table of Correlation Evaluation Criteria for Adverse Events and Treatment Use

	Definitely related	Probably related	Probably unrelated	Definitely unrelated	Unjudged
Have a reasonable chronological order with the study drugs	+	+	+	−	?
For the known reaction type of the study drugs	+	+	−	−	?
Explanation for reasons other than available research equipment	−	±	±	+	?
Responses lessen after decompression of study drugs	+	±	±	−	?
The reaction reappears after the study drugs is reused	+ or ?	?	?	−	?

Note: "+" in the table is affirmative; "-" is negative; "±" is difficult to affirm or deny; "?" indicates that the situation is unknown.

Severity Criteria

Severity should be assessed according to the following graded descriptions:

- Mild: No symptoms or discomfort; does not interfere with daily activities and function; usually does not require medication to relieve symptoms.
- Moderate: Symptoms cause significant discomfort; daily activities and function are affected; study participation can be continued; intervention required to relieve symptoms.
- Severe: Severe causes severe discomfort; symptoms result in loss of function and significantly interfere with daily activities; in severe cases,

study treatment can be discontinued; symptomatic treatment and/or hospitalization are required.

The investigator should use clinical judgment to assess the severity of the event (e.g., abnormal laboratory results) from the subject's direct experience.

8.3 Safety report

All adverse events

All adverse events, regardless of their severity, nature of severity, or their causal relationship to study treatment, from the time of signed informed consent until the last follow-up visit (90 days after first use of the drugs), are to be recorded in the original and recorded in medical terms on the clinical research form. When symptoms and signs are caused by common causes, a diagnosis of the disease should be given where possible (e.g., cough, runny nose, sneezing, sore throat, and headache should be reported as "upper respiratory tract infection"). The investigator must make a judgment on the causal relationship between the adverse event and the study treatment and record it on the clinical research form. All treatments for adverse events should be documented in the original medical record and reported as requested by the sponsor.

All serious adverse events in clinical research must be reported to the ethics committee of the centre, the principal investigator of the centre, the sponsor, the contract research organization, the research team leader unit, and the adverse reaction monitoring centre within 24 hours; Report to the ethics committee and data and safety monitoring committee of the team leader unit within 7 natural days after being informed. Investigators must complete a serious adverse event form to record the time, severity, duration, actions taken and outcomes of serious adverse events. Any follow-up information for serious adverse events should also be reported in writing within 24 hours according to the above process.

All serious adverse events that do not resolve at study termination or subject early withdrawal must be followed up to any of the following:

1. Incident mitigation

2. Events are stable
3. If the baseline value is known, the event returns to the baseline value
4. Events can be attributed to other drugs or factors not related to study
5. It is unlikely that any further information will be available (subject or physician refuses to provide further information and remains lost to follow-up after various follow-up attempts)

Death

Death is the result of an event. The death of a subject in a clinical trial, regardless of whether the event was expected or drug-related, would be considered a serious adverse event. Events leading to death should be recorded in medical terms and reported on the eCRF. All causes of death (death diagnoses) must be reported as serious adverse events. Investigators should make every effort to obtain and send death certificates and autopsy reports to designated personnel.

Pregnancy

If the researcher finds that the subject is pregnant during the research, the researcher should fill out the "Pregnancy Incident Report Form" within 24 hours after learning and report it to the clinical research supervisor, and notify the project leader by phone

Abnormal pregnancy results, considered serious adverse events, should be reported in accordance with the Serious Adverse Event Reporting Procedure.

Abnormal laboratory test results

During the study, when the results of laboratory tests meet the following conditions, they must be regarded as adverse events and recorded in medical terms on the adverse events of the CRF:

1. Accompanying clinical symptoms
2. Causing a change in the trial protocol (e.g., treatment interruption or discontinuation)
3. lead to a change in medical intervention or concomitant treatment
4. Clinically significant as judged by the investigator (medical and scientific methods should be used to judge whether an isolated

laboratory abnormality is an adverse event)

When the adverse event meets the serious criteria, it should be reported in accordance with the serious adverse event reporting procedure.

9. Statistics

9.1 Sample size

This trial mainly detects a 10% absolute difference in the proportion of the dual antiplatelet group with favorable outcome with 80% power and a one-sided type I error rate of 0.025 to test the non-inferiority, and the proportion of 65% of the dual antiplatelet group will experience a favorable outcome referring to previous report.[12] Thus, the sample size of 716 subjects resulted from these assumptions. According to the ITT principle, the maximum sample size is 752 subjects with 5% lost. Finally, a total of 760 subjects are expected to include in this study, with 380 patients in each group.

9.2 Statistical analysis plan

Intention-to-treat (ITT) analysis will be used to analyze the therapeutic effects of the two groups and all the data will be analyzed with SPSS 20.0 Software. The mean ± standard deviation (SD) will be used if the continuous data are normally distributed, and the median and quartile spacing (IQR) will be used if the continuous data are non-normally distributed. Categorical data are expressed as number (percentage). Difference of the primary endpoint and secondary endpoints such as mRS (0-2) at 90 days, incidence of early neurological improvement, incidence of early neurological deterioration, proportion of symptomatic intracranial hemorrhage in 90 days, incidence of any bleeding events in 90 days, and occurrence of all-cause mortality in 90 days will be compared using binary logistic regression. Change in NIHSS score between two groups will be compared using generalized linear model. Time-to-events of stroke recurrence and other vascular events will be compared using Cox regression. Statistical tests were considered significant when the two-sided *P* value was less than 0.05.

An interim analysis will be performed after 50% of subjects have completed follow-up.

Stratification: The primary endpoint in the ARAMIS study will further be stratified by age (<65 vs. ≥65), diabetes (present vs. not present), time from onset to treatment (0–2 hours vs. >2 hours), stroke ethology (arteriosclerosis vs small vessel lesion), degree of vascular stenosis (≤50% vs. >50%), location of index vessel (anterior circulation vs. posterior circulation). Differences of primary endpoint in above specific stratifications will be assessed by testing for interaction of the pre-set baseline variable with primary endpoint.

9.3 Analysis population

Intention-To-Treat (ITT)

The ITT population includes all subjects who were randomly assigned to a treatment group on an intention-to-treat basis, including subjects who planned to receive treatment but did not actually receive it.

Full Analysis Set (FAS)

According to the basic principles of intention-to-treat analysis, all subjects who received at least one study protocol treatment and at least one post-baseline efficacy evaluation were included in the full analysis set.

Per Protocol Set (PPS)

The protocol-compliant set is a subset of the full analysis set, which will include completion of all treatments or at least the determination of the primary endpoint as required by the research protocol, and good compliance (the ratio of the actual dose to the applied dose is between 80% and 120%). Subjects with no serious protocol violation (the definition of serious protocol violation will be specified in the Statistical Analysis Plan) constitute the per-protocol analysis set for this study.

Safety Set (SS)

The safety analysis population included all subjects who received at least one study protocol treatment and had at least one safety evaluation.

10. Data Management and Monitoring

10.1 Training of study site personnel

Before the first patient is entered into the study in each site, the sponsor (Cerebrovascular Disease Collaboration Innovation Alliance (CDCIA) – Liaoning) will organize and train all study site personnel (medical, nursing, and other staff), including the trial protocol, investigator's brochure, the evaluation of related scales, the use of EDC system, drug management, SAE report procedure, etc. The Principal Investigator will ensure that appropriate training relevant to the study cover all these staff.

10.2 Monitoring of the study

During the study, a staff from CDCIA will have regular contacts with the study site, including visits to:

- Provide the related information and support to the Investigator(s)
- Confirm that the investigational team is adhering to the protocol and data are being accurately and timely recorded in the CRFs
- Confirm that the responsibility of study drug management is being implemented and the drugs are available
- Perform source data verification including deferred informed consent, laboratory results, neuroimaging data, clinical data, and neurological function evaluation (NIHSS, mRS) at baseline and follow-up

CDCIA staff will be available whenever the investigator or other personnel at the center needs information and advice about the study.

Appendix

Appendix 1：National Institutes of Health Stroke Scale (NIHSS)

	Check	Score	Point
1a	**Level of consciousness (0-3)** Verbal or painful stimulation of the patient (left to the choice of the examiner)	**0** Aware, responds briskly. **1** Responds to minor stimuli **2** Responds to repeated or painful stimuli **3** Stereotypic or flaccid response	—
1b	**Consciousness level (0-2)** - "How old are you?" - "What month is this?"	**0** Correct answer to the 2 questions **1** One single correct answer or intubated, or severe dysarthria or language barrier **2** No correct response or aphasic	—
1c	**Consciousness-commands (0-2)** - "Open and close your eyes" - "Close and open your hand" *To be imitated if the command is not followed*	**0** Executed the 2 commands correctly **1** One correct response **2** No response	—
2	**Horizontal oculomotilities (0-2)** Test voluntary and reflex horizontal movements without a heat test (finger following): "Follow my finger"	**0** Normal oculomotility **1** Conjugate deviation of the eyes which may be reduced by voluntary or reflex activity or isolated damage to a cranial nerve **2** Complete paralysis of the side	—
3	**3. Visual field (0-3)** Test the visual field by quadrants (upper and lower) using finger counting or if necessary, the menace blink reflex.	**0** Normal visual field **1** Partial HLH or loss of vision **2** Complete HLH **3** Dual HLH or cortical blindness	—

4	**4. Facial paralysis (0-3)** "Show me your teeth, raise your eyebrows and close your eyes" *To be imitated if command not performed or Pierre Marie and Foix manoeuvre*	**0** Normal **1** Slight central facial paralysis (FP) **2** Clear central PF (total inferior) **3** Dual PF or total PF	__
5	**5. Upper limb motility** 5.1 "Stretch out your arm and left hand" **(0-4)** 5.2 "Stretch out your arm and right hand" **(0-4)** for 10 seconds	**0 N**ormal **1** Resists a weight (arm falls within 10 sec) **2** Does not resist (arm touches the bed before 10 sec). **3** Does not lift limb (contraction without movement) **4** No movement	5a Left upper extremity ____ 5b Right upper limb ____
6	**6. Lower limb motility** 6.1 "Stretch out your left leg" (30°) **(0-4)** 6.2 "Stretch out your right leg" **(0-4)** for 5 seconds	**0** Normal **1** Resists a weight (arm falls within 5 sec) **2** Does not resist (arm touches the bed before 5 sec) **3** Does not lift limb (contraction without movement) **4** No movement	6a Left lower extremity _____ 6b Right lower extremity _____
7	**7. Limb ataxia (0-2)** "Place your index finger on your nose" "Place your heel on the opposite knee" *Bilateral manoeuvre*	**0** Normal or impossible because of paralysis or aphasia **1** Ataxia of one limb **2** Ataxia of 2 limbs ***9** Amputation or joint block*	__
8	**8. Sensitivity (0-2)**	**0** Normal.	

	Examine sensation to pin prick or withdrawal following nociceptive stimulation if confused or aphasic (arm, leg, face, trunk, bilaterally)	**1** Hypoesthesia or aphasia or stupor **2** Severe to total deficit	—
9	**9. Language (0-3)** "Describe the following scene" "Tell me the name of these objects" "Read these phrases" If visual disturbance, identify the objects in a hand and have the words repeated *Assess writing in an intubated patient*	**0** Normal **1** Aphasic but communicates **2** Quasi-impossible communication **3** Total aphasia, mutism or coma	—
10	**10. Dysarthria (0-2)** "Repeat the following words" (*cf.* text 2 p 3) ***including** in aphasic patients*	**0** Normal articulation **1** Comprehensible **2** Incomprehensible, anarthria or mutism ***9** Intubation or mechanical obstruction*	—
11	**11. Extinction or negligence** Test bilateral simultaneous sensitivity Test perception in both temporal visual fields simultaneously Investigate for anosognosia and visuospatial neglect	**0** No extinction or complete HLH (if sensory extinction) and vice versa or aphasia or gives the impression of understanding **1** Extinction of one modality **2** Extinction of several modalities or visuospatial neglect or anosognosia	—

Inspection chart for item 9 and item 10

Reading check chart 1

Please read the following sentences:
know
Down the stairs
home cooking
Review at school
Give a great speech

Reading check chart 2

Please read the following words:
mother
the earth
airplane
silk
Start work on time
Eating grapes did not spit grape skins

NIHSS for comatose patient

- For patients with Item 1a less than 3 points, each item should be assessed one by one.
- Item 1a is rated as 3 only when the patient has no response at all to any noxious stimuli (rubbing the sternum, pressing the orbit, etc.) and only has reflex activity.
- If 1a=3 points, other items should be rated as:
- 1b-Awareness level questions: 2 points
- 1c-Level of Consciousness Instructions: 2 points
- 2-Gaze: According to whether it can be overcome by the head-eye reflex, the score is 1 point if it can be overcome by the head-eye reflex, and 2 points if it cannot be overcome.
- 3-Field of View: Use visual threat for assessment.
- 4-Facial paralysis: 3 points.

- 5, 6-Limb Movement: 4 points for each limb.
- 7-Ataxia: Scores can only be given when there is ataxia. If the patient's muscle strength is decreased and cannot complete the examination of fingers, nose, heels, knees, and tibias, a score of 0 will be given.
- 8-Feeling: 2 points.
- 9-Language: 3 points.
- 10-Dysarthria: 2 points.
- 11-Ignore: Coma means losing all cognitive abilities, so 2 points are given.

How to calculate the total NIHSS score?

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

Items 5 and 6 - "9 = Amputation or Joint Fusion" in Limb Movement

Item 7 - Item in Ataxia that identifies the location of the ataxia, i.e. "Left upper limb 1=Yes, 2=No, 9=Amputation or joint fusion, explain:_____"。

Note:

Score according to the table and record the results. Do not change the score. The score reflects the actual situation of the patient, not what the doctor thinks the patient should be. Quickly check while recording results. Do not train the patient (e.g., repeatedly ask the patient to make an effort) unless instructed to do so.

If some items are not evaluated, they should be explained in detail in the form. Unassessed items should be reviewed with surveillance video and discussed with the examiner.

Appendix 2：Modified Rankin Score (mRS)

Grade	Description
0	No symptoms
1	Symptoms without any incapacity (able to perform all usual activities)
2	Mild incapacity (unable to perform all usual activities but able to look after his/her affairs alone)
3	Moderate incapacity (requires assistance but walks alone)
4	Severe incapacity (requires assistance for walking and physical body needs)
5	Severe incapacity (bedbound, incontinent, permanent surveillance required)
6	Death

Appendix 3：TOAST classification

1 Large atherosclerotic type: requires vascular imaging examination to confirm that the intracranial or extracranial large artery stenosis corresponding to the neurological deficit of cerebral infarction is more than 50% or occluded, and the vascular lesions are consistent with atherosclerotic changes; or there is intracranial or Indirect evidence of stenosis or occlusion of extracranial large arteries, such as imaging (CT or MRI) showing cerebral cortex, brainstem, cerebellum or subcortical infarction with a diameter of >1.5cm, and clinical manifestations are mainly signs of cortical damage, such as aphasia , changes in consciousness, body image disturbance, etc., or signs of brainstem and cerebellum damage. Evidence of at least one atherosclerotic stroke risk factor (such as advanced age, hypertension, hyperlipidemia, etc.) or systemic atherosclerosis (such as plaque, coronary heart disease, etc.) is required. At the same time, cerebral infarction caused by cardio embolism should also be excluded, such as no acute infarction outside the stenosis > 50% or occlusion of intracranial or extracranial large arteries, and no high or moderate risk factors for cardioembolic stroke (see Brain Embolization chapter).

2 Cardiogenic cerebral embolism type: the clinical manifestations and imaging studies are the same as those of large atherosclerotic type. This classification is supported if there is more than one vessel innervation or multisystem embolism. The presence of at least one high or moderate risk factor for cardioembolic stroke was required.

3 Small artery occlusion type: There may be no obvious clinical manifestations or various lacunar syndromes, but no cerebral cortex involvement. The head CT or MRI is required to be normal, or the infarct diameter is less than 1.5cm.

4 Other etiological types: refer to other rare etiologies other than the above three types of clear ethology. Such as blood coagulation disorders, changes in blood components, vasculitis due to various reasons, vascular malformations, connective tissue diseases, dissecting aneurysms, fibrous dystrophy and cerebral infarction.

5 Unexplained type: including two or more etiologies, negative auxiliary examinations, no cause found, and insufficient auxiliary examinations.

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PROTOCOL

Version 2.0 of May 06, 2020

Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS): a prospective, randomized, open-label, blinded-endpoint, multi-centre trial

Principal Investigator:

Prof Hui-Sheng Chen

Department of Neurology

General Hospital of Northern Theatre Command

83 Wenhua Rd

Shenyang, China

Tel: 86-13352452086

Fax: 86-024-28897495

E-mail: chszh@aliyun.com

Table of Contents

Abstract

Title	Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS): a prospective, randomized, open-label, blinded-endpoint, multi-centre trial
Sponsor	Cerebrovascular Disease Collaboration Innovation Alliance (CDCIA) – Liaoning
Objective	To explore the efficacy and safety of dual antiplatelet vs intravenous alteplase for nondisabling acute minor ischemic stroke
Efficacy Outcome	**Primary outcome：** 1. Proportion of modified Rankin Score (mRS, 0–1) at 90±7 days after randomization. **Secondary outcome：** 1. Proportion of mRS (0–2) at 90±7 days after randomization; 2. An ordinal shift of the full range of mRS scores at 90 days; 3. Change in National Institute of Health Stroke Scale (NIHSS) score compared with baseline at 24 hours; 4. Incidence of early neurological improvement, defined as more than or equal to 2 NIHSS scores decrease, compared with baseline at 24 hours; 5. Incidence of early neurological deterioration, defined as more than or equal to 2 NIHSS scores increase, but not result of cerebral hemorrhage, compared with baseline at 24 hours; 6. Occurrence of stroke or other vascular events at 90±7 days; 7. Occurrence of all-cause mortality at 90±7 days.
Safety Outcome	1. Proportion of symptomatic intracranial hemorrhage at 90±7 days; 2. Occurrence of any bleeding events at 90±7 days.
Trial Design	This is a prospective, randomized, open-label, blinded-endpoint, multi-centre trial. Subjects included are randomly and divided into two groups: the experiment group and the control group. Follow-up was to be performed at baseline, 24 hours, 7±1 days, 12±2 days, and 90±7 days after

	randomization. All the outcome assessors were masked to the allocation assignment and follow-up.
Trial Population	Patients with nondisabling acute minor ischemic stroke
Sample Size	760
Inclusion criteria	1. Patient age≥18 years; 2. Acute ischemic stroke receiving intravenous thrombolysis within 4.5 hours; 3. NIHSS scores ≤ 5, with ≤ 1 on the NIHSS score in single item scores such as vision, language, neglect and single limb and no score in consciousness item; 4. Ischemic stroke confirmed by head CT or MRI; 5. Signed informed consent.
Exclusion criteria	1. Serve neurological deficit before stroke onset (premorbid mRS ≥ 2); 2. Obvious head injuries or strokes within 3 months; 3. Subarachnoid hemorrhage; 4. History of intracranial hemorrhage; 5. Intracranial tumor, arteriovenous malformation or aneurysm; 6. Intracranial or spinal cord surgery within 3 months; 7. Arterial puncture at a noncompressible site within the previous 7 days; 8. Gastrointestinal or urinary tract hemorrhage within the previous 21 days; 9. Major surgery within 1 month; 10. Uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg after drug treatment); 11. Blood glucose < 50 mg/dl (2.7 mmol/L); 12. Heparin therapy or oral anticoagulation therapy within 48 hours; 13. Platelet count of < 100,000/mm^3 (This does not need to be verified prior to randomization if clinical abnormality is not suspected); 14. Oral warfarin is being taken and INR > 1.6; 15. Abnormal APTT;

	16. Pregnancy; 17. Neurological deficit after epileptic seizures; 18. Myocardial infarction within 3 months; 19. Cerebral infarction with definite anticoagulation indications, such as cerebral infarction caused by cardiogenic embolism; 20. Oral administration is not allowed due to dysphagia; 21. Allergy to test drugs; 22. Other serious illness that would confound the clinical outcome at 90 days; 23. Participating in other clinical trials within 3 months; 24. Patients not suitable for this trial considered by investigators.
Trial Cycle	All included patients were given dual antiplatelet or intravenous alteplase on the guideline-based therapy and were followed up at baseline, 24 hours, 7 ± 1 days, 12 ± 2 days, and 90 ± 7 days after randomization, respectively.
Treatment Regimens	Patients with nondisabling acute minor ischemic stroke within 4.5 hours of onset were randomly divided into the experimental group and the control group in a ratio of 1:1. The patients in the experimental group will receive dual antiplatelet (orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily) for 10–14 days; The patients in the control group will receive intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, followed by guideline-based antithrombotic treatment 24 hours after thrombolysis.
Procedure	**Screening period:** On day 0 (baseline period), it is necessary to complete enrolment screening, and collect demographic characteristics, medical history (including history of hypertension, diabetes and drug treatment history), brain imaging (computer tomography, computed tomography angiography or magnetic resonance imaging), neurological measurements (NIHSS score, mRS score), haematological examination (blood routine, blood glucose, hepatic and renal function, coagulation routine, urine routine, electrocardiogram, etc) and other information. **Treatment period:** After randomization, the patients were given orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days

	and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days (experimental group) or intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg (control group), and then patients were given standard guideline-based antithrombotic treatment. **Follow-up period:** NIHSS score was assessed at 24 hours, 7 ± 1 days, and 12 ± 2 days after randomization. The mRS score was assessed at 90 ± 7 days after randomization. All concomitant medications, adverse events, stroke recurrence and other vascular events of each visit were recorded since the last visit. All the adverse events of included subjects should be recorded and tracked until properly resolved. All the serious adverse events of included subjects should be recorded and tracked, even if the subjects have finished the trial, until the events were resolved, or stabilization judged by the investigator.
Concomitant Treatment	Guideline-based treatment
Statistical Analysis	Intention-to-treat analysis will be used to compare the treatment effect between two groups and all the data will be analyzed with Statistical Product and Service Solutions, SAS, and R software. The mean standard deviation will be used if the continuous data were normally distributed, and the median and interquartile range will be used if the continuous data were non-normally distributed. Categorical data will be expressed as number (percentage). When comparing the data of two groups, t test or Mann–Whitney test was used for continuous data, and chi-square test was used for categorical data. The proportion of mRS 0-1 at 90 days, mRS 0-2 at 90 days, early neurological improvement within 24 hours, early neurological deterioration within 24 hours, symptomatic intracranial haemorrhage at 90 days, any bleeding events at 90 days, and all-cause mortality within 90 days between two groups will be compared through binary logistic analysis with calculated risk difference and 95% confidence interval. The occurrence of time-to-events of stroke and other vascular events will be compared through cox logistic analysis with calculated hazard ratio and 95% confidence interval. The change in NIHSS at 24 hours compared baseline will be

	compared through generalized liner model. Statistical tests were considered significant when the two-sided *P* value was less than 0.05.
Sites Number	20
Duration	18 months

Abbreviation

Abbreviation	Full title
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATS	As Treated Set
BUN	Blood Urea Nitrogen
CDCIA	Cerebrovascular Disease Collaboration Innovation Alliance
Cr	Creatinine
CT	Computed Tomography
CTA	Computed Tomography Angiography
CRF	Case Report Form
DBIL	Direct Bilirubin
ECG	Electrocardiogram
FAS	Full Analysis Set
FIB	Human Fibrinogen
GCP	Good Clinical Practice
GLU	Glucose
HGB	Hemoglobin
HDL	High Density Lipoprotein
ID	Identification
ITT	Intention to Treat
IQR	Inter-Quartile Range
LDL	Low Density Lipoprotein
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NRBC	Urine Red Blood Cell
NWBC	Urine White Blood Cell

NIHSS	National Institute of Health Stroke Scale
PT	Prothrombin Time
PRO	Urine Protein
PPS	Per Protocol Set
PLT	Platelets
RBC	Red Blood Cell
RIC	Remote Ischemic Conditioning
SCr	Serum Creatinine
SAE	Serious Adverse Event
SD	Standard Deviation
SS	Safety Set
TBIL	Total Bilirubin
TC	Total Cholesterol
TG	Triglyceride
TOAST	Trial of Org 10 172 in acute stroke treatment
TT	Thrombin Time
WBC	White Blood Cell

1.Background and current state of knowledge

Acute ischemic stroke (AIS) is one of common diseases with significant morbidity, mortality, and disability. A wide array of studies have confirmed that intravenous thrombolytic therapy with alteplase can effectively improve the functional prognosis in AIS,[1] thus all guidelines recommended the intravenous thrombolytic therapy with alteplase for AIS within 4.5 hours from stroke onset.[2]

Minor stroke is usually defined as NIHSS score ≤ 3 or 5, that accounts for 1/2-2/3 of AIS,[3-4] but the evidence of intravenous thrombolysis of those without clearly disabling deficits is still insufficient.[5-6] A study from Canada shows that 28.5% of patients with minor stroke and without receiving alteplase therapy were unable to walk independently when discharged.[7] The PRISMS study is designed to further compare the efficacy and safety of intravenous alteplase vs. aspirin alone in patients with minor stroke (NIHSS ≤ 5) and without clearly disabling deficits.[8] Unfortunately, the study has been prematurely terminated due to the sponsorship reason in 2018, with only 313 cases enrolled. The preliminary results show that there is no significant difference of the 90-day neurological function between the two groups, while the treatment group with alteplase has a higher rate of symptomatic intracranial hemorrhage than the control group with aspirin alone. Furthermore, the guidelines recommend that once the patients received thrombolysis, antithrombotic therapy cannot be given within 24 hours after thrombolysis. The recommendation makes clinical doctors puzzled to treat the early neurological deterioration, especially in minor stroke patients.

The CHANCE trial in 2013 shows that the efficacy of the combination of aspirin with clopidogrel is superior to aspirin alone with minor stroke (NIHSS ≤ 3) or TIA (ABCD2 ≤ 4).[9] The post hoc analysis of the CHANCE trial in 2017 indicates that bleeding risk outweighs benefit after the 10th day.[10] The POINT study in 2018 further confirmed the efficacy and safety of intensive antiplatelet therapy in minor stroke within 12 hours of onset.[11]

2.Objectives of the trial

2.1 Hypothesis tested

This study intends to demonstrate that dual antiplatelet have similar effect with alteplase on 90-day functional outcome in nondisabling mild stroke population, and have more less symptomatic intracranial hemorrhage.

2.2 Primary objective

To test the hypothesis that dual antiplatelet have similar effect with alteplase on 90-day excellent functional outcome in nondisabling mild stroke population.

2.3 Secondary objectives

1. To determine the proportion of favorable functional outcome at 90 days by treatment group.
2. To determine an ordinal shift of the full range of mRS scores at 90 days.
3. To determine change in neurological function at 24 hours by treatment group.
4. To determine occurrence of early neurological improvement at 24 hours by treatment group.
5. To determine occurrence of early neurological deterioration at 24 hours by treatment group.
6. To determine occurrence of stroke or other vascular events at 90 days by treatment group.
7. To determine all-cause mortality at 90 days by treatment group.

3. Design and selection of patients

3.1 Trial plan

This is a multi-centre, randomized, open-label, blinded-endpoint, non-inferiority trial.

The patients were randomly divided into the two groups:

Experimental group: orally administered with 300 mg clopidogrel and 100 mg

aspirin after randomization, followed by 75 mg clopidogrel and 100 mg aspirin for 10-14 days;

Control group: intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg after randomization;

Both groups of patients were given standard guideline-based treatment until to 90 days.

Follow-up was performed at baseline, 24 hours, 7 ± 1 days, 12 ± 2 days, and 90 ± 7 days after randomization, respectively.

3.**2 Selection criteria:**

Inclusion criteria: in order to be eligible, the patients must meet all of the following criteria:

1. Patient age≥18 years;
2. Acute ischemic stroke receiving intravenous thrombolysis within 4.5 hours;
3. NIHSS scores ≤ 5, with ≤ 1 on the NIHSS score in single item scores such as vision, language, neglect and single limb and no score in consciousness item;
4. Ischemic stroke confirmed by head CT or MRI;
5. Signed informed consent.

Exclusion criteria: in order to be included the patients must not have any of the following criteria:

1. Serve neurological deficit before stroke onset (premorbid mRS ≥ 2);
2. Obvious head injuries or strokes within 3 months;
3. Subarachnoid hemorrhage;
4. History of intracranial hemorrhage;
5. Intracranial tumor, arteriovenous malformation or aneurysm;
6. Intracranial or spinal cord surgery within 3 months;
7. Arterial puncture at a noncompressible site within the previous 7 days;
8. Gastrointestinal or urinary tract hemorrhage within the previous 21 days;
9. Major surgery within 1 month;

10. Uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg after drug treatment);
11. Blood glucose < 50 mg/dl (2.7 mmol/L);
12. Heparin therapy or oral anticoagulation therapy within 48 hours;
13. Platelet count of < 100,000/mm^3 (This does not need to be verified prior to randomization if clinical abnormality is not suspected);
14. Oral warfarin is being taken and INR > 1.6;
15. Abnormal APTT;
16. Pregnancy;
17. Neurological deficit after epileptic seizures;
18. Myocardial infarction within 3 months;
19. Cerebral infarction with definite anticoagulation indications, such as cerebral infarction caused by cardiogenic embolism;
20. Oral administration is not allowed due to dysphagia;
21. Allergy to test drugs;
22. Other serious illness that would confound the clinical outcome at 90 days;
23. Participating in other clinical trials within 3 months;
24. Patients not suitable for this trial considered by investigators.

Suspension Criteria:

Trial suspension means that the clinical trial has not finished as planned, and all trials are stopped in the middle period. The purpose of trial suspension is to protect the rights and interests of subjects, ensure the quality of the trial, and avoid unnecessary economic losses:

1. The proportion of serious adverse events during the trial is higher than 10%, and Data Monitoring Committee (DMC) has the right to terminate the study unconditionally.

2. Trial should be discontinued when one treatment is found to be significantly better than the other.

3.3 Duration of participation for each subject:

Each subject will be followed up in the trial for 3 months.

3.4 Randomization and measures to reduce bias:

In the trial, included patients were randomly assigned into the experiment group or control group using a randomization (1:1) method with minimization algorithm through a computer-generated random sequence that was centrally administrated via a password-protected, web-based program at http://aramis.medsci.cn (Shanghai Meisi Medical Technology Co., Ltd). The number of randomized patients planned for this study is approximately 760.

Final follow-up was done at 90 days, in person or by telephone, by one or two trained and certified assessors in each site who were unaware of the randomized allocation assignment. Central adjudication of clinical and safety outcomes was also done by assessors who were unaware of the randomized allocation assignment or clinical details.

4 Plan and conduct of the trial

4.1 Clinical trial flow chart

Item \ Period	Screening	Treatment	Follow-up		
Visit	1	2	3	4	5
Time	0 day[1]	24 hours after randomization	7 ± 1 days after randomization	12 ± 2 days after randomization	90 ± 7 days after randomization
Inclusion/Exclusion Criteria	x				
Sign informed consent	x				
Randomization	x				
Demographic characteristics[2]	x				
Medical history	x				
Physical examination	x	x	x	x	x
Brain CT/MRI	x	x			
TOAST classification				x	
ECG（12 lead）	x			x	
24h ambulatory ECG [3]				x [3]	
Blood routine [4]	x			x	
Urine routine [5]	x				
Blood biochemistry [6]	x			x	
Coagulation routine [7]	x	x	x	x	
NIHSS score	x	x	x	x	
mRS score	x				x
Concomitant medication		x	x	x	x
Adverse events		x	x	x	x
Stroke recurrence and other		x	x	x	x

vascular events [8]					

1. Day 0: limited to the period from the onset of stroke to the time before randomization;
2. Demographic characteristics: The age of the subjects is calculated based on the identification (ID) card information;
3. 24h ambulatory electrocardiogram: required to be completed within 7 days of admission;
4. Blood routine: including total number of red blood cells (RBC), total number of white blood cells (WBC), platelet count (PLT), hemoglobin (HGB). The results are measured within 24 hours before screening;
5. Urine routine: including urine red blood cells (NRBC), urine white blood cells (NWBC), urine protein (PRO), and urine sugar (GLU). The results are measured within 24 hours before screening;
6. Blood biochemistry: Hepatic function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL); Renal function tests: serum urea nitrogen (BUN), Creatinine (Cr); Blood Glucose (GLU); Lipid, including total cholesterol (TC), triglycerides (TG), high density cholesterol (HDL), low density cholesterol (LDL). The results are measured within 24 hours before screening;
7. Coagulation examination: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT). The results are measured within 24 hours before screening;
8. Stroke recurrence and other vascular events: occurrence of stroke recurrence and other vascular events within 90 days from randomization.

4.2 Study completion

The study is considered to be finished when the last visit of the last subject in the trial is completed.

4.3 Study termination

The sponsor reserves the right to close the study centre or suspend the study at any time. The study centre should be closed after the study is completed. The centre is considered closed after all required documentation and study supplies have been collected and a centre closure visit has been conducted.

Investigators can also request to suspend the study, but they must give reasonable reasons in advance.

Reasons for the sponsor or investigator to close the centre in advance may include, but are not limited to:

1. Investigator fails to comply with the requirements of the study protocol, IEC/IRB or local regulatory authorities, sponsor's operating procedures or GCP guidelines;
2. Security considerations;
3. Investigators are not recruiting enough subjects.

5. Study medications

5.1 Identification of study drugs

Alteplase (specification: 20 mg/ampoule or 50 mg/ ampoule, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer: Boehringer Ingelheim Co., Ltd)

Clopidogrel tablet (specification: 75 mg/tablet, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer: Shenzhen Salubris Pharmaceutical Co., Ltd)

Aspirin enteric-coated tablet (specification: 100 mg/tablet, batch size: subject to the actual batch number of the drug issued, storage: sealed preservation, manufacturer:

ORIGINAL PHARMACOLABO Corporation)

5.2 Responsibilities of study drugs administration

The investigator of the clinical trial is responsible for ensuring that the study drugs received by the study centre are counted and recorded during the whole process of the study, and the distribution and recovery of the drug must be recorded in the Drug Dispensing and Recycling Record Form. The original packaging of the study drug must be returned, whether there is any remaining study drug in it. Returned study drugs should be kept at the site designated by the study centre and separate from unused study drugs. Do not destroy or mix medicines in different packages until inspectors have counted them. The use of the study drug must strictly follow the instructions in the protocol and the package label. The sponsor monitor must be allowed to count and reconcile unused and returned study drugs at each monitoring. Unused or returned study drugs to be destroyed must be recorded on the Drug Recycling Record Form and returned to the medication destruction centre.

6. Treatment administered to included subjects

6.1 Description of the treatment required to conduct the study

The experimental group were administrated orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days. Patients were then given standard guideline-based antithrombotic therapy from 14 days to 90 days.

The control group were administrated intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg, followed by guideline-based antithrombotic therapy from 24 hours after intravenous thrombolysis to 90 days.

6.2 Permitted and prohibited medical drugs and treatments in the study

There are no specific medical treatments for this study.

7. Outcome measurements

7.1 Primary efficacy outcome

Proportion of mRS (0−1) at 90±7 days after randomization.

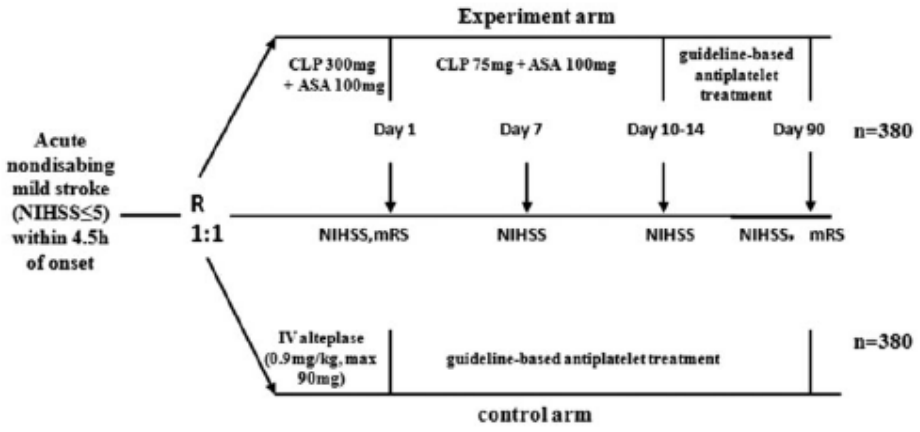
7.2 Secondary efficacy outcomes

1. Proportion of mRS (0−2) at 90±7 days after randomization;
2. An ordinal shift of the full range of mRS scores at 90 days;
3. Change in National Institute of Health Stroke Scale (NIHSS) score compared with baseline at 24 hours;
4. Incidence of early neurological improvement, defined as more than or equal to 2 NIHSS scores decrease, compared with baseline at 24 hours;
5. Incidence of early neurological deterioration, defined as more than or equal to 2 NIHSS scores increase, but not result of cerebral hemorrhage, compared with baseline at 24 hours;
6. Occurrence of stroke or other vascular events at 90±7 days;
7. Occurrence of all-cause mortality at 90±7 days.

7.3 Safety outcomes

1. Proportion of symptomatic intracranial hemorrhage at 90±7 days;
2. Occurrence of any bleeding events at 90±7 days.

7.4 Study procedure



7.5 Study periods

Screening period: On day 0 (baseline period), it is necessary to complete enrolment screening, and collect demographic characteristics, medical history (including history of hypertension, diabetes and drug treatment history), brain imaging (computer tomography, computed tomography angiography or magnetic resonance imaging), neurological measurements (NIHSS score, mRS score), hematological examination (blood routine, blood glucose, hepatic and renal function, coagulation routine, urine routine, electrocardiogram, etc.) and other information.

Treatment period: After randomization, the two groups were given orally 300-mg clopidogrel on the first day followed by 75 mg daily for 10–14 days and 100-mg aspirin on the first day immediately followed by 100 mg daily for 10–14 days (experimental group) or intravenous alteplase with standard dose of 0.9 mg/kg, up to a maximum of 90 mg (control group), and then patients were given standard guideline-based treatment.

Follow-up period: NIHSS score was assessed at 24 hours, 7 ± 1 days, and 12 ± 2 days after randomization. The mRS score was assessed at 90 ± 7 days after randomization. All concomitant medications, adverse events, stroke recurrence and other vascular events of each visit were recorded since the last visit.

All the adverse events of included subjects should be recorded and tracked until properly resolved.

All the serious adverse events of included subjects should be recorded and tracked, even if the subjects have finished the trial, until the events were resolved, or stabilization judged by the investigator.

8. Description of safety assessment parameters

8.1 Evaluate clinical safety:

Physical examinations, including neurological assessments, imaging studies, were performed at baseline, Hour 24, Day 7 ± 1, Day 12 ± 2, and Day 90 ± 7 after

randomization; adverse event of each visit was collected after baseline visit.

Adverse events monitoring

All information on adverse events, whether mentioned by subjects, discovered by investigators, or discovered through physical examination, laboratory tests, and other methods, should be recorded on the adverse events page of the case report form and handled in accordance with appropriate regulations and report.

Adverse Event (AE)

The adverse event (AE) is any adverse medical event that occurs in a study subject during a study that is not necessarily related to this treatment. Thus, the adverse event (AE) can be any unfavorable and unexpected sign (including abnormal laboratory findings), symptom or disease temporally related to the use of study drugs, regardless of whether it is related to the study drugs or not.

It is included that any events that are new or that have worsened in severity and frequency from baseline, including abnormal results from diagnostic methods such as laboratory tests.

Note: Adverse event collection begins with signed informed consent.

Serious Adverse Event (SAE)

Serious adverse event (SAE) is any adverse medical event at any dose that meets one or more of the following criteria:

- cause death (note: death is a consequence, not an event);
- Life-threatening (Note: "Life-threatening" means that the subject is in immediate danger of death at the time of the event, not the assumption that death would have occurred if the event is more severe);
- cause significant or permanent disability or impairment of organ function;
- Teratogenic and birth defects;

- Causing or prolonging hospitalization;
- Significant medical event or need for intervention (occur without treatment)’

Note: Any event requiring hospitalization (or prolonged hospitalization) that occurs during the subject's participation in the study must be reported as a serious adverse event. The following circumstances leading to hospitalization are not considered serious adverse events:

- Hospitalization for social reasons other than adverse events
- Hospitalization for a scheduled surgery or other treatment or examination prior to study entry (must be recorded on the case report form)
- Hospitalization for elective surgery or treatment or examination due to anticipated disease progression

8.2 Safety assessment

For all adverse events in clinical studies, the following factors must be evaluated for safety:

- Severity criteria for SAE
- The causal relationship between the event and the investigational drug
- Severity of incident
- Anticipation of events

Causal relationship between events and the study drugs

Regardless of serious adverse events or non-serious adverse events, the investigator must evaluate the relevance of the event to the use of the study drugs according to the following criteria:

Evaluating association between adverse events and study treatments Criteria

5-level classification	Judgment criteria
Definitely related	The time of initiation of use is reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event reduce or disappear after study treatment dose reduction or discontinuation; similar adverse events (non-essential) can occur with re-use of study treatment.
Probably related	The time of initiation of use is reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; it is not sure whether similar adverse events (non-essential) can occur with re-use of study treatment.
Probably unrelated	The time of initiation of use is not reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse

5-level classification	Judgment criteria
	event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; it is not sure whether similar adverse events (non-essential) can occur with re-use of study treatment.
Definitely unrelated	The time of initiation of use is not reasonably related to the time of occurrence of the adverse event; the adverse event corresponds to the known adverse reaction type of the study treatment; the occurrence of the adverse event can or cannot be explained by factors other than the study treatment (such as concomitant medication); the adverse event can or cannot reduce or disappear after study treatment dose reduction or discontinuation; similar adverse events (non-essential) cannot occur with re-use of study treatment.
Unjudged	The judgment cannot be made due to incomplete, contradictory information or the fact that the information cannot be supplemented and verified.

Table of Correlation Evaluation Criteria for Adverse Events and Treatment Use

	Definitely related	Probably related	Probably unrelated	Definitely unrelated	Unjudged
Have a reasonable chronological order with the study drugs	+	+	+	−	?
For the known reaction type of the study drugs	+	+	−	−	?
Explanation for reasons other than available research equipment	−	±	±	+	?
Responses lessen after decompression of study drugs	+	±	±	−	?
The reaction reappears after the study drugs is reused	+ or ?	?	?	−	?

Note: "+" in the table is affirmative; "-" is negative; "±" is difficult to affirm or deny; "?" indicates that the situation is unknown.

Severity Criteria

Severity should be assessed according to the following graded descriptions:

- Mild: No symptoms or discomfort; does not interfere with daily activities and function; usually does not require medication to relieve symptoms.
- Moderate: Symptoms cause significant discomfort; daily activities and function are affected; study participation can be continued; intervention required to relieve symptoms.
- Severe: Severe causes severe discomfort; symptoms result in loss of function and significantly interfere with daily activities; in severe cases,

study treatment can be discontinued; symptomatic treatment and/or hospitalization are required.

The investigator should use clinical judgment to assess the severity of the event (e.g., abnormal laboratory results) from the subject's direct experience.

8.3 Safety report

All adverse events

All adverse events, regardless of their severity, nature of severity, or their causal relationship to study treatment, from the time of signed informed consent until the last follow-up visit (90 days after first use of the drugs), are to be recorded in the original and recorded in medical terms on the clinical research form. When symptoms and signs are caused by common causes, a diagnosis of the disease should be given where possible (e.g., cough, runny nose, sneezing, sore throat, and headache should be reported as "upper respiratory tract infection"). The investigator must make a judgment on the causal relationship between the adverse event and the study treatment and record it on the clinical research form. All treatments for adverse events should be documented in the original medical record and reported as requested by the sponsor.

All serious adverse events in clinical research must be reported to the ethics committee of the centre, the principal investigator of the centre, the sponsor, the contract research organization, the research team leader unit, and the adverse reaction monitoring centre within 24 hours; Report to the ethics committee and data and safety monitoring committee of the team leader unit within 7 natural days after being informed. Investigators must complete a serious adverse event form to record the time, severity, duration, actions taken and outcomes of serious adverse events. Any follow-up information for serious adverse events should also be reported in writing within 24 hours according to the above process.

All serious adverse events that do not resolve at study termination or subject early withdrawal must be followed up to any of the following:

1. Incident mitigation

2. Events are stable
3. If the baseline value is known, the event returns to the baseline value
4. Events can be attributed to other drugs or factors not related to study
5. It is unlikely that any further information will be available (subject or physician refuses to provide further information and remains lost to follow-up after various follow-up attempts)

Death

Death is the result of an event. The death of a subject in a clinical trial, regardless of whether the event was expected or drug-related, would be considered a serious adverse event. Events leading to death should be recorded in medical terms and reported on the eCRF. All causes of death (death diagnoses) must be reported as serious adverse events. Investigators should make every effort to obtain and send death certificates and autopsy reports to designated personnel.

Pregnancy

If the researcher finds that the subject is pregnant during the research, the researcher should fill out the "Pregnancy Incident Report Form" within 24 hours after learning and report it to the clinical research supervisor, and notify the project leader by phone

Abnormal pregnancy results, considered serious adverse events, should be reported in accordance with the Serious Adverse Event Reporting Procedure.

Abnormal laboratory test results

During the study, when the results of laboratory tests meet the following conditions, they must be regarded as adverse events and recorded in medical terms on the adverse events of the CRF:

1. Accompanying clinical symptoms
2. Causing a change in the trial protocol (e.g., treatment interruption or discontinuation)
3. lead to a change in medical intervention or concomitant treatment
4. Clinically significant as judged by the investigator (medical and scientific methods should be used to judge whether an isolated

laboratory abnormality is an adverse event)

When the adverse event meets the serious criteria, it should be reported in accordance with the serious adverse event reporting procedure.

9. Statistics

9.1 Sample size

According to our recent unpublished data, the proportion of expected excellent functional outcome (mRS 0-1) at 90 days in control group is estimated to be about 87%, and the proportion in the experimental group is estimated to be about 89.5% based on PRISMS.[8] The margin of non-inferiority was defined as 4.5% in our trial, which was based on the subset analysis of the third international stroke trial (IST-3) showing a 9% absolute difference in the proportion of favorable outcome in minor nondisabling patients treated versus untreated with intravenous alteplase.[13] Using power = 80% and $\alpha = 0.05$ to carry out the two-side test, the required sample size to test the non-inferiority hypothesis is 666. In consideration of 12% lost to follow-up, the total sample size is 757. Therefore, this study still included 760 patients, with 380 patients in each group.

9.2 Statistical analysis plan

Intention-to-treat (ITT) analysis will be used to analyze the therapeutic effects of the two groups and all the data will be analyzed with SPSS 23.0 Software, SAS software or R software. The mean ± standard deviation (SD) will be used if the continuous data are normally distributed, and the median and quartile spacing (IQR) will be used if the continuous data are non-normally distributed. Categorical data are expressed as number (percentage). Difference of the primary endpoint and secondary endpoints such as mRS (0-2) at 90 days, incidence of early neurological improvement, incidence of early neurological deterioration, proportion of symptomatic intracranial hemorrhage in 90 days, incidence of any bleeding events in 90 days, and occurrence of all-cause mortality in 90 days will be compared using binary logistic regression. Change in NIHSS score between two groups will be compared using generalized

linear model. Time-to-events of stroke recurrence and other vascular events will be compared using Cox regression. Statistical tests were considered significant when the two-sided *P* value was less than 0.05.

Stratification: The primary endpoint in the ARAMIS study will further be stratified by age (<65 years vs. ≥65 years), sex (male vs. female), diabetes (present vs. not present), NIHSS score at randomisation (0-3 vs. 4-5), time from onset to treatment (<2 hours vs. ≥2 hours), stroke etiology (arteriosclerosis vs. small vessel lesion), degree of vascular stenosis (≤ 50% vs. > 50%), location of index vessel (anterior circulation vs. posterior circulation). Differences of primary endpoint in above specific stratifications will be assessed by testing for interaction of the pre-set baseline variable with primary endpoint.

9.3 Analysis population

Intention-To-Treat (ITT)

The ITT population includes all subjects who were randomly assigned to a treatment group on an intention-to-treat basis, including subjects who planned to receive treatment but did not actually receive it.

Full Analysis Set (FAS)

According to the basic principles of intention-to-treat analysis, all subjects who received at least one study protocol treatment and at least one post-baseline efficacy evaluation were included in the full analysis set.

Per Protocol Set (PPS)

The protocol-compliant set is a subset of the full analysis set, which will include completion of all treatments or at least the determination of the primary endpoint as required by the research protocol, and good compliance (the ratio of the actual dose to the applied dose is between 80% and 120%). Subjects with no serious protocol violation (the definition of serious protocol violation will be specified in the Statistical Analysis Plan) constitute the per-protocol analysis set for this study.

As Treated Set (ATS)

As-treated (AT) population is based on the treatment actually received. There is no single CRF question that determines the As-treated arm, and the arm will be determined by the trial statistician.

Safety Set (SS)

The safety analysis population included all subjects who received at least one study protocol treatment and had at least one safety evaluation.

10. Data Management and Monitoring

10.1 Training of study site personnel

Before the first patient is entered into the study in each site, the sponsor (Cerebrovascular Disease Collaboration Innovation Alliance (CDCIA) – Liaoning) will organize and train all study site personnel (medical, nursing, and other staff), including the trial protocol, investigator's brochure, the evaluation of related scales, the use of EDC system, drug management, SAE report procedure, etc. The Principal Investigator will ensure that appropriate training relevant to the study cover all these staff.

10.2 Monitoring of the study

During the study, the staffs from CDCIA and independent contract research organization (Liaoning Zhongshuang Medical Technology Co., Ltd.) will have regular contacts with the study site, including visits to:

- Provide the related information and support to the Investigator(s)
- Confirm that the investigational team is adhering to the protocol and data are being accurately and timely recorded in the CRFs
- Confirm that the responsibility of study drug management is being implemented and the drugs are available
- Perform source data verification including deferred informed consent, laboratory results, neuroimaging data, clinical data, and neurological function evaluation (NIHSS, mRS) at baseline and follow-up

CDCIA staff will be available whenever the investigator or other personnel at the center needs information and advice about the study.

Appendix

Appendix 1：National Institutes of Health Stroke Scale (NIHSS)

	Check	Score	Point
1a	**Level of consciousness (0-3)** Verbal or painful stimulation of the patient (left to the choice of the examiner)	**0** Aware, responds briskly. **1** Responds to minor stimuli **2** Responds to repeated or painful stimuli **3** Stereotypic or flaccid response	—
1b	**Consciousness level (0-2)** - "How old are you?" - "What month is this?"	**0** Correct answer to the 2 questions **1** One single correct answer or intubated, or severe dysarthria or language barrier **2** No correct response or aphasic	—
1c	**Consciousness-commands (0-2)** - "Open and close your eyes" - "Close and open your hand" *To be imitated if the command is not followed*	**0** Executed the 2 commands correctly **1** One correct response **2** No response	—
2	**Horizontal oculomotilities (0-2)** Test voluntary and reflex horizontal movements without a heat test (finger following): "Follow my finger"	**0** Normal oculomotility **1** Conjugate deviation of the eyes which may be reduced by voluntary or reflex activity or isolated damage to a cranial nerve **2** Complete paralysis of the side	—
3	**3. Visual field (0-3)** Test the visual field by quadrants (upper and lower) using finger counting or if necessary, the menace blink reflex.	**0** Normal visual field **1** Partial HLH or loss of vision **2** Complete HLH **3** Dual HLH or cortical blindness	—

4	**4. Facial paralysis (0-3)** "Show me your teeth, raise your eyebrows and close your eyes" *To be imitated if command not performed or Pierre Marie and Foix manoeuvre*	**0** Normal **1** Slight central facial paralysis (FP) **2** Clear central PF (total inferior) **3** Dual PF or total PF	__
5	**5. Upper limb motility** 5.1 "Stretch out your arm and left hand" **(0-4)** 5.2 "Stretch out your arm and right hand" **(0-4)** for 10 seconds	**0 N**ormal **1** Resists a weight (arm falls within 10 sec) **2** Does not resist (arm touches the bed before 10 sec). **3** Does not lift limb (contraction without movement) **4** No movement	5a Left upper extremity ____ 5b Right upper limb ____
6	**6. Lower limb motility** 6.1 "Stretch out your left leg" (30°) **(0-4)** 6.2 "Stretch out your right leg" **(0-4)** for 5 seconds	**0** Normal **1** Resists a weight (arm falls within 5 sec) **2** Does not resist (arm touches the bed before 5 sec) **3** Does not lift limb (contraction without movement) **4** No movement	6a Left lower extremity _____ 6b Right lower extremity _____
7	**7. Limb ataxia (0-2)** "Place your index finger on your nose" "Place your heel on the opposite knee" *Bilateral manoeuvre*	**0** Normal or impossible because of paralysis or aphasia **1** Ataxia of one limb **2** Ataxia of 2 limbs ***9** Amputation or joint block*	__
8	**8. Sensitivity (0-2)**	**0** Normal.	

	Examine sensation to pin prick or withdrawal following nociceptive stimulation if confused or aphasic (arm, leg, face, trunk, bilaterally)	**1** Hypoesthesia or aphasia or stupor **2** Severe to total deficit	—
9	**9. Language (0-3)** "Describe the following scene" "Tell me the name of these objects" "Read these phrases" If visual disturbance, identify the objects in a hand and have the words repeated *Assess writing in an intubated patient*	**0** Normal **1** Aphasic but communicates **2** Quasi-impossible communication **3** Total aphasia, mutism or coma	—
10	**10. Dysarthria (0-2)** "Repeat the following words" (*cf.* text 2 p 3) ***including** in aphasic patients*	**0** Normal articulation **1** Comprehensible **2** Incomprehensible, anarthria or mutism ***9** Intubation or mechanical obstruction*	—
11	**11. Extinction or negligence** Test bilateral simultaneous sensitivity Test perception in both temporal visual fields simultaneously Investigate for anosognosia and visuospatial neglect	**0** No extinction or complete HLH (if sensory extinction) and vice versa or aphasia or gives the impression of understanding **1** Extinction of one modality **2** Extinction of several modalities or visuospatial neglect or anosognosia	—

Inspection chart for item 9 and item 10

Reading check chart 1

Please read the following sentences:
know
Down the stairs
home cooking
Review at school
Give a great speech

Reading check chart 2

Please read the following words:
mother
the earth
airplane
silk
Start work on time
Eating grapes did not spit grape skins

NIHSS for comatose patient

- For patients with Item 1a less than 3 points, each item should be assessed one by one.
- Item 1a is rated as 3 only when the patient has no response at all to any noxious stimuli (rubbing the sternum, pressing the orbit, etc.) and only has reflex activity.
- If 1a=3 points, other items should be rated as:
- 1b-Awareness level questions: 2 points
- 1c-Level of Consciousness Instructions: 2 points
- 2-Gaze: According to whether it can be overcome by the head-eye reflex, the score is 1 point if it can be overcome by the head-eye reflex, and 2 points if it cannot be overcome.
- 3-Field of View: Use visual threat for assessment.
- 4-Facial paralysis: 3 points.

- 5, 6-Limb Movement: 4 points for each limb.
- 7-Ataxia: Scores can only be given when there is ataxia. If the patient's muscle strength is decreased and cannot complete the examination of fingers, nose, heels, knees, and tibias, a score of 0 will be given.
- 8-Feeling: 2 points.
- 9-Language: 3 points.
- 10-Dysarthria: 2 points.
- 11-Ignore: Coma means losing all cognitive abilities, so 2 points are given.

How to calculate the total NIHSS score?

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

Items 5 and 6 - "9 = Amputation or Joint Fusion" in Limb Movement

Item 7 - Item in Ataxia that identifies the location of the ataxia, i.e. "Left upper limb 1=Yes, 2=No, 9=Amputation or joint fusion, explain:_____"。

Note:

Score according to the table and record the results. Do not change the score. The score reflects the actual situation of the patient, not what the doctor thinks the patient should be. Quickly check while recording results. Do not train the patient (e.g., repeatedly ask the patient to make an effort) unless instructed to do so.

If some items are not evaluated, they should be explained in detail in the form. Unassessed items should be reviewed with surveillance video and discussed with the examiner.

Appendix 2：Modified Rankin Score (mRS)

Grade	Description
0	No symptoms
1	Symptoms without any incapacity (able to perform all usual activities)
2	Mild incapacity (unable to perform all usual activities but able to look after his/her affairs alone)
3	Moderate incapacity (requires assistance but walks alone)
4	Severe incapacity (requires assistance for walking and physical body needs)
5	Severe incapacity (bedbound, incontinent, permanent surveillance required)
6	Death

Appendix 3：TOAST classification

1 Large atherosclerotic type: requires vascular imaging examination to confirm that the intracranial or extracranial large artery stenosis corresponding to the neurological deficit of cerebral infarction is more than 50% or occluded, and the vascular lesions are consistent with atherosclerotic changes; or there is intracranial or Indirect evidence of stenosis or occlusion of extracranial large arteries, such as imaging (CT or MRI) showing cerebral cortex, brainstem, cerebellum or subcortical infarction with a diameter of >1.5cm, and clinical manifestations are mainly signs of cortical damage, such as aphasia , changes in consciousness, body image disturbance, etc., or signs of brainstem and cerebellum damage. Evidence of at least one atherosclerotic stroke risk factor (such as advanced age, hypertension, hyperlipidemia, etc.) or systemic atherosclerosis (such as plaque, coronary heart disease, etc.) is required. At the same time, cerebral infarction caused by cardio embolism should also be excluded, such as no acute infarction outside the stenosis > 50% or occlusion of intracranial or extracranial large arteries, and no high or moderate risk factors for cardioembolic stroke (see Brain Embolization chapter).

2 Cardiogenic cerebral embolism type: the clinical manifestations and imaging studies are the same as those of large atherosclerotic type. This classification is supported if there is more than one vessel innervation or multisystem embolism. The presence of at least one high or moderate risk factor for cardioembolic stroke was required.

3 Small artery occlusion type: There may be no obvious clinical manifestations or various lacunar syndromes, but no cerebral cortex involvement. The head CT or MRI is required to be normal, or the infarct diameter is less than 1.5cm.

4 Other etiological types: refer to other rare etiologies other than the above three types of clear ethology. Such as blood coagulation disorders, changes in blood components, vasculitis due to various reasons, vascular malformations, connective tissue diseases, dissecting aneurysms, fibrous dystrophy and cerebral infarction.

5 Unexplained type: including two or more etiologies, negative auxiliary examinations, no cause found, and insufficient auxiliary examinations.

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Detail of Protocol Change

Page, Section	**Version 1.0**	**Version 2.0**
P1, Version date	August 03, 2018	**Change:** May 06, 2020
P4, Efficacy Outcome/Secondary outcome	-	**Add:** 2. An ordinal shift of the full range of mRS scores at 90 days;
P7, Statistical Analysis	all the data will be analyzed with Software Statistical Product and Service Solutions.	**Change:** all the data will be analyzed with Statistical Product and Service Solutions, SAS, and R software.
P9, Abbreviation	-	**Add:** CDCIA Cerebrovascular Disease Collaboration Innovation Alliance ATS As Treated Set
P12, 2.3 Secondary objectives	-	**Add:** 2. To determine an ordinal shift of the full range of mRS scores at 90 days.
P20, 7.2 Secondary efficacy outcomes	-	**Add:** 2. An ordinal shift of the full range of mRS scores at 90 days;

P29, 9.1 Sample size	This trial mainly detects a 10% absolute difference in the proportion of the dual antiplatelet group with favorable outcome with 80% power and a one-sided type I error rate of 0.025 to test the non-inferiority, and the proportion of 65% of the dual antiplatelet group will experience a favorable outcome referring to previous report.[12] Thus, the sample size of 716 subjects resulted from these assumptions. According to the ITT principle, the maximum sample size is 752 subjects with 5% lost. Finally, a total of 760 subjects are expected to include in this study, with 380 patients in each group.	**Change:** According to our recent unpublished data, the proportion of expected excellent functional outcome (mRS 0-1) at 90 days in the control group is estimated to be 87%, and the proportion in the experimental group is estimated to be 89.5%. based on the PRISMS trial.[8] The margin of non-inferiority was defined as 4.5% in our trial, which was based on the subset analysis of the Third International Stroke Trial (IST-3) showing a 9% absolute difference in the proportion of favorable outcome in minor nondisabling patients treated with intravenous alteplase compared to standard medical treatment.[12] Using a power of 80% and α of 0.05 to carry the two-sided test, the required sample size to test the non-inferiority hypothesis is 666. In consideration of 12% of patients lost to follow-up, the total sample size is 757. Therefore, this study still included 760 patients, with 380 patients in each group. **Rationale:**

		(1) The trial was originally planned as a noninferiority study but the sample size calculation was erroneously made for a superiority trial. This error was found by the DMC statistician (Dr. Yi-Long Wang) on April 2020 and was corrected in this version. (2) We found that 65% of the estimated primary outcome in the original protocol was not correct regarding excellent functional outcome in the alteplase arm. Our cohort study found that among patients with minor stroke, 85% achieved excellent outcome at 90 days [1]. Based on this result and the nature of nondisabling minor stroke in the current trial, the proportion of excellent outcome was estimated as 87% in the alteplase arm in final protocol. Referring to the results of PRISMS trial showing numerically higher proportion of excellent outcome in the aspirin arm compared to the alteplase arm [2], the proportion of excellent outcome in DAPT arm was changed from 65% to 89.5% in the final protocol.

		(3) The assumption of a 10% absolute difference in the original protocol was not appropriate. Given the noninferiority design, the noninferiority margin of -4.5 percentage points was chosen in the final protocol, which was based on the Third International Stroke Trial, where subgroup analysis showed a 9% absolute difference in the proportion of favorable outcome as measured by the Oxfordfordshire Handicap Score (OHS 0 to 1) in patients with minor stroke who were treated with intravenous alteplase compared to standard medical treatment [3]. (4) The changes were not informed by review of the study data.
P29, 9.2 Statistical analysis plan	all data will be analyzed with SPSS 20.0 Software.	**Change:** all data will be analyzed with SPSS 23.0 Software, SAS software or R software.
P29, 9.2 Statistical analysis plan	An interim analysis will be performed after	**Delete:** An interim analysis will be performed after 50% of

	50% of subjects have completed follow-up.	subjects have completed follow-up.
P30, 9.2 Statistical analysis plan Stratification:		**Add:** sex (male vs. female), NIHSS score at randomization (0-3 vs. 4-5)
P30, 9.3 Analysis population		**Add:** As Treated Set (ATS) As-treated (AT) population is based on the treatment actually received. There is no single CRF question that determines the As-treated arm, and the arm will be determined by the trial statistician.
P31, 10.2 Monitoring of the study	A staff from CDCIA will have regular contacts with the study site	**Change:** The staff from CDCIA and independent contract research organization (Liaoning Zhongshuang Medical Technology Co., Ltd.) will have regular contact with the study site.
P40, Reference	12. Yeatts SD, Broderick JP, Chatterjee A, et al. Alteplase for the treatment of acute ischemic stroke in patients with low National Institutes of Health Stroke Scale	12. Khatri P, Tayama D, Cohen G, et al. Effect of Intravenous Recombinant Tissue-Type Plasminogen Activator in Patients With Mild Stroke in the Third International Stroke Trial-3: Post Hoc Analysis. Stroke

	and not clearly disabling deficits (Potential of rtPA for Ischemic Strokes with Mild Symptoms PRISMS): Rationale and design. Int J Stroke 2018; 13: 654-661.	2015; 46: 2325-2327.

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3. Khatri P, Tayama D, Cohen G, et al. Effect of Intravenous Recombinant Tissue-Type Plasminogen Activator in Patients With Mild Stroke in the Third International Stroke Trial-3: Post Hoc Analysis. Stroke 2015; 46: 2325-2327.