A double-blind, placebo-controlled, randomized, multicenter study to investigate CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study)

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Rationale **Traditional Chinese Medications(TCM) have been reported to have beneficial effects in stroke patients, but were not rigorously evaluated by GCP standards.**

Aim **This study tests the hypothesis that Neuroaid, a TCM widely used in China post-stroke, is superior to placebo in reducing neurological deficit and improving functional outcome in patients with acute cerebral infarction of an intermediate severity.**

Design **This is a multicenter, randomised, double-blind, placebo-controlled study of Neuroaid in ischemic stroke patients with National Institute of Health Stroke Scale(NIHSS) 6–14 treated within 48 h of stroke onset. Neuroaid or placebo is taken (4 capsules) 3 times daily for 3 months. Treatments are assigned using block randomization, stratified for centers, via a central web-randomization system. With a power of 90% and two-sided test of 5% type I error, a sample size is 874. Allowing for a drop-out rate of up to 20%, 1100 individuals should be enrolled in this study.**

Study Outcomes **The primary efficacy endpoint is the modified Rankin Scale(mRS) grades at 3 months. Secondary efficacy endpoints are the NIHSS score at 3 months; difference of NIHSS scores between baseline and 10 days, and between baseline and 3 months; difference of NIHSS sub-scores between baseline and 10 days, and between baseline and 3 months; mRS at 10 days, 1 month, and 3 months; Barthel index at 3 months; Mini Mental State Examination at 10 days and 3 months. Safety outcomes include complete blood count, renal and liver panels, and electrocardiogram.**

Study registration: ClinicalTrials.gov identifier: NCT00554723.

Key words: acute stroke therapy, Asia, cerebral infarction, ischemic stroke, therapy, treatment

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Introduction

Stroke is a major cause of death and disability in many countries of the world, placing a heavy burden on patients, families, healthcare systems, and economies (1). Only a few therapies have consistently reduced death and/or disability poststroke – intravenous thrombolysis with recombinant tissue plasminogen within 3 h of stroke onset (2), hemicraniectomy for malignant middle cerebral artery territory infarction (3), early administration of aspirin (4), and organized in-patient stroke care (5). The former is given to only a small proportion of stroke patients due to its many contraindications and short window of treatment opportunity, while the latter are generally more applicable but may not be widely practiced due to delayed patient arrival or organizational challenges. Despite these evidence-based interventions, recovery is still incomplete in many stroke patients. There is thus a real need for better treatments to enhance poststroke recovery.

Neuroaid is a Traditional Chinese Medicine (TCM) product, combining nine herbal components and five animal components, manufactured by Shitian Pharmaceuticals

(Tianjin, China). It was certified as Good Manufacturing Practice compliant and registered under the Chinese name Danqi Piantan Jiaonang with the Sino-Food and Drug Administration (Sino-FDA) in August 2001 for the treatment of stroke recovery. Previous clinical studies performed in China under Chinese Standard Guidelines have shown that it increased stroke patients' recovery from their neurological disability and functional outcome (6). It was found to be superior in reducing neurological deficit compared with another TCM, Buchang Naoxintong Jiaonang, which was previously shown to be at least as effective as citicoline (7, 8). It was found to be safe and well tolerated, without any effect on hemorrhagic or thrombotic risks or blood pressure (9).

But the China trials were not International Conference of Harmonisation/Good Clinical Practice (ICH/GCP) compliant (Sino-FDA did not require it), and used positive controls. The sample sizes were also small, had a wide window of recruitment after stroke onset, a short duration of treatment, and used nonstandard measurements of functional and neurological outcomes. A longer duration, well-conducted trial with large patient numbers is needed, performed in accordance with ICH/GCP guidelines.

We have thus planned this trial of Neuroaid to assess its efficacy in improving outcomes poststroke.

Study objective

To test the hypothesis that Neuroaid is superior to Placebo in reducing neurological deficit and improving the functional outcome in patients with cerebral infarction of an intermediate range of severity.

Methods

Design

CHInese Medicine Neuroaid Efficacy on Stroke (CHIMES) is a prospective, multicenter, randomized, placebo-controlled, double-blinded clinical trial of Neuroaid among patients with acute ischemic stroke. Participating centers are from Hong Kong, Philippines, Singapore, and Thailand. The study will be conducted according to ICH/GCP guidelines. Local ethics committee approval will be obtained before commencing the trial at a site.

Patient population

Inclusion criteria: A subject will be eligible for inclusion in the trial only if all the following criteria are fulfilled at baseline:

- age 21 years old and above;
- time window is <48 h after the onset of symptoms;
- on antiplatelet therapy;
- prestroke modified Rankin Scale (mRS) less than or equal to 1;
- intermediate severity range: $6 \leq$ National Institute of Health Stroke Scale score (NIHSS) ≤ 14;
- cerebral infarction with compatible imaging on computed tomography (CT) scan or magnetic resonance imaging (MRI);
- females are eligible to participate in the trial if they are of non-child-bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is postmenopausal); and
- subject or his/her legally acceptable representative is willing to provide written informed consent.

Exclusion criteria: A subject will *not* be eligible for inclusion in the trial if any of the following criteria apply at baseline:

- received thrombolysis;
- evidence of intracerebral hemorrhage on brain CT scan or MRI;
- rapidly improving neurological deficit;
- definite indication for full-dose or long-term anticoagulation therapy;
- other significant nonischemic brain lesions that could affect function disability;
- coexisting systemic diseases: terminal cancer, renal failure (creatinine >200 μmol/l, if known), cirrhosis, severe dementia, or psychosis; and
- participated in another clinical trial within the last 3 months.

Baseline measurements

CT scan or MRI must be performed to exclude hemorrhagic stroke. If the subject is eligible, the following variables will be recorded: normal, recent cerebral infarction, or others.

Information on the following variables will be collected at the baseline assessment (Table 1):

- demographic data: date of birth and gender;
- vital signs: temperature, blood pressure, pulse rate, body weight, and height;
- time from stroke onset;
- medical history: neurological, cardiovascular, endocrine, hematological, eyes, ear–nose–throat (ENT), peripheral vascular, respiratory, gastrointestinal, hepatic, renal, genitor–urinary, dermatological, musculoskeletal, neoplasia, immune, and psychiatric;
- physical examination: general appearance, neurological, eyes, head and neck, ENT, heart, lungs, abdomen, lymph nodes, genito–urinary, extremities, skin, musculoskeletal, immune, and psychiatric;
- stroke history: date of previous stroke, type of stroke;
- risk factors: previous myocardial infarction, angina, hypertension, peripheral vascular disease, diabetes mellitus, hyperlipidemia, smoking history, and habitual drinking;
- previous and ongoing medications: name of drugs, route, dosage, frequency, date started, date stopped, and indication;

Table 1 Schedule of trial-related activities

	Baseline	Treatment		
	Day 1	Day 10 (or at discharge if earlier)	1 month	3 months
Eligibility check	X			
Informed consent	X			
Demographic data	X			
Vital signs	X			X
Time from stroke onset	X			
Medical history	X			
Physical examination	X			X
Neurological evaluation	X	X		X
Stroke history	X			
Risk factors	X			
Previous medication	X			
Ongoing medication/ change in concomitant medication	X	X	X	X
CT scan/MRI	X			
Laboratory examination	X			X
NIHSS	X	X		X
Modified Rankin Score	X	X	X	X
Barthel index				X
Mini-Mental State Examination	X	X		X
Drug accountability and compliance		X	X	X
Adverse event		X	X	X

CT, computed tomography; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale.

- routine laboratory investigations i.e. complete blood count, blood urea, serum creatinine, serum uric acid, blood glucose, serum alkaline phosphatase, glutamate oxaloacetate transaminase (also called aspartate transaminase), glutamate pyruvate transaminase(also called alanine transaminase), serum bilirubin, serum electrolytes, total proteins with albumin and globulin, and electrocardiogram;
- NIHSS;
- mRS; and
- Mini-Mental State Examination (MMSE).

Randomization

Treatments will be assigned using block randomization, stratified for centers.

A web-based randomization/registration system will be provided by the Clinical Trials and Epidemiology Research Unit (CTERU), Singapore. When a subject meets the inclusion/exclusion criteria and gives written informed consent, the investigator will register this subject in the web system. A subject number will then be assigned to this subject by the system.

In the case that the web system fails to operate, investigators will be asked to use the back-up envelope system and take the next subject number available at their respective site, complete the subject registration form, and fax the form to CTERU. Once the web system resumes functioning, investigators will need to register these subjects in the web system according to the information recorded in the subject registration form, before a new subject can be registered via web registration. CTERU will verify the web registration notification against the received registration fax.

Blinding

As this is a double-blind study, the following persons will be blinded:

- Patients;
- CHIMES Investigators and their study-related staff;
- CHIMES Society Members;
- Data and Safety Monitoring Board (DSMB) Members; and
- the CTERU Clinical Project Coordinator.

The following persons will not be blinded:

- CTERU statistician;
- statistician (CTERU) who will prepare the emergency envelopes (one envelope will refer to one randomized subject);
- Neuroaid/Placebo manufacturer or any independent staff appointed to be assigned to put the sticker/treatment identification number based on the randomization list; and
- DSMB statistician.

Treatment (Fig. 1)

Subjects are randomly assigned to receiving a 3-month course of either:

- Neuroaid or
- a matched placebo of Neuroaid.

Both involve the subject taking four capsules, three times daily.

If the subject is unable to swallow the capsules, the capsule contents are removed and diluted in water before serving by mouth or by a nasogastric tube.

Neuroaid is manufactured by Shitian Pharmaceuticals. It contains 0·4 g of medicinal extracts of plant and animal origins – animal origins include scorpion and leech (Table 2).

The placebo of Neuroaid will be manufactured by the same manufacturer as Neuroaid. Its composition will include four constituents sold as food in China and known to have no active effect (Table 3).

Neuroaid and placebo capsules have an identical appearance, smell, and taste.

All patients will receive standard stroke care, which will include antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation.

Antiplatelets used in the trial will depend on standard practice and the licensing situation in each participating study country. Any of the following five oral antiplatelet therapies will be allowed. A combination of two oral antiplatelets will also be allowed.

- Aspirin (acetylsalicylic acid, aspirin): the dosage is 75–300 mg per day;
- Clopidogrel Plavix®: the dosage is 75–300 mg per day;
- Ticlopidine Ticlid®: the dosage is 250 mg twice a day;

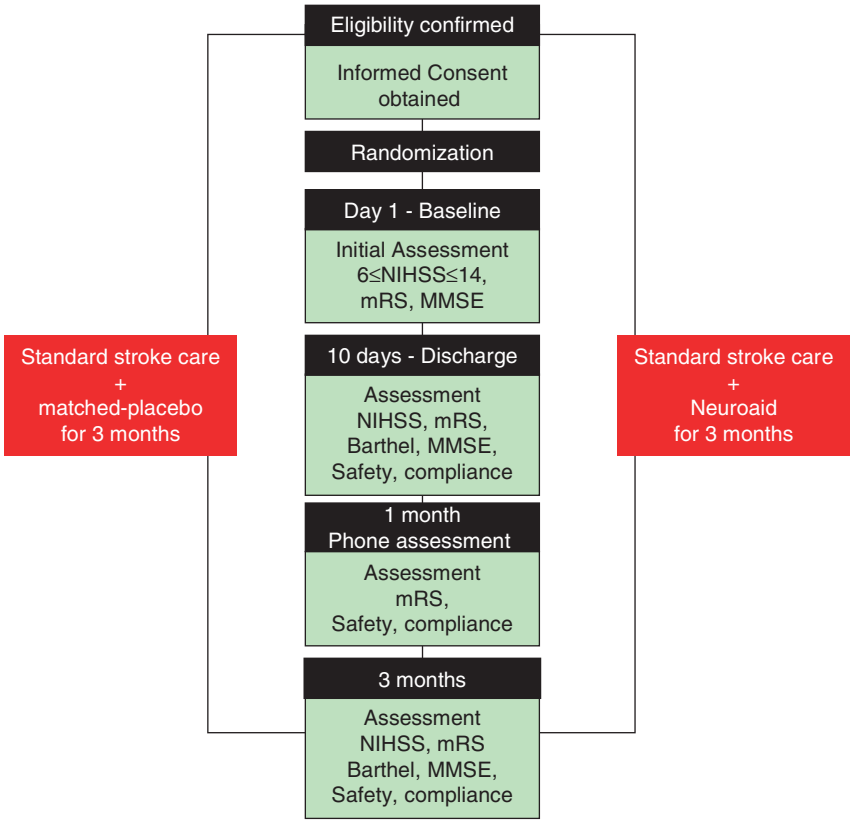

Fig. 1 Flow diagram for CHInese Medicine Neuroaid Efficacy on Stroke.

Table 2 Composition of Neuroaid

Ingredients (Latin name)	Content per capsule in mg (equivalent of raw abstracts)
Radix astragali	570
Radix salviae miltiorrhiza	114
Radix paeoniae rubra	114
Rhizoma chuanxiong	114
Radix angelicae sinensis	114
Carthamus tinctoruis	114
Prunus persica	114
Radix polygalae	114
Rhizoma acori tatarinowii	114
Buthus martensii*	95
Hirudo*	66.5
Eupolyphaga seu steleophaga*	66.5
Calculus bovis artifactus*	28.5
Saigae tataricae cornu*	28.5

*Refers to ingredients of animal origin.

Table 3 Composition of placebo to Neuroaid

Ingredients	Content per capsule in mg
Barley	227·27
Dried ripe fruit	45·45
Noodle fish	90·91
Citric acid	5·00

- Dipyridamole Persantine®: the dosage is 75–150 mg three times daily; and
- Cilostazol Pletal/Pletaal®: the dosage is 100 mg twice a day.

Treatments to be excluded during the 3-month study are:

- oral anticoagulants;
- fibrinolytics; and
- heparins(including low-molecular-weight heparins) or heparinoids.

Other concomitant medications will be allowed throughout the trial but should be recorded in the subjects' Case Report Form during the study.

Trials' medication management

If a subject is not compliant to the treatment (<80% of the treatment), they will not be withdrawn from the trial, but will still be included in the 'Intention-to-treat' analysis; however, they will be excluded from the 'Per protocol' analysis.

Primary outcomes

The primary efficacy end-point is the mRS grades at 3 months for all randomized subjects.

Secondary outcomes

The secondary efficacy end-point measures will be the recovery of the subjects as assessed by:

- NIHSS score response at 3 months (plus or minus 1 week);
- difference of NIHSS scores between baseline and 10 days (plus or minus 2 days), and between baseline and 3 months (plus or minus 1 week);
- difference of NIHSS sub-scores between baseline and 10 days (plus or minus 2 days) or discharge, and between baseline and 3 months (plus or minus 1 week);
- mRS response at 10 days (plus or minus 2 days), at 1 month (plus or minus 1 week), and at 3 months (plus or minus 1 week);
- Barthel index (BI) at 3 months (plus or minus 1 week); and
- MMSE at 10 days (plus or minus 2 days), and at 3 months (plus or minus 1 week).

DSMB

The purpose of a DSMBis to assess at intervals the progress of a clinical trial, the safety data, and the clinical efficacy end-points. The Board will then recommend to the Trial Steering Committee whether to continue, modify, or terminate the trial based on the data of either the present trial or from other studies on a similar drug or of a similar nature.

In particular, the DSMB will help:

- review the research protocol and plan for data and safety monitoring;
- ensure patient safety (i.e. to minimize the avoidable risk of subjects' participation);
- ensure that the trial can be stopped as soon as a reliable conclusion can be drawn from the data;
- ensure continued scientific validity, and to ensure that the trial is stopped if it is unlikely to be able to answer the original question (for trial 'futility'); and
- protect the confidentiality of the trial data and the results of monitoring.

Two interim efficacy analyses are scheduled. A first DSMB report shall be prepared after 20% or 220 patients have been recruited. The second DSMB report will be prepared after 60% or 660 patients have been recruited. The DSMB will have the option to request an additional report if considered necessary.

In order to set very stringent criteria for stopping the trial at the earliest interim analysis, 'stopping guidelines' based on O'Brien-Fleming's method will be adopted, with the significance level for each analysis time-point being as follows:

Analysis	Interim 1	Interim 2	Final
Significance level	0·0006	0·0156	0·05

However, it should be emphasized that the DSMB will use these stopping criteria as guidelines to assist their decision making rather than to follow them dogmatically.

Sample size

Based on the distribution of mRS at 6 months obtained in the FISS-Tris study (10) and if we assume an average odds ratio (OR) of 1·5 for the Neuroaid group, we then obtain the distribution (Table 4). With a power of 90% and a two-sided test of a 5% type I error, a total sample size of 874 would be needed. To allow for a maximum drop-out rate of up to 20%, 1100 individuals should be enrolled in this study.

Statistical analyses

An 'Intention-to-treat' analysis will be carried out.

Primary efficacy outcomes – mRS grades at 3 months. Tabulation of frequency will be presented and the difference in the distribution of subjects within each range of mRS between the placebo group and the Neuroaid group will be tested by the Mann–Whitney *U*-test, with allowance for ties (3). This is equivalent to ordinal logistic regression using treatment groups as the independent variable, which then provides an estimate of the OR and the corresponding 95% confidence interval. Further, ordinal logistic regression allows the observed treatment difference to be adjusted by potentially prognostic factors.

Secondary efficacy outcomes

NIHSS score response at 3 months (plus or minus 1 week). Patients will be deemed to be responders if their NIHSS scores improve by five points or more from the NIHSS score at baseline and at 10 days. Tabulation of frequency for responders will be presented. The χ^2-test will be performed and/or presented where appropriate.

- Difference of NIHSS scores between baseline and 10 days (plus or less 2 days), and between baseline and 3 months (plus or minus 1 week) between two groups. The two-sample *t*-test will be performed, with appropriate transformation carried out on NIHSS scores if necessary.
- Difference of NIHSS sub-scores (such as motor function) between baseline and 10 days (plus or minus 2 days) or discharge, and between baseline and 3 months (plus or minus 1 week between two groups. The Mann–Whitney *U*-test, with allowance for ties, will be performed.

Table 4 mRS scores from the FISS-Tris study

	Proportion of patients in mRS at 6 months (%)					
6 months	0	1	2	3	4	5 & 6
Placebo group (from FISS-Tris, $n = 292$)	8	45	19	16	6	6
Proposed Neuroaid group	11·5	51·3	16·6	12·3	4·3	4·1
Average proportion of Placebo and Neuroaid group	9·8	48·2	17·8	14·1	5·1	5·0

mRS, modified Rankin Scale.

- mRS response (1) at 10 days (plus or minus 2 days), at 1 month (plus or minus 1 week), and at 3 months Patients will be deemed to be responders if their mRS is less than or equal to one. Tabulation of frequency for responders will be presented. The χ^2-test will be performed and OR will be presented where appropriate.
- mRS response (2) at 10 days (plus or minus 2 days), at 1 month (plus or minus 1 week), and at 3 months (plus or minus 1 week). Patients will be deemed to be responders if their mRS is less than or equal to two. Tabulation of frequency for responders will be presented. The χ^2-test will be performed and OR will be presented where appropriate.
- BI at 3 months (plus or minus 1 week) will be analyzed for both groups. The two-sample *t*-test will be performed.
- MMSE at 10 days and at 3 months (plus or minus 1 week). MMSE for both groups will be analyzed. The two-sample *t*-test will be performed.

Per protocol and sub-group analysis

Per protocol analysis will also be performed for primary and secondary efficacy outcomes on subjects who have not had any deviation from the protocol.

Sub-group analysis will be performed for the following sub-groups:

- time from stroke onset: therapeutic window ≤ 24 h and therapeutic window > 24 h;
- NIHSS score: patients with $6 \leq \text{NIHSS} \leq 10$ and patients with $10 < \text{NIHSS} \leq 14$;
- type of cerebral infarction: patients presenting with lacunar infarction and patients with large artery occlusive disease;
- antiplatelet treatment received; and
- other prespecified sub-groups.

Study organization and funding

The study is headed by a Steering Committee, assisted by an independent DSMB. The CTERU will handle trial monitoring, data management, and storage as well as statistical analysis.

The study is funded internationally in part by a grant from the CHIMES Society, a nonprofit charity organization based in Singapore. Additional local funding in each center is listed in Table 5.

Table 5 Funding sources per country/center

	National Medical Research Council (Singapore)	CHIMES Society	Moleac
Overall coordination	X	X	X
Singapore sites	X	X	X
Philippines sites		X	X
Thailand sites			X

CHIMES, CHInese Medicine Neuroaid Efficacy on Stroke.

Conclusions

CHIMES will be the first multicenter, randomized, double-blinded, placebo-controlled trial assessing the efficacy and safety of a TCM in the management of acute ischemic stroke according to GCP guidelines. It will provide valuable information on the conduct of randomized-controlled trials involving TCMs and similar botanicals. If Neuroaid is efficacious, further studies may be needed to assess which component of Neuroaid is most efficacious. It will also spur GCP-based evaluations of other TCMs in stroke.

CHIMES investigators

Steering committee members: C.L.H. Chen (chair), M.G. Bousser (co-chair), A.C. Baroque, B.P.L. Chan, R. Gan, H.M. Chang, J.C. Navarro, D. Picard, S.B. Tan, N. Venketasubramanian, K.S. Wong.
DSMB members: G.A. Donnan (chair), D. Machin, C. Tzourio
CTERU members: H.B. Wong, A. Panchalingham, L.T. Koh, C. Pavithra, K.T. Tun, E.S.Y. Chan, M. Zhu, S.B. Tan

Sites

Philippines

University of Santo Tomas Hospital, Manila – J.C. Navarro, A. Baroque, J. Lokin, M. Yumul
Jose R. Reyes Medical Center, Manila – H. Gan, J.C. Navarro.
San Pedro Hospital, Davao City – A. Lao.

Singapore

Changi General Hospital – N. Venketasubramanian, R. Gan.
National University Hospital – B.P.L. Chan.
National Neuroscience Institute (Singapore General Hospital) – H.M. Chang.
National Neuroscience Institute (Tan Tock Seng Hospital) – N. Venketasubramanian, R. Gan.

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