CHIMES-I: sub-group analyzes of the effects of NeuroAiD according to baseline brain imaging characteristics among patients randomized in the CHIMES study

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Rationale **The clinical effects of neuroprotective and/or neurorestorative therapies may vary according to location and size of the ischemic injury. Imaging techniques can be useful in stratifying patients for trials that may be beneficial against particular ischemic lesion characteristics.**

Aim **To test the hypothesis that the efficacy of NeuroAiD compared with placebo in improving functional outcome and reducing neurological deficit in patients with cerebral infarction of intermediate severity varies between sub-groups of patients randomized in the main Chinese Medicine Neuroaid Efficacy on Stroke study when categorized according to baseline imaging characteristics.**

Design **This is a retrospective cohort sub-group analysis of patients who participated in the main Chinese Medicine Neuroaid Efficacy on Stroke study, a multicenter, double-blind, placebo-controlled trial that recruited 1100 patients within 72 h of ischemic stroke onset with National Institutes of Health Stroke Scale 6–14 and were randomized to either NeuroAiD or placebo taken four capsules three times daily for three months. Review of the baseline images to classify the acute stroke lesions in terms of size, location, and extent of involvement will be performed retrospectively by two readers who will remain blinded as to treatment allocation and outcomes of the subjects.**

Study outcomes **The primary efficacy end-point in the main Chinese Medicine Neuroaid Efficacy on Stroke study is the modified Rankin Scale grades at three-months. Secondary efficacy end-points are the National Institutes of Health Stroke Scale score at three-months; difference of National Institutes of Health Stroke Scale scores between baseline and 10 days and between baseline and three-months; difference of National Institutes of Health Stroke Scale sub-scores between baseline and 10 days and between baseline and three-months; modified Rankin Scale at 10 days, one-month, and three-months; Barthel index at three-months; and Mini Mental State Examination at 10 days and three-months. Analysis of these primary and secondary end-points will be performed for sub-groups defined in this study after review of the baseline brain imaging: nonlacunar and lacunar, cortical and sub-cortical, hemispheric vs. brainstem, Alberta Stroke Program Early CT score <7 and 7–10, and score <8 and 8–10.**

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Introduction

NeuroAiD combines 14 natural ingredients indicated as treatment for poststroke recovery in China. In Singapore, NeuroAiD is listed as a Chinese Proprietary Medicine since 2006. It is widely available in China and in many countries in Asia. In Europe, a simplified formulation (MLC901) consisting of the nine herbal components is available.

NeuroAiD was first registered with the Sino Food and Drug Administration in 2001 after being evaluated in two randomized, double-blind, positive-controlled clinical trials (1). Pooled analysis of data from these studies that included 605 patients with ischemic stroke within two-weeks to six-months of onset has shown that NeuroAiD improved functional outcome and was safe in patients with ischemic stroke (2). Other studies further supported the efficacy and safety of NeuroAiD in different phases after ischemic stroke (3–9).

The protocol of a double-blind, placebo-controlled, randomized trial to investigate Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES study) was previously published in this journal (10). Chinese Medicine Neuroaid Efficacy on Stroke is the first large-scale multicenter clinical trial to assess the efficacy and safety of a traditional Chinese medicine in the management of acute ischemic stroke conducted according to GCP guidelines and has recently completed recruitment of the target 1100 patients [*Clinicaltrials.gov Identifier: NCT00554723* (http://clinicaltrials.gov/)].

The properties of NeuroAiD have more recently been elucidated in animal and *in vitro* models (11,12). NeuroAiD has been shown to have both neuroprotective and neuroproliferative properties. It reduces infarct size and protects against glutamate-induced neuronal injury. It also protects the hippocampal CA1 cells from global ischemia, partly via reducing lipid peroxidation (as indicator of oxidative stress) and the role of Akt. More remarkable is the effect of NeuroAiD on neurogenesis beyond mere neuronal protection. *In vivo* and *in vitro* experiments showed how NeuroAiD increases cell proliferation, neuritic outgrowth, and synaptogenesis.

A long series of failed neuroprotection clinical trials in stroke has been reported, analyzed, and debated (13–16). Lessons were learned and rethinking the designs of trials was imperative. Looking at a more homogenous study, population and brain pathology may improve the chances of success. Furthermore, rather than addressing one specific target in the ischemic cascade,

drugs with multiple sites of action may be more clinically relevant. Given that NeuroAiD has such possible multimodal action and its demonstrated properties extend from neuroprotection to neurorestoration, it is reasonable to suspect that its clinical effects among stroke patients may vary to a certain degree according to location and size of the ischemic injury. Imaging techniques that distinguish gray from white matter injuries can be useful in stratifying patients for trials that may be beneficial against particular lesions (16).

In this sub-study, we aimed to analyze the primary and secondary efficacy outcomes of the CHIMES study in sub-groups of patients categorized according to baseline imaging characteristics.

Study objectives

To test the hypothesis that the efficacy of NeuroAiD compared with placebo in improving functional outcome and reducing neurological deficit in patients with cerebral infarction of intermediate severity [National Institutes of Health Stroke Scale (NIHSS) 6–14, inclusive] varies between sub-groups of patients randomized in the main CHIMES study when categorized according to baseline imaging characteristics.

Methods

Design

The CHIMES-I is a retrospective cohort sub-group analysis of patients who participated in the main CHIMES study. Participating CHIMES centers are from Hong Kong, Malaysia, Philippines, Singapore, Sri Lanka, and Thailand. Retrospective review of the baseline images will be performed by two readers who remain blinded as to treatment allocation and outcomes of the subjects (Fig. 1).

Patient population

All baseline brain scans of subjects included in the CHIMES study are eligible to be evaluated.

Randomization

As CHIMES-I is a noninterventional study, no randomization is required.

Treatment or intervention

CHIMES was a multicenter, placebo-controlled, double-blind, parallel group, phase III study including 1100 subjects randomly assigned to receive a three-month course of either of the following:

- NeuroAiD four capsules three times daily or
- a matched placebo four capsules three times daily.

Treatment was started within 72 h of stroke onset and all patients received standard stroke care, including antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation.

CHIMES-I does not require any additional treatment or intervention.

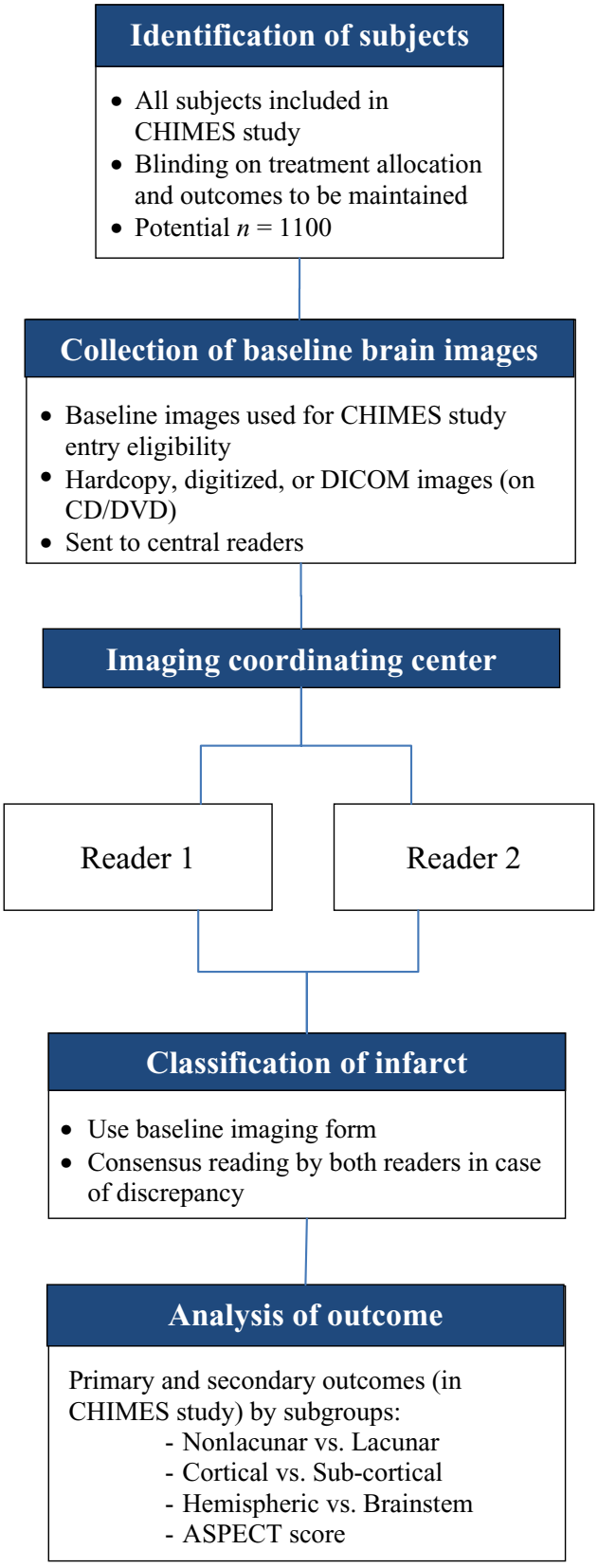

Fig. 1 Schematic flow chart of the study design. ASPECT, Alberta Stroke Program Early CT; CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke; DICOM, Digital Imaging and Communications in Medicine.

Primary outcomes

Primary efficacy end-point is the modified Rankin Scale (mRS) grade at month 3 for all subjects included in this study.

Secondary outcomes

The secondary efficacy end-point measures will be the recovery of the subjects included in this study as assessed by the following:

- NIHSS score response at month 3 (plus or minus one-week)
- difference in NIHSS scores between baseline and day 10 (plus or minus two-days) and between baseline and month 3 (plus or minus one-week)
- difference in NIHSS sub-scores between baseline and day 10 (plus or minus two-days) or at discharge and between baseline and month 3 (plus or minus one-week)
- mRS response at day 10 (plus or minus two-days), at month 1 (plus or minus one-week), and at month 3 (plus or minus one-week)
- Barthel Index at month 3 (plus or minus one-week)
- Mini Mental State Examination at day 10 (plus or minus two-days) and at month 3 (plus or minus one-week).

Data collection

Baseline images used for CHIMES study entry of each subject will be collected from participating sites either as hardcopies, digitized, or Digital Imaging and Communications in Medicine images. The imaging coordinating center shall send the images to two central readers for independent reading.

As the objective in CHIMES-I is not merely to assess the images for presence or absence of lesion, but rather to be able to characterize the acute lesion responsible for the index stroke, e.g., cortical involvement, size, and location, it would be important that the readers evaluate the actual brain area of interest. Considering that some baseline images used for CHIMES eligibility may be CT scans rather than MRI, that patients may have had the scans performed within 24 h of symptom onset leading to poor visualization of the acute lesion, and that incidental ischemic lesions in the brain are not uncommon in stroke patients, a summary baseline NIHSS of each subject will be provided together with the images to guide the readers to focus on the likely brain area acutely affected. As the data are blinded as to treatment allocation and outcomes, there will be no risk of accidentally unblinding the patients in the main CHIMES study.

Baseline imaging form will be provided to each of the reader (Appendix S1). Each reader will fill in the form independently, i.e., each subject will have two separate readings recorded on separate forms. The forms shall be collated by the imaging coordinating center and matched for consistency. In case of discrepancy, both readers will be requested to review the images again together, discuss, and provide a consensus reading agreed on by both.

Prior to start of the central readings, both readers will be instructed on the process and definitions of each item in the brain imaging form:

- consider only the lesion(s) related to the index acute stroke lesion of interest
- ignore any incidental old strokes or nonstroke lesions seen on the scan (e.g., small meningioma, etc.)
- may refer to the summary baseline NIHSS to determine the laterality (side) and the accompanying signs of the acute stroke
- size of lesion must be measure against largest diameter
- choose more than one answer only if findings are definite.

A pilot inter-reader agreement study on 20 brain images using the same form shall be performed to assess consistency between readers.

As the CHIMES study was started in November 2007, it is possible that some baseline images may no longer be available. Subjects with baseline images that are no longer available for central readings will not be included in the analyses.

Sample size

The CHIMES study sample size of 874 was based on a power of 90% and alpha of 0·05 to detect an odds ratio of 1·5 for the NeuroAiD group compared with placebo based on the mRS distribution obtained in the Fraxiparin in Stroke Study for the treatment of ischemic stroke study (17). The target of 1100 subjects enrolled in the study was to allow for a maximum dropout rate of up to 20%.

Being a sub-group analysis of the main study and with no intention or possibility of adjusting the sample size of the main study, the results of CHIMES-I shall be considered hypothesis generating.

Statistical analyses

Both 'intention-to-treat' and 'per-protocol' analyses as outlined in the main CHIMES study will be performed for the following sub-groups derived from central reading of the baseline imaging data:

- nonlacunar and lacunar infarction

'Lacunar' is defined as a sub-cortical lesion (infarct) with maximum diameter not more than 1·5 cm, while 'nonlacunar' is defined as a lesion (infarct) that involves the cortical or has a maximum diameter of more than 1·5 cm (even if sub-cortical in location).

- cortical (with or without sub-cortical components) and only sub-cortical location
- cortical only, sub-cortical only, and combined cortical–sub-cortical location
- hemispheric and brainstem location
- Alberta Stroke Program Early CT (ASPECT) score <7 and 7–10
- ASPECT score <8 and 8–10.

Study organization and funding

This sub-study will be coordinated by an imaging coordinating center at the University of Santo Tomas Hospital, Manila, Philippines. Baseline NIHSS data will be provided by the Singapore Clinical Research Institute (formerly Clinical Trials and Epidemiology Research Unit), which is responsible for monitoring, data management, storage, and statistical analysis in the main CHIMES study.

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Penang General Hospital (Malaysia) – G. B. Eow

Conclusion

The CHIMES study is among the largest trial to investigate the use of a traditional Chinese medicine in the setting of acute stroke. Drawing from this strength, CHIMES-I will be an opportunity to investigate the hypothesis that treatment effects may vary according to brain tissue affected by the ischemic lesion. While clinical parameters can imply such classification, assessment of brain images in terms of infarct size, extent, and location provides more objective parameters of categorizing lesions and correlation with natural course or prognosis and outcomes after treatment.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Baseline imaging form to be used by independent blinded readers. CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke.