Original Contribution

Chinese Medicine Neuroaid Efficacy on Stroke Recovery
A Double-Blind, Placebo-Controlled, Randomized Study

Christopher L.H. Chen, FRCP; Sherry H.Y. Young, MD; Herminigildo H. Gan, MD; Rajinder Singh, FRCP; Annabelle Y. Lao, MD; Alejandro C. Baroque II, MD; Hui Meng Chang, MD; John Harold B. Hiyadan, MD; Carlos L. Chua, MD; Joel M. Advincula, MD; Sombat Muengtaweepongsa, MD; Bernard P.L. Chan, MRCP; H. Asita de Silva, DPhil; Somchai Towanabut, MD; Nijasri C. Suwanwela, MD; Niphon Poungvarin, FRCP; Siwaporn Chankrachang, MD; K.S. Lawrence Wong, MD; Gaik Bee Eow, FRCP; Jose C. Navarro, MD; Narayanaswamy Venketasubramanian, FRCP; Chun Fan Lee, PhD; Marie-Germaine Bousser, MD; for the CHIMES Study Investigators

Background and Purpose—Previous clinical studies suggested benefit for poststroke recovery when MLC601 was administered between 2 weeks and 6 months of stroke onset. The Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study tested the hypothesis that MLC601 is superior to placebo in acute, moderately severe ischemic stroke within a 72-hour time window.

Methods—This multicenter, double-blind, placebo-controlled trial randomized 1100 patients with a National Institutes of Health Stroke Scale score 6 to 14, within 72 hours of onset, to trial medications for 3 months. The primary outcome was a shift in the modified Rankin Scale. Secondary outcomes were modified Rankin Scale dichotomy, National Institutes of Health Stroke Scale improvement, difference in National Institutes of Health Stroke Scale total and motor scores, Barthel index, and mini-mental state examination. Planned subgroup analyses were performed according to age, sex, time to first dose, baseline National Institutes of Health Stroke Scale, presence of cortical signs, and antiplatelet use.

Results—The modified Rankin Scale shift analysis–adjusted odds ratio was 1.09 (95% confidence interval, 0.86–1.32). Statistical difference was not detected between the treatment groups for any of the secondary outcomes. Subgroup analyses showed no statistical heterogeneity for the primary outcome; however, a trend toward benefit in the subgroup receiving treatment beyond 48 hours from stroke onset was noted. Serious and nonserious adverse events rates were similar between the 2 groups.

Conclusions—MLC601 is statistically no better than placebo in improving outcomes at 3 months when used among patients with acute ischemic stroke of intermediate severity. Longer treatment duration and follow-up of participants with treatment initiated after 48 hours may be considered in future studies.

Clinical Trial Registration—URL:http://www.clinicaltrials.gov.Unique identifier:NCT00554723. **(*Stroke*.2013;44:00-00.)**

Key Words: clinical trial ■ medicine, Chinese traditional ■ NeuroAiD ■ stroke, acute ■ recovery of function

Stroke is a major cause of death and disability. Despite extensive research efforts, only a limited number of treatment options have been shown to improve functional outcome after stroke, which include stroke unit care, thrombolytic therapy, early use of aspirin, and hemicraniectomy for malignant middle cerebral artery infarction.[1] Alternative strategies using

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From the Department of Pharmacology, National University of Singapore, Clinical Research Centre, Singapore, Singapore (C.L.H.C.); Changi General Hospital, Singapore, Singapore (S.H.Y.Y); Jose Reyes Memorial Medical Center, Santa Cruz, Manila, Philippines (H.H.G.); National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore (R.S.); Davao Medical School Foundation Hospital, San Pedro Hospital, Davao City, Philippines (A.Y.L.); University of Santo Tomas Hospital, Manila, Philippines (A.C.B.); National Neuroscience Institute-Singapore General Hospital Campus, Singapore General Hospital, Singapore, Singapore (H.M.C.); Baguio General Hospital and Medical Center, Baguio City, Philippines (J.H.B.H.); Philippine General Hospital, University of the Philippines Manila, Manila, Philippines (C.L.C.); West Visayas State University Medical Center, Lapaz, Philippines (J.M.A.); Thammasat University, Prathumthani, Thailand (S.M.); Division of Neurology, National University Hospital, National University Health System, Singapore, Singapore (B.P.L.C.); Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka (H.A.d.S.); Prasat Neurological Institute, Rajthevi Bangkok, Thailand (S.T.); Division of Neurology, Faculty of Medicine, Chulalongkorn University, Pathunwan, Bangkok, Thailand (N.C.S.); Siriraj Hospital, Bangkoknoi, Bangkok, Thailand (N.P.); Chiang Mai University, Amphur Muang, Chiang Mai, Thailand (S.C.); Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories of Hong Kong (K.S.L.W.); Penang Hospital, Jalan Residensi, Georgetown, Penang, Malaysia (G.B.E.); University of Santo Tomas Hospital, Manila, Philippines (J.C.N.); Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore (N.V.); Singapore Clinical Research Institute, Singapore, Singapore (C.F.L.); and Lariboisière University Hospital, Paris, France (M.G.B.).

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Correspondence to Christopher L.H. Chen, FRCP, Department of Pharmacology, National University of Singapore, Clinical Research Centre, Bldg MD11, Level 5, 05-09, 10 Medical Dr, Singapore 117597. E-mail phccclh@nus.edu.sg

neuroprotectants have failed to live up to their potential.[2] Hence, better treatments are needed to enhance poststroke recovery.

Traditional Chinese medicine (TCM) is used extensively in Asia to facilitate recovery after stroke.[3] Pharmacological studies have demonstrated some TCM to have antioxidant, anti-inflammatory, vasodilatory, antiplatelet, antiglutamate, and protective effects against ischemia and reperfusion injury.[4,5] However, meta-analyses of TCM in stroke have concluded that the evidence for efficacy and safety is scanty because of the lack of well-designed randomized placebo-controlled clinical trials.[6,7]

MLC601 (NeuroAiD), a TCM that combines extracts of 9 herbal and 5 animal components in capsule form, has been shown to restore neurological and cellular function in animal models of ischemic stroke.[8–10] Initial clinical studies on patients who were 2 weeks to 6 months after index stroke showed MLC601 improved recovery in terms of functional outcome and neurological disability.[11] More studies have since been published assessing the benefit and safety of MLC601 in nonacute stroke patients using different clinical outcomes.[12–19]

Although most patients experience some spontaneous recovery in the months after a stroke, the degree and timing of recovery are variable. Improving functional outcomes through specific interventions is a relatively unexplored area of great public health potential. Furthermore, the first 3 months after stroke may offer the most significant window of opportunity for recovery of function. Given the demonstration of both neuroprotective and neuroregenerative properties in models of focal and global brain ischemia[8–10] and the excellent safety profile[18,19] of MLC601, it is an attractive candidate to be evaluated in acute ischemic stroke.

The overall objective of this study was to test the hypothesis that MLC601is superior to placebo in improving functional outcome and reducing neurological deficit in patients who experienced an ischemic stroke of intermediate severity in the preceding 72 hours.

Methods

Study Design and Participants

The CHInese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) study was an international, multicenter, randomized, placebo-controlled, double-blind, parallel group, phase III trial. The trial protocol has been published.[20] An independent data and safety monitoring board assessed the progress of the trial at intervals by performing safety reviews and predefined interim analyses. An independent academic research organization (Singapore Clinical Research Institute) was responsible for managing study conduct, monitoring data, and performing statistical analysis according to a preapproved statistical analysis plan.

The inclusion/exclusion criteria are summarized in Table I in the online-only Data Supplement. This study is registered with ClinicalTrials.gov and was approved by the respective institutional review board or ethics committee of participating sites/countries. All subjects or their legally acceptable representatives provided written informed consent.

Randomization and Masking

Subjects were randomly assigned to receive either MLC601 or placebo using block randomization, randomly permutated with lengths of 4 and 6, stratified for 21 centers. A web-based randomization structure and backup randomization envelopes in case of web registration malfunction were provided. The backup envelopes were prepared and sealed by the trial statistician, and unused envelopes were returned to Singapore Clinical Research Institute after completion of recruitment. Registration and subject number allocation occurred only after subjects fulfilled eligibility criteria and written informed consent was obtained. Subjects, their caregivers, investigators, study-related staff, sponsor, and study project coordinators were blinded to treatment allocation.

Study Treatment

MLC601 or matching placebo was given at a dose of 4 capsules 3 times daily for 3 months, as in previous clinical trials.[11–18]

MLC601 and matching placebo were provided by Moleac (Singapore). Each 400 mg MLC601 capsule contains 9 herbal components (extracts derived from raw herbs consisting of Radix astragali, Radix salviae miltorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae, and Rhizoma acori tatarinowii) and 5 animal components (Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensii, and Cornu saigae tataricae). Placebo included 4 constituents known to have no active effect (barley, dried ripe fruit, noodle fish, and citric acid) to give a similar appearance, smell, and taste as the active treatment.

All subjects received standard stroke care, including antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation. Antiplatelets used in the trial were based on standard practice and the licensing situation in each participating country. Disallowed treatments during the 3-month study included oral anticoagulants, fibrinolytics, and heparins or heparinoids.

Study Procedures

Potential subjects were screened for eligibility at baseline, and subjects included were assessed at study entry, day 10 (±2 days) or discharge if earlier, and month 3 (±1 week). Telephone assessment was performed at month 1 (±1 week).

At baseline, computed tomography or MRI was performed. Demographic information, medical history, concomitant medications, and prestroke modified Rankin Scale (mRS) score were ascertained. Vital signs were recorded; physical examination, National Institutes of Health Stroke Scale (NIHSS), and mini-mental status examination were performed.

NIHSS, mRS, and mini-mental status examination were assessed at day 10 (or discharge, if earlier) and month 3 visits. In addition, month 3 assessment included Barthel index, vital signs, and physical examination. Month 1 telephone assessment included mRS. For all follow-up visits, any occurrence of nonserious or serious adverse events (SAE), concomitant medications, neurological status of the subject since the last assessment, and information on rehabilitation were recorded.

At site initiation visits, investigators were provided with web-based training material on the NIHSS: http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx

Study End Points and Efficacy Analyses

The primary efficacy end point was a shift in mRS at month 3. Secondary end points were mRS response (mRS 0–1 and 0–2) at day 10, month 1, and month 3; NIHSS score response (improvement by ≥5 points) at month 3 compared with baseline and day 10; difference in NIHSS scores and subscores (ie, motor) between baseline and day 10 and between baseline and month 3; Barthel index at month 3; and mini-mental status examination at day 10 and month 3. Safety end points included death, SAEs, and non-SAEs for all patients who received any study treatment.

Sample Size Calculation

Based on the distribution of mRS at 6 months of the aspirin group in the FISS-tris study[21] and the assumption of an average odds ratio (OR) of 1.5 for the MLC601 group, to achieve a power of 90% and 2-sided test of 5% type I error, a sample size of 874 was needed. A target of 1100 randomized subjects was set for the study to allow a maximum dropout rate of 20%.

Statistical Analysis

Efficacy analyses were based on the intention-to-treat principle. For the primary efficacy outcome, the difference in distribution of subjects within each range of mRS between placebo and MLC601 groups was tested by univariable ordinal logistic regression using treatment group as an independent variable. Multivariable ordinal logistic regression adjusting for potential prognostic factors was also conducted. The resulting estimates of the unadjusted and adjusted cumulative OR and associated 95% confidence interval (CI) obtained were reported. Proportional odds assumption and stochastic ordering assumption were also checked. For subjects whose mRS scores were not available at 3 months, the score was imputed by the last observation carried forward method.

Categorical secondary efficacy outcomes were compared using χ^2 test or Fisher exact test. Logistic regression adjusting for potential prognostic factors was also performed when necessary. The mean difference between treatment groups was assessed by the 2-sample *t* test, if normality assumption was valid. For non-normal data, the Mann–Whitney *U* test was applied.

Per-protocol analysis was performed for primary and secondary efficacy outcomes. Subjects not satisfying all inclusion/exclusion criteria and subjects not compliant to ≥80% of the study treatment were excluded from the per-protocol analysis. As-treated analysis, by including subjects who have actually taken ≥1 dose of the allocated drug, was performed for safety outcomes. Pre-specified subgroup analyses included time from stroke onset, baseline NIHSS score, presence of cortical signs on baseline NIHSS, and antiplatelet treatment received.

Interim Analysis

Two interim efficacy analyses were scheduled, performed, and presented to the Data and Safety Monitoring Board after 220 subjects and 660 subjects had been recruited. The stopping guidelines were based on the O'Brien-Fleming method, with a significance level of 0.0006 for the first and 0.0156 for the second interim analysis. In both reviews (October 25, 2009, and March 28, 2011), the Data and Safety Monitoring Board recommended continuation of recruitment up to the target of 1100 patients.

Results

From November 5, 2007, to May 8, 2012, 1100 subjects were randomized. One patient withdrew consent soon after randomization and was excluded as directed by the responsible ethics committee. Of the remaining 1099 patients, 550 subjects were allocated to MLC601 and 549 to placebo (Figure 1). Study treatment was not received by 8 subjects assigned to MLC601 and by 4 subjects assigned to placebo.

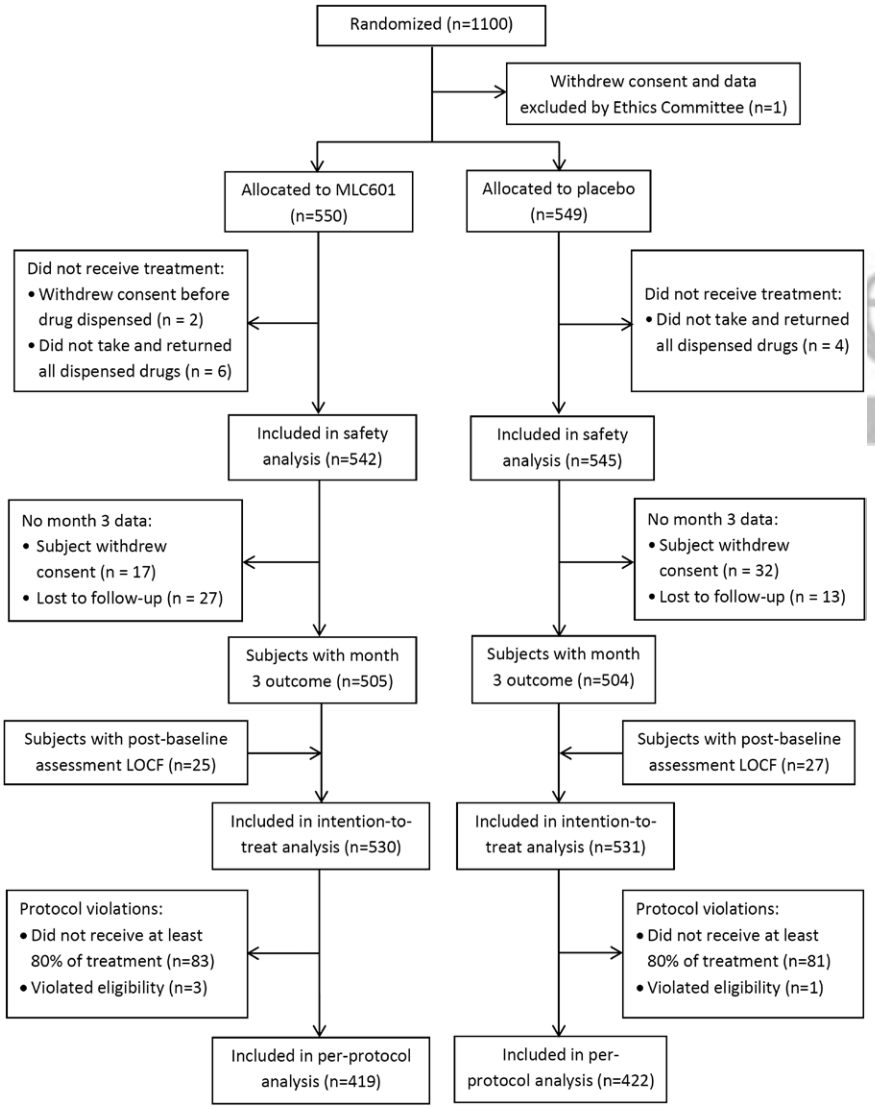

Figure 1. Flow diagram of patients in the CHInese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) Study. LOCF indicates last observation carried forward.

Table 1. Baseline Characteristics

	NeuroAiD (n=550)	Placebo (n=549)
Age, y	61.3 (10.8)	61.5 (11.8)
Women	210 (38.2%)	196 (35.7%)
NIHSS score	8.8 (2.5)	8.6 (2.5)
Prestroke mRS		
0	505 (91.8%)	513 (93.4%)
1	45 (8.2%)	36 (6.6%)
MMSE score	24.5 (6.2)	24.9 (6.0)
Stroke onset to randomization, h	45.4 (16.9)	44.1 (17.4)
Stroke onset to first dose, h	48.5 (17.2)	47.4 (17.5)
Previous history of cerebrovascular event		
TIA	17 (3.1%)	14 (2.6%)
Ischemic stroke	49 (8.9%)	50 (9.1%)
Hemorrhagic stroke	5 (0.9%)	3 (0.6%)
Medical history of		
Myocardial infarction	14 (2.6%)	20 (3.6%)
Angina	13 (2.4%)	23 (4.2%)
Hypertension	448 (81.4%)	444 (80.9%)
DM, insulin dependent	10 (1.8%)	16 (2.9%)
DM, noninsulin dependent	161 (29.3%)	164 (29.9%)
Hyperlipidemia	264 (48.0%)	267 (48.6%)
Peripheral vascular disease	5 (0.9%)	3 (0.6%)
Smoking	255 (46.4%)	247 (45.0%)
Habitual alcohol intake	158 (28.7%)	157 (28.6%)
Ethnicity		
Chinese	181 (32.9%)	182 (33.2%)
Malay	35 (6.4%)	38 (6.9%)
Indian	12 (2.2%)	11 (2.0%)
Filipino	253 (46.0%)	252 (45.9%)
Thai	46 (8.4%)	47 (8.6%)
Others	23 (4.2%)	19 (3.5%)
Weight, kg	64.0 (12.4)	64.1 (11.6)
Height, cm	161.2 (10.3)	161.7 (8.8)
Systolic blood pressure, mm Hg	153.0 (25.6)	152.3 (26.2)
Diastolic blood pressure, mm Hg	86.8 (14.3)	87.4 (16.0)

Data are number (%) or mean (SD). DM indicates diabetes mellitus; MMSE, mini-mental status examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

The overall study population had a mean age of 61.4±11.3 years, with 406 (37%) women. The 2 treatment groups were well balanced in baseline characteristics (Table 1). A total of 505 (92%) in the MLC601 group and 504 (92%) in the placebo group had month 3 data. With last observation carried forward method, a total of 530 (96%) in the MLC601 group and 531 (97%) in the placebo group had month 3 data.

The distributions of mRS at month 3 in the MLC601 and placebo groups for the intention-to-treat and per-protocol analyses are shown in Figure 2. Age, female sex, habitual drinking, and baseline NIHSS total score were found to be significant prognostic factors for worse mRS at month 3 (Table II in the online-only Data Supplement). The multivariable ordinal logistic regression adjusting for prognostic factors showed an

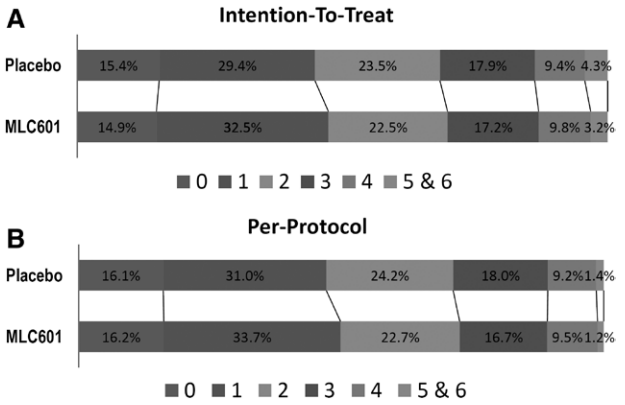

Figure 2. Shift analysis–modified Rankin scale at month 3. **A**, Intention-to-treat population. **B**, Per-protocol population.

adjusted OR of 1.09 (95% CI, 0.88–1.36; *P*=0.422). Similar nonsignificant results were found in the per-protocol analyses (details not reported).

Secondary outcome analyses showed an OR of 1.11 (95% CI, 0.86–1.42) for achieving an mRS of 0 to 1 at month 3 in favor of MLC601, although none of the mRS and NIHSS responders at various time points reached statistical significance. Similarly, no statistical differences were detected between the treatment groups in improvements in total NIHSS or motor score, Barthel index, and mini-mental status examination (Figure 3).

Subgroup analyses showed no statistical heterogeneity for the primary outcome, although trends for better treatment effects for MLC601 were observed in women and in those who received their first treatment dose >48 hours from stroke onset.

Safety was assessed in the 1087 subjects who received the study treatment. The occurrence of adverse events was similar between the 2 groups, with 230 (42%) subjects on MLC601 and 218 (40%) subjects on placebo reporting ≥1 adverse event. There were a total of 459 adverse events in the MLC601 group and 504 in the placebo group (Table 2). Sixty (11%) subjects in the MLC601 group experienced a total of 64 SAEs, of which only 4 were considered to be possibly, probably, or definitely related to study treatment, whereas 74 (14%) subjects in the placebo group experienced a total of 98 SAEs. There were 28 deaths, 13 (2.4%) in the MLC601 group and 15 (2.8%) in the placebo group. Among the deaths, 1 subject on MLC601 and 4 subjects on placebo died of progression of disease, whereas the rest died of other causes. No treatment allocation code was unblinded as a result of SAE.

Patients on anticoagulation were excluded because of safety concerns caused by the lack of published data on the interaction of MLC601with anticoagulants, particularly in the acute phase of stroke. At baseline, 7 patients had atrial fibrillation, but none were on anticoagulation because of patient or physician choice. A total of 8 patients were reported to have developed atrial fibrillation during the course of the trial. Seven had their trial medication permanently discontinued. In 1 case, the trial medication was temporarily discontinued because the patient was anticoagulated for 10 days.

Concomitant medications were recorded throughout the trial, and only 3 patients received open-labeled TCM: 2 of ginkgo and 1 unspecified TCM. Hence, cross-contamination by use of open-labeled TCM is negligible.

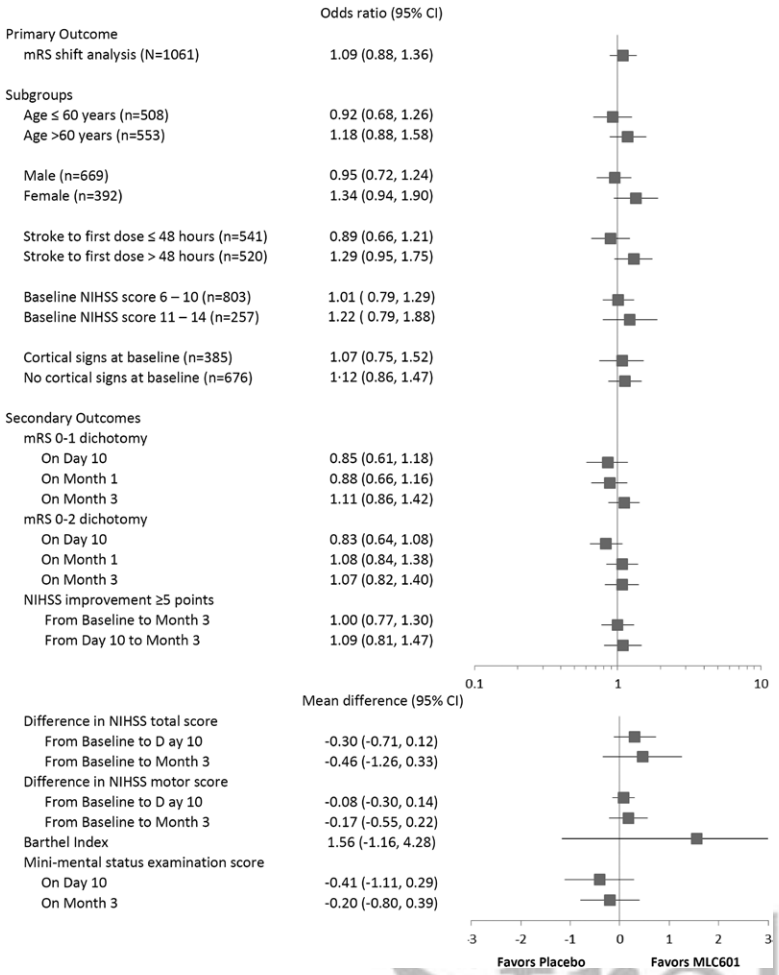

Figure 3. Forest plots of outcomes and subgroups by intention-to-treat analyses. CI indicates confidence interval; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Discussion

The CHIMES Study is the largest randomized placebo-controlled clinical trial of traditional medicine in ischemic stroke. Because previous studies on MLC601 suggested a benefit in nonacute ischemic stroke patients,[11–17] the time window of 72 hours was chosen for this study in an attempt to test both the neuroprotective and neurorestorative properties of MLC601.

There was no statistical difference between MLC601 and placebo for the primary and secondary outcomes. The point estimates of the mRS shift analysis–adjusted OR of 1.09 and mRS ≤1 dichotomy OR of 1.11 in favor of MLC601 were higher than those in recently completed stroke neuroprotection trials.[22–24] The absolute benefit of achieving an independent functional outcome (mRS, 0–1) was 26 per 1000 patients treated. It is plausible that with a larger study population, such a moderate clinically relevant treatment effect may be detected with statistical significance.

The safety of MLC601 was confirmed by this study. There was no difference between MLC601 and placebo for all serious and non-SAEs. Although more adverse events were reported in this study compared with previous publications, this may reflect the quality of monitoring in this trial and the recruitment of acute instead of chronic patients rather than reduced safety.

In CHIMES, nearly half of the patients in the placebo group achieved independence (mRS, 0–1), more than two-thirds achieved an mRS of 0 to 2, whereas <5% were deceased or completely disabled at 3 months. This was likely because of the exclusion of more severe strokes in the study and may also reflect the general improvement in acute stroke care since the study was designed. The rate of good outcomes at month 3 in the CHIMES study was higher than in other recently completed trials[22–25] and has been shown to affect the potential of detecting treatment effects.[26]

The subgroup analysis suggests that MLC601 may be more likely to benefit patients who are treated beyond 48 hours from stroke onset. This is consistent with previously published studies on MLC601, which detected improved functional outcomes and motor recovery among mainly nonacute ischemic stroke patients.[11,12,14] These findings support the possible neurorestorative effects of MLC601 and would be topics of interest for further nonclinical and clinical investigations.

A recent systematic review on the efficacy and safety of MLC601 in ischemic stroke showed an OR of 2.35 (95% CI, 1.31–4.23) for good functional recovery by the end of the studies.[27] We updated the meta-analysis to include all CHIMES patients, and this showed an OR for good functional outcome at the end of study period of 1.25 (95% CI, 1.00–1.56; P=0.05) in favor of MLC601 (Figure 4). Because all the studies in the systematic review had nonacute strokes with onset-to-treatment windows of ≤1 week to 6 months, we explored the effect of time window by including only CHIMES patients who started treatment >48 hours from stroke onset. This increased the OR to 1.63 (95%

Table 2. Adverse Events Reported in the Study

	MLC601 (n=542)	Placebo (n=545)
AEs	459	504
AE relatedness to treatment		
Not related	297	318
Unlikely	117	151
Possibly/probably/definitely	36	29
Unknown	9	6
Study treatment		
Temporarily interrupted	28	36
Permanently discontinued	50	39
Serious adverse events	64	98
SAE criteria		
Death	13	16
Life-threatening	6	14
Inpatient hospitalization	29	42
Prolonged hospitalization	7	25
Resulted in disability/incapacity	9	6
Important medical event	8	16
Other	0	1
SAE relatedness to treatment		
Not related	37	56
Unlikely	22	35
Possibly/probably/definitely	4	5
Unknown	1	3
Ten most common SAEs		
Recurrent stroke	10	18
Stroke progression	9	12
Acute coronary syndrome/ischemic heart disease	3	13
Gastrointestinal bleeding	4	13
Sepsis	4	7
Pneumonia	5	4
Urinary tract infection	3	3
Intracerebral hemorrhage	3	2
Heart failure	2	2
Hypertension, uncontrolled	1	3

AE indicates adverse event; and SAE, serious adverse event.

CI, 1.20–2.22; *P*=0.002) and further reduced heterogeneity, suggesting that the patients treated later in the CHIMES study were more comparable with those included in previous studies.

In searching for an effective stroke treatment that could span the acute phase (to reduce cellular injury and death) to the recovery phase (to repair the brain and restore function), it is important to appreciate that the highly regulated and complex responses of the brain to injury after a stroke mean that many therapeutic targets have temporal profiles. Although particular targets may mediate injury in the acute phase, the same target may mediate neurovascular restoration in the chronic phase. Conversely, a target of potential benefit in the chronic phase may not be so in the acute phase. Treatment candidates should take into consideration this transition from injury to repair.[28]

There are several study limitations: (1) 100% follow-up was not achieved, but CHIMES is comparable with most recently published neuroprotectant studies, and the last observation carried forward is an acceptable statistical technique to address this issue by increasing follow-up from 92% to 97%; (2) a large proportion of mild strokes; (3) the time window was ≤72 hours; and (4) the follow-up period was short.

A longer duration of treatment and follow-up of patients could improve the sensitivity of detecting the effects on long-term recovery for a treatment like MLC601, which has both neuroprotective properties and neurorestorative properties based on nonclinical studies. It is well known that patients with stroke recover spontaneously mostly during the first 3 months after a stroke.[29] However, there remains the possibility of further recovery subsequently. Hence, 3 months of follow-up, as is the case in many, if not all, previous trials, may be of insufficient length to detect a treatment effect. CHIMES-E, an extension study that follows up patients who participated in the main CHIMES Study for ≤2 years from stroke, is currently ongoing.[30] Nevertheless, the main strengths of our study are that it is a well-conducted, multicenter study with a large sample size, performed in a blinded, placebo-controlled manner.

Traditional medicine is widely used globally, but many Western-trained professionals have strong reservations about its benefits. This conflict between uncritical enthusiasm and uninformed skepticism can only be resolved by large controlled randomized clinical trials such as the CHIMES study, which is among the first to investigate the use of a product from traditional natural substances in reducing disability after an acute stroke in a rigorous manner. Although the study overall did not reach statistical significance in outcome measures, despite point estimates in favor of MLC601, the long-term treatment effect of MLC601 in nonacute strokes would merit further exploration.

Acknowledgments

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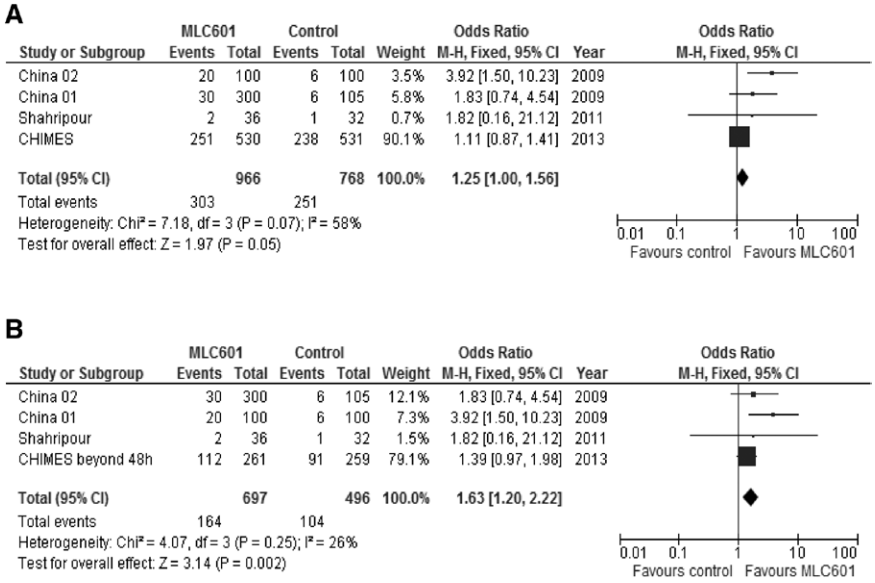

Figure 4. Forest plots for updated meta-analysis on MLC601. **A**, Functional outcome at end of study, including all patients in the CHInese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) Study; **B**, Functional outcome at end of study, including patients treated >48 hours from stroke onset in the CHIMES Study.

Medical Center (48; Dr Advincula, Eli John Berame), Cebu Hospitals (Visayas Community Center and Chong Hua Hospital; 3; Maria Teresa Canete) Singapore (n=455, National Coordinator: Dr Venketasubramanian)–Changi General Hospital (223; Dr Young, Marlie Jane Mamauag, San San Tay, Shrikant Pande), National Neuroscience Institute-Tan Tock Seng Hospital (120; Umapathi Thirugnanam, Dr Singh), National Neuroscience Institute-Singapore General Hospital (74; Hui Meng Chang, Deidre Anne De Silva), National University Hospital (38; Dr Chan, Vijay Sharma, Teoh Hock Luen) Thailand (n=94; National Coordinator: Dr Poungvarin)–Thammasat University Hospital (42; Dr Muengtaweepongsa), Prasat Neurological Institute (15; Dr Towanabut), King Chulalongkorm Memorial Hospital (13; Dr Suwanwela), Siriraj Hospital (12; Songkram Chotickanuchit), Chiang Mai University Hospital (11; Dr Chankrachang), Phramongkutklao Hospital (1; Samart Nitinun) Sri Lanka (n=28; National Coordinator: Dr de Silva)–University of Kelaniya (Udaya Ranawake, Nirmala Wijekoon) Hong Kong (n=10)–Prince of Wales Hospital (Dr Wong) Malaysia (n=9)–Penang General Hospital (Dr Eow).

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References

1. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.
2. Ginsberg MD. Current status of neuroprotection for cerebral ischemia: synoptic overview. *Stroke*. 2009;40(3 Suppl):S111–S114.
3. Pandian JD, Liu M, Misbach J, Venketasubramanian N. Alternative therapies for stroke treatment in Asia. *Int J Stroke*. 2011;6:541–543.
4. Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. *Acta Neurobiol Exp (Wars)*. 2006;66:369–375.
5. Bei W, Peng W, Zang L, Xie Z, Hu D, Xu A. Neuroprotective effects of a standardized extract of Diospyros kaki leaves on MCAO transient focal cerebral ischemic rats and cultured neurons injured by glutamate or hypoxia. *Planta Med*. 2007;73:636–643.
6. Wu B, Liu M, Liu H, Li W, Tan S, Zhang S, et al. Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke*. 2007;38:1973–1979.
7. Junhua Z, Menniti-Ippolito F, Xiumei G, Firenzuoli F, Boli Z, Massari M, et al. Complex traditional Chinese medicine for poststroke motor dysfunction: a systematic review. *Stroke*. 2009;40:2797–2804.
8. Heurteaux C, Gandin C, Borsotto M, Widmann C, Brau F, Lhuillier M, et al. Neuroprotective and neuroproliferative activities of NeuroAid (MLC601, MLC901), a Chinese medicine, in vitro and in vivo. *Neuropharmacology*. 2010;58:987–1001.
9. Quintard H, Borsotto M, Veyssiere J, Gandin C, Labbal F, Widmann C, et al. MLC901, a traditional Chinese medicine protects the brain against global ischemia. *Neuropharmacology*. 2011;61:622–631.
10. Moha Ou Maati H, Borsotto M, Chatelain F, Widmann C, Lazdunski M, Heurteaux C. Activation of ATP-sensitive potassium channels as an element of the neuroprotective effects of the Traditional Chinese Medicine MLC901 against oxygen glucose deprivation. *Neuropharmacology*. 2012;63:692–700.
11. Chen C, Venketasubramanian N, Gan RN, Lambert C, Picard D, Chan BP, et al. Danqi Piantang Jiaonang (DJ), a traditional Chinese medicine, in poststroke recovery. *Stroke*. 2009;40:859–863.
12. Harandi AA, Abolfazli R, Hatemian A, Ghragozlee K, Ghaffar-Pour M, Karimi M, et al. Safety and efficacy of MLC601 in Iranian patients after stroke: a double-blind, placebo-controlled clinical trial. *StrokeRes Treat*. 2011;2011:721613.
13. Kong KH, Wee SK, Ng CY, Chua K, Chan KF, Venketasubramanian N, et al. A double-blind, placebo-controlled, randomized phase II pilot study to investigate the potential efficacy of the traditional Chinese medicine Neuroaid (MLC 601) in enhancing recovery after stroke (TIERS). *Cerebrovasc Dis*. 2009;28:514–521.
14. Bavarsad Shahripour R, Shamsaei G, Pakdaman H, Majdinasab N, Nejad EM, Sajedi SA, et al. The effect of NeuroAiD™ (MLC601) on cerebral blood flow velocity in subjects' post brain infarct in the middle cerebral artery territory. *Eur J Intern Med*. 2011;22:509–513.
15. Ghandehari K, Mood ZI, Ebrahimzadeh S, Picard D, Zhang Y. NeuroAid (MLC601) versus piracetam in the recovery of post-infarct homonymous hemianopsia. *Neural Regener Res*. 2011;6:418–422.
16. Navarro JC, Molina MC, Baroque Ii AC, Lokin JK. The use of NeuroAiD (MLC601) in postischemic stroke patients. *Rehabil Res Pract*. 2012;2012:506387.
17. Siow CH. Neuroaid in stroke recovery. *Eur Neurol*. 2008;60:264–266.

18. Young SHY, Zhao Y, Koh A, Singh R, Chan BP, Chang HM et al. Safety profile of MLC601 (Neuroaid) in acute ischemic stroke patients: a Singaporean substudy on the Chinese Medicine Neuroaid efficacy on Stroke Recovery Study. *Cerebrovasc Dis*. 2010;30:1–6.
19. Gan R, Lambert C, Lianting J, Chan ES, Venketasubramanian N, Chen C, et al. Danqi Piantan Jiaonang does not modify hemostasis, hematology, and biochemistry in normal subjects and stroke patients. *Cerebrovasc Dis*. 2008;25:450–456.
20. Venketasubramanian N, Chen CL, Gan RN, Chan BP, Chang HM, Tan SB, et al.; CHIMES Investigators. A double-blind, placebo-controlled, randomized, multicenter study to investigate CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study). *Int J Stroke*. 2009;4:54–60.
21. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, et al; FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol*. 2007;6:407–413.
22. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, et al; SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med*. 2007;357:562–571.
23. Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, et al; International Citicoline Trial on acUte Stroke (ICTUS) trial investigators. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet*. 2012;380:349–357.
24. Lees KR, Bornstein N, Diener HC, Gorelick PB, Rosenberg G, Shuaib A; MACSI Investigators. Results of membrane-activated chelator stroke intervention randomized trial of DP-b99 in acute ischemic stroke. *Stroke*. 2013;44:580–584.
25. Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z; Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke*. 2012;43:630–636.
26. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8:141–150.
27. Siddiqui FJ, Venketasubramanian N, Chan ES, Chen C. Efficacy and safety of MLC601 (NeuroAiD®), a traditional Chinese medicine, in poststroke recovery: a systematic review. *Cerebrovasc Dis*. 2013;35(Suppl 1):8–17.
28. Lo EH. A new penumbra: transitioning from injury into repair after stroke. *Nat Med*. 2008;14:497–500.
29. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. *Stroke*. 1992;23:1084–1089.
30. Venketasubramanian N, Young S, Tay SS, Chang HM, Umapathi T, Chan B, et al. Chinese medicine NeuroAiD efficacy stroke recovery-extension study (CHIMES-E study): an observational multicenter study to investigate the longer-term efficacy of NeuroAiD in stroke recovery. *Cerebrovasc Dis*. 2013;35(Suppl 1):18–22.

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Chinese Medicine Neuroaid Efficacy on Stroke Recovery: A Double-Blind, Placebo-Controlled, Randomized Study

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SUPPLEMENTAL MATERIAL

Online Supplemental Tables:

I. Inclusion and exclusion criteria in the CHIMES Study

Inclusion Criteria	Exclusion Criteria
• Males and females aged 18 years or older • Ischemic stroke of intermediate severity (National Institutes of Health Stroke Scale 6 to 14) • Stroke onset in the preceding 72 hours • Computed tomography (CT) or magnetic resonance imaging (MRI) data compatible with cerebral infarction • On anti-platelet therapy • Have a pre-stroke Modified Rankin Scale (mRS)</=1	• A rapidly improving neurological deficit • Evidence of intracerebral hemorrhage on brain CT scan or MRI • Unstable post-thrombolysis • Other significant non-ischemic brain lesions which could affect function or disability • Definite indication for full-dose or long-term anticoagulation therapy • Co-existing systemic diseases which could affect assessment or follow-up: renal failure (creatinine >200umol/L if known), cirrhosis, severe dementia or psychosis • Participation in another clinical trial within the preceding three months • Women of childbearing potential

II. Univariable and multivariable ordinal logistic regression analysis of primary outcome and baseline prognostic factors.

	Estimated coefficient (SE)	Odds Ratio (95% CI)	p-value
Treatment - Neuroaid (Unadjusted)	0.06 (0.11)	1.07 (0.86 - 1.32)	0.5545
Treatment - Neuroaid (Adjusted)	0.09 (0.11)	1.09 (0.88 - 1.36)	0.4218
Age	-0.04 (0.01)	0.96 (0.95 - 0.97)	<0.0001
Sex (Female)	-0.48 (0.13)	0.62 (0.48 - 0.80)	0.0002
Habitual Drinking (Yes)	-0.34 (0.14)	0.71 (0.55 - 0.93)	0.0135
Baseline NIHSS total score	-0.37 (0.02)	0.69 (0.66 - 0.73)	<0.0001