Original Contribution

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

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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...
neuroprotectants have failed to live up to their potential.\textsuperscript{2} Hence, better treatments are needed to enhance poststroke recovery.

Traditional Chinese medicine (TCM) is used extensively in Asia to facilitate recovery after stroke.\textsuperscript{1} Pharmacological studies have demonstrated some TCM to have antioxidant, anti-inflammatory, vasodilatory, antiplatelet, antitumour, and protective effects against ischemia and reperfusion injury.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11} More studies have since been published assessing the benefit and safety of MLC601 in nonacute stroke patients using different clinical outcomes.\textsuperscript{12–19} Although most patients experience some spontaneous recovery in the months after a stroke, the degree and timing of recovery vary. 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\textsuperscript{4–10} and the excellent safety profile\textsuperscript{14,19} 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 MLC601 is 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.\textsuperscript{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 1 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 permuted 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.\textsuperscript{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 miltiorrhizea, Radix peoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae, and Rhizoma acori tatarinowii) and 5 animal components (Hirudo, Eupolyphaga seulestheopaha, Calceulus bovis artifactus, Buthus martensi, 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 assessed. Vital signs were recorded; physical examination, National Institutes of Health Stroke Scale (NIHSS), and mini-mental status examination were assessed.

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/us/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\textsuperscript{19} 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 χ² 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.
Table 1. Baseline Characteristics

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

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 504 (92%) 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 MLC601 with 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.
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, 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. 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 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. 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, and has been shown to affect the potential of detecting treatment effects.

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. 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. 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%
take into consideration this transition from injury to repair.\(^{28}\) Conversely, a target of potential benefit in the chronic phase may mediate neurovascular restoration in the chronic phase. Targets may mediate injury in the acute phase, the same target was more comparable with those included in previous studies. \(P=0.002\) 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.\(^{28}\)

### Table 2. Adverse Events Reported in the Study

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

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

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.\(^{39}\) 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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**References**


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


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### I. Inclusion and exclusion criteria in the CHIMES Study

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

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