Baseline characteristics and treatment response of patients from the Philippines in the CHIMES study

Jose C. Navarro[1,*], Herminigildo H. Gan[2], Annabelle Y. Lao[3], Alejandro C. Baroque II[1], John H. B. Hiyadan[4], Carlos L. Chua[5], Ma. Cristina San Jose[5], Joel M. Advincula[6], Chun Fan Lee[7], Marie-Germaine Bousser[8], Christopher L. H. Chen[9], for the CHIMES Study Investigators

Background **The CHIMES Study compared MLC601 with placebo in patients with ischemic stroke of intermediate severity in the preceding 72 h. Sites from the Philippines randomized 504 of 1099 (46%) patients in the study. We aimed to define the patient characteristics and treatment responses in this subgroup to better plan future trials.**

Methods **The CHIMES dataset was used to compare the baseline characteristics, time from stroke onset to study treatment initiation, and treatment responses to MLC601 between patients recruited from Philippines and the rest of the cohort. Treatment effect was analyzed using end-points at month 3 as described in the primary publication, that is, modified Rankin Score, National Institutes of Health Stroke Scale, and Barthel Index.**

Results **The Philippine cohort was younger, had more women, worse baseline National Institutes of Health Stroke Scale, and longer time delay from stroke onset to study treatment compared with the rest of the cohort. Age ($P = 0{\cdot}003$), baseline National Institutes of Health Stroke Scale ($P < 0{\cdot}001$), and stroke onset to study treatment initiation ($P = 0{\cdot}016$) were predictors of modified Rankin Score at three-months. Primary analysis of modified Rankin Score shift was in favor of MLC601 (adjusted odds ratio 1·41, 95% confidence interval 1·01–1·96). Secondary analyses were likewise in favor of MLC601 for modified Rankin Score dichotomy 0–1, improvement in National Institutes of Health Stroke Scale (total and motor scores), and Barthel Index.**

Conclusions **The treatment effects in the Philippine cohort were in favor of MLC601. This may be due to inclusion of more patients with predictors of poorer outcome.**

Key words: acute stroke, clinical trial, MLC601, NeuroAiD, Philippines, stroke recovery

Correspondence: Jose C. Navarro*, Neurology and Psychiatry, University of Santo Tomas Hospital, España Boulevard, Manila 1008, Philippines.
E-mail: josecnavarromd@gmail.com
[1]Neurology and Psychiatry, University of Santo Tomas Hospital, Manila, Philippines
[2]Neurology, Jose Reyes Memorial Medical Center, Manila, Philippines
[3]San Pedro Hospital, Davao Medical School Foundation Hospital, Davao City, Philippines
[4]Neurology, Baguio General Hospital and Medical Center, Baguio City, Philippines
[5]Neurosciences, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines
[6]Neurology, West Visayas State University Medical Center, Iloilo City, Philippines
[7]Statistics, Singapore Clinical Research Institute, Singapore, Singapore
[8]Neurology, Lariboisière University Hospital, Paris, France
[9]Pharmacology, Clinical Research Centre, National University of Singapore, Singapore, Singapore

Received: 11 March 2014; Accepted: 2 June 2014; Published online 7 July 2014

Conflict of interest: C. L. H. C. received grants from the National Medical Research Council of Singapore and funding from the CHIMES Society for conferences and meetings for presentation of CHIMES data. The other authors received funding for the trial and accommodation and transportation support for meetings from the CHIMES Society. Moleac (Singapore) provided grants to the CHIMES Society of which the society had sole discretion on use. J. C. N., H. H. G., A. Y. L., and A. C. B. have minor shares in E*Chimes, the Philippine distributor of NeuroAiD.

Funding: The CHIMES study was supported by grants from the National Medical Research Council of Singapore (NMRC/1288/2011 and NMRC/1096/2006) and the CHIMES Society.

DOI: 10.1111/ijs.12324

Introduction

MLC601 (NeuroAiD), a product combining extracts of nine herbal and five animal components in capsule form, has been shown to restore neurological and cellular function in nonclinical models of ischemic stroke (1–3). Clinical studies in patients with nonacute stroke show that MLC601 enhances recovery of functional outcome and neurological disability (4). The CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study is an international, randomized, placebo-controlled, double-blind trial that compared MLC601 with placebo in 1099 patients with acute ischemic stroke of intermediate severity [baseline National Institutes of Health Stroke Scale (NIHSS) of 6 to 14] in the preceding 72 h, with sites from Hong Kong, Malaysia, Philippines, Singapore, Sri Lanka, and Thailand (5,6). The study had a major contribution from the Philippines (6,7) (PH) where sites recruited 504 (46%) of the 1099 total study population. In this preplanned secondary analysis, we aimed to define the patient characteristics and treatment response in this subgroup of patients to better plan future trials.

Methods

Analysis was performed using data from the CHIMES Study (www.clinicaltrials.gov NCT00554723). Subjects in the study were allocated by block randomization stratified for centers to either MLC601 or placebo for three-months as add-on to standard stroke care (5,6).

We compared the baseline characteristics of patients, risk factors, and time from stroke onset with study treatment initiation among patients recruited from PH sites and from other countries. Multivariable logistic regression analysis was

Table 1 Comparison of baseline characteristics and risk factor profiles of patients included in the CHIMES Study from the Philippines and other countries

	Philippines (n = 504)	Other countries (n = 595)	OR (95% CI)
Age (>60 years)	239 (47%)	328 (55%)	0·73 (0·58–0·93)*
Sex (female)	228 (45%)	178 (30%)	1·94 (1·51–2·48)*
Baseline NIHSS score ≥ 10	226 (45%)	137 (23%)	2·72 (2·10–3·52)*
Stroke onset to first dose (≥48 h)	269 (54%)	261 (44%)	1·49 (1·17–1·89)*
Previous history of:			
TIA	16 (3%)	15 (3%)	1·27 (0·62–2·59)
Ischemic stroke	32 (6%)	67 (11%)	0·53 (0·34–0·83)*
Hemorrhagic stroke	3 (1%)	5 (1%)	0·71 (0·17–2·97)
Myocardial infarction or angina	18 (4%)	52 (9%)	0·39 (0·22–0·67)*
Hypertension	460 (91%)	432 (73%)	3·95 (2·76–5·65)*
Diabetes mellitus	120 (24%)	231 (39%)	0·49 (0·38–0·64)*
Hyperlipidemia	38 (8%)	493 (83%)	0·02 (0·01–0·03)*
Smoking	218 (43%)	284 (48%)	0·84 (0·66–1·06)
Habitual alcohol intake	166 (33%)	149 (25%)	1·49 (1·15–1·93)*

*Statistically significant. CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke recovery; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TIA, transient ischemic attack.

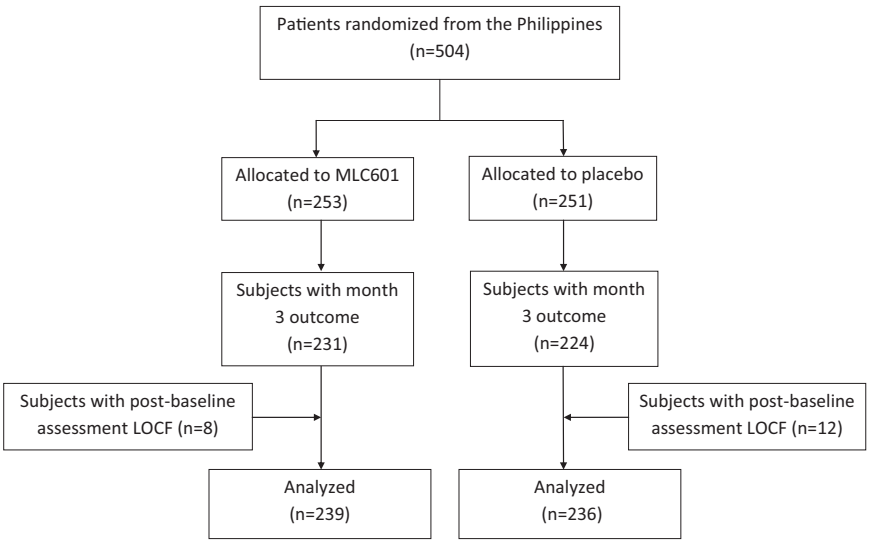

Fig. 1 Flow diagram of patients randomized from the Philippines in the CHIMES Study. LOCF, last observation carried forward.

performed to identify predictors of month 3 mRS. Adjusted odds ratio (OR) and the corresponding 95% confidence intervals (CIs) were used to estimate treatment effect size using the same primary and secondary end-points at month 3 as described in the primary publication, that is, modified Rankin Score (mRS), National Institutes of Health Stroke Scale (NIHSS), and Barthel Index (BI), using the last observation carried forward method for missing month 3 data.

Results

The overall baseline characteristics and study flow of patients in the CHIMES Study were previously described (6). Patients from PH were younger but had more women, worse baseline NIHSS, and longer delay between stroke onset and initiation of study treatment, and different vascular risk factor profile compared with patients from other countries in the CHIMES study (Table 1). Figure 1 shows the study flow of Filipino patients randomized in the CHIMES Study.

Overall, age ($P = 0·003$), baseline NIHSS ($P < 0·001$), and stroke onset to study treatment initiation ($P = 0·016$) were predictors of mRS at three-months in the PH cohort. Treatment effect in the PH cohort was in favor of MLC601, with an adjusted OR of 1·41 (95% CI 1·01–1·96) for the primary analysis of mRS shift (Table 2). Secondary outcomes were likewise in favor of MLC601 for mRS dichotomy 0–1, improvement in total NIHSS score, improvement in NIHSS motor score, and BI (Fig. 2).

Safety assessment of the PH cohort showed similar rates of adverse events (serious or nonserious) between the two groups, with very few events considered to be possibly, probably, or definitely related to study treatment (Table 3). No treatment allocation code was unblinded due to adverse event.

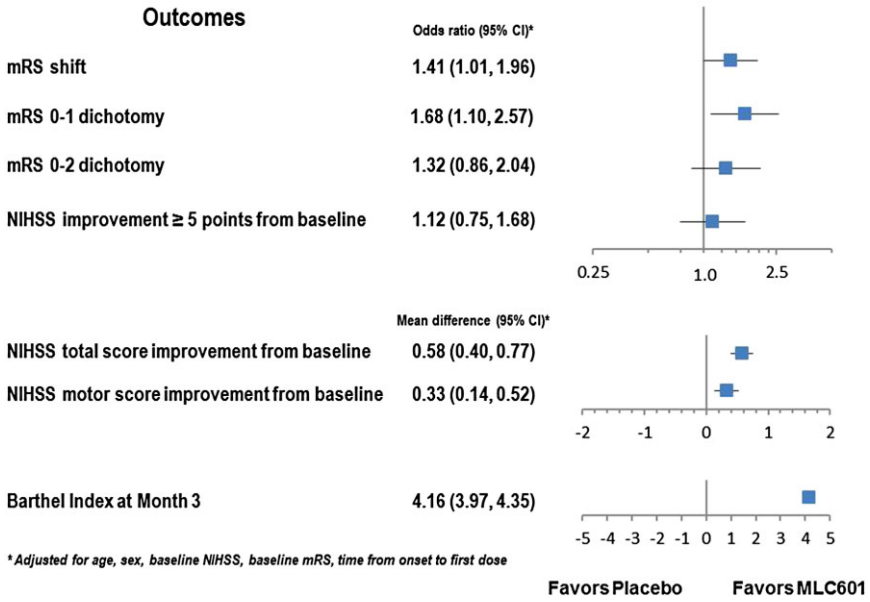

Fig. 2 Forest plot of primary and secondary outcomes by intention-to-treat analyses in the CHIMES Study Philippine cohort. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2 Univariable and multivariable ordinal logistic regression analysis of primary outcome and baseline prognostic factors

Variable	OR (95% CI)	*P* value
Treatment – MLC601 (unadjusted)	1·28 (0·92, 1·76)	0·138
Treatment – MLC601 (adjusted)	1·41 (1·01, 1·96)	0·043
Age	0·98 (0·96, 0·99)	0·003
Female gender	0·80 (0·57, 1·12)	0·200
Baseline NIHSS	0·67 (0·63, 0·72)	<0·001
Stroke onset to first dose >48 h	0·67 (0·48, 0·93)	0·016
Prestroke mRS = 1	0·59 (0·30, 1·17)	0·134

CI, confidence interval; mRS, modified Rankin Scale ; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table 3 Adverse events reported among patients recruited from the Philippines in the CHIMES Study

	MLC601 (*n* = 253)	Placebo (*n* = 251)
Adverse events	92	102
Relatedness		
Not related	88	89
Unlikely	3	11
Possibly/probably/definitely	0	2
Unknown	1	0
Serious adverse events	16	27
Seriousness criteria		
Death	10	11
Life-threatening	3	2
Inpatient hospitalization	3	7
Prolonged hospitalization	1	4
Resulted in disability/incapacity	0	0
Important medical event	4	7
Other	0	0
Relatedness		
Not related	14	21
Unlikely	2	4
Possibly/probably/definitely	0	2
Unknown	0	0

CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke recovery.

Discussion

Our analyses performed on the Filipino subgroup of the CHIMES Study showed favorable treatment effects of MLC601 as measured by primary and several secondary outcome measures. Compared with other countries, PH sites included more female patients and those with worse baseline NIHSS score and longer treatment delay from stroke onset which are predictors of poorer recovery.

Stroke patient outcome in clinical trials varies between countries and may partly be accounted for, albeit not fully explained, by differences in baseline characteristics ('case mix') and process of stroke care (8,9). Hence, it is important to prospectively balance treatment allocation within sites and countries to avoid biases from such factors.

The primary overall results of the CHIMES study was in favor of MLC601, although this did not reach statistical significance. The sample size of 1100 was based on the distribution of mRS at six-months of the control (aspirin-treated) group in the Fraxiparine in Ischemic Stroke Study-tris (10), with a power of 90% and 5% type I error to detect an assumption of an average OR of 1·5 for the MLC601 group. The OR of 1·09 seen in the study would require a bigger sample size to reach statistical significance.

The inclusion of more women and relatively more severe stroke patients in the PH cohort is likely to have improved the potential of statistically detecting a treatment effect when assessed using the same predefined outcome measure than patients with excellent prognosis for natural recovery (11). Baseline characteristics like age, gender, and stroke severity may affect the chances of identifying a treatment-related effect in clinical trials (12,13). In addition, it is plausible that differences in processes of stroke care may

account for country to country variation. In the CHIMES Study, more patients from PH were initiated on the study treatment after 48 h from stroke onset compared with patients from other countries. The reasons for prehospital and hospital delays in the care of stroke patients in PH have previously been reported (14).

Nevertheless, adjusting for the above variables as well as age did not alter qualitatively the treatment effects seen in the PH cohort, suggesting that other unmeasured factors may play a role. Bias, chance, and confounding factors may underlie some of the residual variation (8,9) and will need to be controlled by achieving a more homogeneous case mix in future trials.

There are some limitations in this study. The number of patients recruited was not comparable among the different countries, making country-to-country comparisons difficult. Other possibly important variables which may contribute to subtle forms of bias, for example, economic, nutritional, quality of care indicators, genomic, were not collected in the study to enable their assessment as confounders. In addition, our findings may not be extrapolated beyond the population included in the study, that is, more severe strokes or those occurring outside of the 72-h time window. The strengths of the study are the randomized double-blind study design, the large number of patients, and high quality of follow-up.

In summary, the PH cohort in the CHIMES study has prognostic and vascular risk factor profiles that are different from those recruited from other countries. The larger treatment effect of MLC601 in the PH cohort as compared with the overall population in the CHIMES Study was likely due to inclusion of patients with more predictors for poorer outcome, as well as possibly other unmeasured baseline factors. These hypothesis-generating insights would be helpful in the design of stroke trials. As a next step, we propose an analysis of the role of baseline prognostic factors and how they affect treatment-related effects in the whole CHIMES cohort and in other clinical trial databases to guide patient selection and analyses in future clinical trials.

Acknowledgements

CHIMES Study Investigators: Philippines – Jose C. Navarro, Herminigildo H. Gan, Annabelle Y. Lao, Alejandro C. Baroque II, Johnny Lokin, John H. B. Hiyadan, Ma. Socorro Sarfati, Randolph John Fangonillo, Neil Ambasing, Carlos L. Chua, Ma. Cristina San Jose, Joel M. Advincula, Eli John Berame, Maria Teresa Canete. Singapore – Narayanaswamy Venketasubramanian, Sherry H. Y. Young, Marlie Jane Mamauag, San SanTay, Shrikant Pande, Umapathi Thirugnanam, Rajinder Singh, Hui Meng Chang, Deidre Anne De Silva, Bernard P. L. Chan, Vijay Sharma, Teoh Hock Luen. Thailand – Niphon Poungvarin, Sombat Muengtaweepongsa, Somchai Towanabut, Nijasri Suwanwela, Songkram Chotickanuchit, Siwaporn Chankrachang, Samart Nitinun. Sri Lanka – H. Asita de Silva, Udaya Ranawake, Nirmala Wijekoon. Hong Kong – K. S. Lawrence Wong. Malaysia – Gaik Bee Eow.

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