

# Effect of Combined Treatment with MLC601 (NeuroAiD™) and Rehabilitation on Post-Stroke Recovery: The CHIMES and CHIMES-E Studies

Nijasri C. Suwanwela<sup>a</sup> Christopher L.H. Chen<sup>b</sup> Chun Fan Lee<sup>c</sup>  
Sherry H. Young<sup>d</sup> San San Tay<sup>d</sup> Thirugnanam Umapathi<sup>e</sup> Annabelle Y. Lao<sup>f</sup>  
Herminigildo H. Gan<sup>g</sup> Alejandro C. Baroque II<sup>h</sup> Jose C. Navarro<sup>i</sup> Hui Meng Chang<sup>j</sup>  
Joel M. Advincula<sup>k</sup> Sombat Muengtawepong<sup>l</sup> Bernard P.L. Chan<sup>m</sup>  
Carlos L. Chua<sup>n</sup> Nirmala Wijekoon<sup>o</sup> H. Asita de Silva<sup>p</sup> John Harold B. Hiyadan<sup>q</sup>  
Ka Sing Lawrence Wong<sup>r</sup> Niphon Pongvarin<sup>s</sup> Gaik Bee Eow<sup>t</sup>  
Narayanaswamy Venketasubramanian<sup>u</sup> CHIMES-E Study Investigators

<sup>a</sup>Chulalongkorn University, Chulalongkorn Stroke Centre, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; <sup>b</sup>Memory Aging and Cognition Centre, Department of Pharmacology, National University of Singapore, Singapore, Singapore; <sup>c</sup>School of Public Health, The University of Hong Kong, Pokfulam, Hong Kong; <sup>d</sup>Changi General Hospital, Singapore, Singapore; <sup>e</sup>National Neuroscience Institute, Tan Tock Seng Hospital Campus, Singapore, Singapore; <sup>f</sup>Southern Philippines Medical Center, Davao, Philippines; <sup>g</sup>Jose Reyes Memorial Medical Center, San Lazaro Compound, Manila, Philippines; <sup>h</sup>University of Santo Tomas Hospital, Manila, Philippines; <sup>i</sup>Jose R Reyes Medical Center, Neuroscience Institute St Luke's Medical Center, University of Santo Tomas Hospital, Manila, Philippines; <sup>j</sup>National Neuroscience Institute, Singapore General Hospital Campus, Singapore, Singapore; <sup>k</sup>West Visayas State University Medical Center, Iloilo, Philippines; <sup>l</sup>Thammasat University, Pathum Thani, Thailand; <sup>m</sup>National University Hospital, National University Health System, Singapore, Singapore; <sup>n</sup>Philippine General Hospital, University of the Philippines, Manila, Philippines; <sup>o</sup>University of Kelaniya, Annasihena Road, Ragama, Sri Lanka; <sup>p</sup>Clinical Trials Unit, Faculty of Medicine, University of Kelaniya, Annasihena Road, Ragama, Sri Lanka; <sup>q</sup>Baguio General Hospital and Medical Centre, Baguio, Philippines; <sup>r</sup>Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; <sup>s</sup>Siriraj Hospital, Bangkoknoi, Bangkok, Thailand; <sup>t</sup>Penang Hospital, Jalan Residensi, George Town, Malaysia; <sup>u</sup>Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore

## Keywords

Acute stroke · Stroke recovery · MLC601 · NeuroAiD · Rehabilitation · Combination · Clinical trial · Long-term outcome

## Abstract

**Background and Purpose:** MLC601 has been shown in pre-clinical studies to enhance neurorestorative mechanisms after stroke. The aim of this post hoc analysis was to assess

whether combining MLC601 and rehabilitation has an effect on improving functional outcomes after stroke. **Methods:** Data from the CHinese Medicine NeuroAiD Efficacy on Stroke (CHIMES) and CHIMES-Extension (CHIMES-E) studies were analyzed. CHIMES-E was a 24-month follow-up study of subjects included in CHIMES, a multi-centre, double-blind placebo-controlled trial which randomized subjects with acute ischemic stroke, to either MLC601 or placebo for 3 months in addition to standard stroke treatment and rehabilitation. Subjects were stratified according to whether they received

or did not receive persistent rehabilitation up to month (M)3 (non- randomized allocation) and by treatment group. The modified Rankin Scale (mRS) and Barthel Index were assessed at month (M) 3, M6, M12, M18, and M24. **Results:** Of 880 subjects in CHIMES-E, data on rehabilitation at M3 were available in 807 (91.7%, mean age  $61.8 \pm 11.3$  years, 36% female). After adjusting for prognostic factors of poor outcome (age, sex, pre-stroke mRS, baseline National Institute of Health Stroke Scale, and stroke onset-to-study-treatment time), subjects who received persistent rehabilitation showed consistently higher treatment effect in favor of MLC601 for all time points on mRS 0–1 dichotomy analysis (ORs 1.85 at M3, 2.18 at M6, 2.42 at M12, 1.94 at M18, 1.87 at M24), mRS ordinal analysis (ORs 1.37 at M3, 1.40 at M6, 1.53 at M12, 1.50 at M18, 1.38 at M24), and BI  $\geq 95$  dichotomy analysis (ORs 1.39 at M3, 1.95 at M6, 1.56 at M12, 1.56 at M18, 1.46 at M24) compared to those who did not receive persistent rehabilitation. **Conclusions:** More subjects on MLC601 improved to functional independence compared to placebo among subjects receiving persistent rehabilitation up to M3. The larger treatment effect of MLC601 was sustained over 2 years which supports the hypothesis that MLC601 combined with rehabilitation might have beneficial and sustained effects on neuro-repair processes after stroke. There is a need for more data on the effect of combining rehabilitation programs with stroke recovery treatments.

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## Introduction

Stroke recovery is complex and is likely to occur through a combination of spontaneous recovery and learning-dependent processes such as restitution, substitution, and compensation which are aided by rehabilitation [1]. While patients show substantial neurological improvement due to endogenous mechanisms after stroke [2], these are often not sufficient to achieve complete recovery in many patients. Hence neurorehabilitation remains one of the cornerstones for post-stroke management. With the growth of the world population, increased longevity and increasing prevalence of vascular risk factors, stroke-related disability is expected to increase globally, impacting upon families, healthcare systems, and economies.

In response to focal cerebral ischemia, endogenous neurorestorative processes are spontaneously induced, characterized by neuronal sprouting, glial cell activation, and capillary sprouting [3, 4]; this leads to a favorable environment for the neurons to grow and promote neuro-

plasticity. Brain remodeling and synaptic plasticity is required for stroke recovery [5, 6]. MLC601, a product combining herbal and non-herbal extracts, has been shown to have neuroproliferative and neurorestorative properties in cellular and animal ischemic models [7, 8]. The clinical evidence base for the efficacy and safety of MLC601 after acute ischemic stroke is provided by the large CHINESE Medicine NeuroAiD Efficacy on Stroke Recovery (CHIMES; ClinicalTrials.gov: NCT00554723) and CHIMES-Extension (CHIMES-E) Studies [9, 10]. In a post-hoc analysis, MLC601 showed a favorable effect on post-stroke recovery at 3 months in patients with persisting and/or moderately severe neurological deficit [11]. It also showed significant benefit (mRS  $< 1$ ) at 6 months persisting up to 18 months [10], providing clinical evidence that supports the pre-clinical studies demonstrating neurorestorative effects.

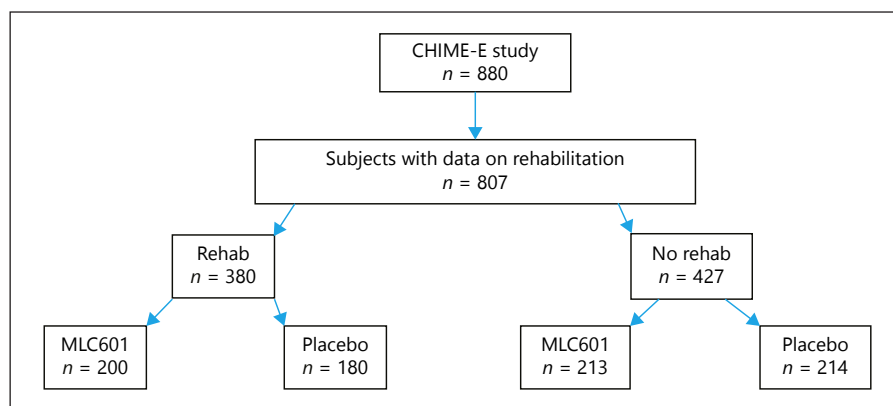
MLC601, having both neurorestorative and neuroproliferative effects, may enhance the endogenous repair process and hence have a positive effect when combined with rehabilitation. Our aim was to assess if MLC601 and rehabilitation will have an effect on improving functional outcomes after stroke. We hypothesize that in stroke patients receiving standard treatment and rehabilitation, addition of MLC601 will enhance the recovery process and lead to better functional outcomes.

## Methods

This post hoc analysis was performed using data from the CHIMES-E Study ( $n = 880$ ) which was a 2-year extension study of CHIMES ( $n = 1,100$ ), a randomized, double-blind placebo-controlled trial where participants were aged  $\geq 18$  years with acute ischemic stroke, National Institute of Health Stroke Scale (NIHSS) 6–14, and pre-stroke modified Rankin Scale (mRS)  $\leq 1$  (clinicaltrials.gov NCT00554723). As the primary outcome of CHIMES was assessed at M3, an analysis of CHIMES-E was performed to investigate the long-term effect of combining MLC601 with rehabilitation. Eligible subjects received MLC601 (400 mg capsules) 4 capsules 3 times a day or matching placebo for 3 months in addition to standard stroke treatment and rehabilitation as prescribed by the treating physicians [12]. Blinding was maintained throughout the follow-up duration of 2 years [13].

For the present analyses, data on patients in CHIMES-E were divided in 2 groups based on whether they received persistent rehabilitation (Rehab group) or not (No Rehab group) up to 3 months after stroke onset. Rehabilitation was prescribed by the treating physician and was not randomized. Among Rehab and No Rehab groups, subjects were further separated into groups receiving MLC601 or placebo (Fig. 1). As outcome measures, mRS and Barthel Index (BI) were compared from month (M) 3 to M 24 between groups.

Subjects were included in this analysis if they had the primary outcome, mRS, assessed in-person at M3 and by telephone at M6,



**Fig. 1.** Patient flow for analysis.

M12, M18, or M24, and if they had the persistent rehabilitation data at M3. The question posed at M3 was if the subject received any rehabilitation since the last assessment; therefore, it was largely based on whether rehabilitation has been received or not since day 10 or discharge from the hospital (whichever came first). Baseline data were compared using the chi-square ( $\chi^2$ ) test or Fisher's exact test for categorical data, and  $t$  test for continuous data.

Efficacy analyses were based on the intention-to-treat principle. The primary outcome measure was mRS, while BI was used as supportive secondary outcome measure. Analysis of mRS was performed at M3, M6, M12, M18, and M24 by dichotomy 0–1 vs. 2–6 and by ordinal (shift) analysis to provide an estimate of the OR with corresponding 95% CI for each time point. BI total score was analyzed as  $\geq 95$  vs.  $\leq 90$  dichotomy at M3, M6, M12, M18, and M24. Ordinal or logistic regression was performed as necessary, and ORs and the corresponding 95% CIs derived to estimate overall treatment effects were adjusted for potential prognostic factors, that is, age, sex, pre-stroke mRS, NIHSS, and stroke onset to study treatment time (OTT), which have been showed to influence the outcome and treatment effect of MLC601 both in the medium and long-term [9, 10, 14]. Percentages of patients who improved to mRS  $\leq 1$  and BI  $\geq 95$  were calculated. The numbers needed to treat (NNT) were derived using the inverse of absolute relative risk to estimate the clinical benefit of MLC601. Statistical analysis was performed using SAS version 9.4.

## Results

Of the 880 participants in CHIMES-E, data on rehabilitation at M3 were available in 807 (91.5%; MLC601  $n = 413$ , placebo  $n = 394$ ). The baseline characteristics of the 73 subjects which did not have rehabilitation data at M3 were similar to the rest of the 807 subjects who did ( $p > 0.3$ ) except that the former group had a higher NIHSS score ( $p = 0.0019$ ) and higher proportions of NIHSS score between 10 and 14 ( $p = 0.0059$ ) and previous history of TIA ( $p = 0.016$ ). The overall analysis population ( $n = 807$ ) had a mean age of  $61.8 \pm 11.3$  years, 291 (36%) were female, mean baseline NIHSS was  $8.6 \pm 2.5$ , and mean OTT

was  $48.1 \pm 17.2$  h (Table 1). There was no difference in baseline characteristics between treatment groups in the Rehab and No Rehab groups, apart from NIHSS mean score and the proportion of subjects with NIHSS 10–14, which were higher in the Rehab group ( $p = 0.013$  and  $p = 0.033$ , respectively).

Among the 807 CHIMES-E patients who had data on rehabilitation during the treatment period, 380 (57.1%) received persistent rehabilitation up to M3. Study treatment, MLC601 ( $n = 200$ ) or placebo ( $n = 180$ ), had been randomly allocated and remained blinded. These treatment groups did not show any difference in most baseline characteristics, except for a higher proportion of females in the MLC601 group as compared to placebo (38 vs. 28.3%;  $p = 0.0504$ ). The type of rehabilitation received was also similar.

A total of 427 (53%) subjects were reported as having not received persistent rehabilitation. These were evenly divided between study treatments: MLC601 ( $n = 213$ ) and placebo ( $n = 214$ ). At baseline, the main prognostic factors were well-balanced between the 2 treatment groups.

The subjects who received rehabilitation and MLC601, were consistently associated with higher proportions of functional recovery and independence as compared to rehabilitation and placebo for all time points on mRS 0–1 vs. 2–6 dichotomy with ORs of 1.85 (95% CI 1.18–2.91) at M3, 2.18 (95% CI 1.39–3.42) at M6, 2.42 (95% CI 1.53–3.81) at M12, 1.94 (95% CI 1.24–3.03) at M18, and 1.87 (95% CI 1.19–2.94) at M24 (Fig. 2). The treatment effects were likewise significant on mRS ordinal analysis at M12 (OR 1.53, 95% CI 1.06–2.21) and M18 (OR 1.50, 95% CI 1.04–2.17) and on BI  $\geq 95$  vs.  $\leq 90$  dichotomy at M6 (OR 1.95, 95% CI 1.24–3.05). In subjects receiving rehabilitation and MLC601, NNTs ranged from 5 to 7 in mRS 0–1 vs. 2–6 dichotomy and from 7 to 14 in BI  $\geq 95$  vs.  $\leq 90$  dichotomy (Fig. 2).

**Table 1.** Baseline characteristics of subjects in the CHIMES-E study according to treatment groups.

Variables	MLC601 ( <i>n</i> = 413)		Placebo ( <i>n</i> = 394)		<i>p</i> value	
	rehab ( <i>n</i> = 200)	no rehab ( <i>n</i> = 213)	rehab ( <i>n</i> = 180)	no rehab ( <i>n</i> = 214)	rehab ( <i>n</i> = 380) vs. no rehab ( <i>n</i> = 427)	MLC601 + rehab ( <i>n</i> = 200) vs. placebo + rehab ( <i>n</i> = 180)
Age, years, mean (SD)	61.63 (10.47)	61.08 (11.04)	63.16 (11.26)	61.23 (12.02)	0.130	0.171
Women, <i>n</i> (%)	76 (38.0)	79 (37.1)	51 (28.3)	85 (39.7)	0.143	0.050
Pre-stroke mRS, <i>n</i> (%)					0.113	0.282
0	185 (92.5)	191 (89.7)	172 (95.6)	197 (92.1)		
1	15 (7.5)	22 (10.3)	8 (4.4)	17 (7.9)		
NIHSS score, mean (SD)	8.67 (2.41)	8.39 (2.42)	8.86 (2.41)	8.26 (2.59)	0.013	0.428
NIHSS score 10–14, <i>n</i> (%)	69 (34.5)	63 (29.6)	65 (36.1)	57 (26.6)	0.033	0.748
OTT, h, mean (SD)	49.15 (16.25)	47.72 (18.23)	49.44 (16.94)	46.88 (17.35)	0.102	0.866
OTT >48 h, <i>n</i> (%)	98 (49.0)	102 (47.9)	100 (55.6)	99 (46.3)	0.159	0.218
Previous history of cerebrovascular event, <i>n</i> (%)	28 (14.0)	23 (10.7)	15 (8.3)	30 (14.0)	0.748	0.217
Transient ischaemic attack	8 (4)	2 (0.9)	2 (1.1)	8 (3.7)		
Ischaemic stroke	20 (10)	18 (8.4)	13 (7.2)	23 (10.74)		
Haemorrhagic stroke	1 (0.5)	3 (1.4)	1 (0.5)	0		
Received rehabilitation during first 3 months, <i>n</i> (%)	200 (100)		180 (100)			
Physiotherapy	186 (93.0)		168 (93.3)			
Occupational therapy	111 (55.5)		92 (51.1)			
Speech therapy	41 (20.5)		35 (19.4)			

Data presented as number (percent) or mean (SD).

NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; OTT, stroke onset to study treatment.

By contrast, there was no statistically significant difference seen in outcomes, that is, (mRS dichotomy or mRS ordinal and BI) between MLC601 and placebo in subjects who did not receive persistent rehabilitation (No rehab group).

The outcomes at 3 months for MLC601 vs. placebo in the Rehab and No rehab groups in all CHIMES patients and those in CHIMES-E were similar (Table 2). The data were adjusted for age, sex, baseline NIHSS, and stroke onset-to-treatment delay. As the CHIMES-E study was conducted in 6 countries (Singapore, Malaysia, Thailand, Philippines, Sri Lanka, Hong Kong), we assessed the allocation of rehabilitation services across different countries. Rehabilitation was received by 59.6% patients in Singapore (*n* = 389), 32.8% in Philippines (*n* = 326), and 44.6% in other countries (*n* = 92) which included Malaysia (*n* = 6), Thailand (*n* = 51), Sri Lanka (*n* = 25), and Hong Kong (*n* = 10). The directions for outcomes across different countries were all same (OR >1).

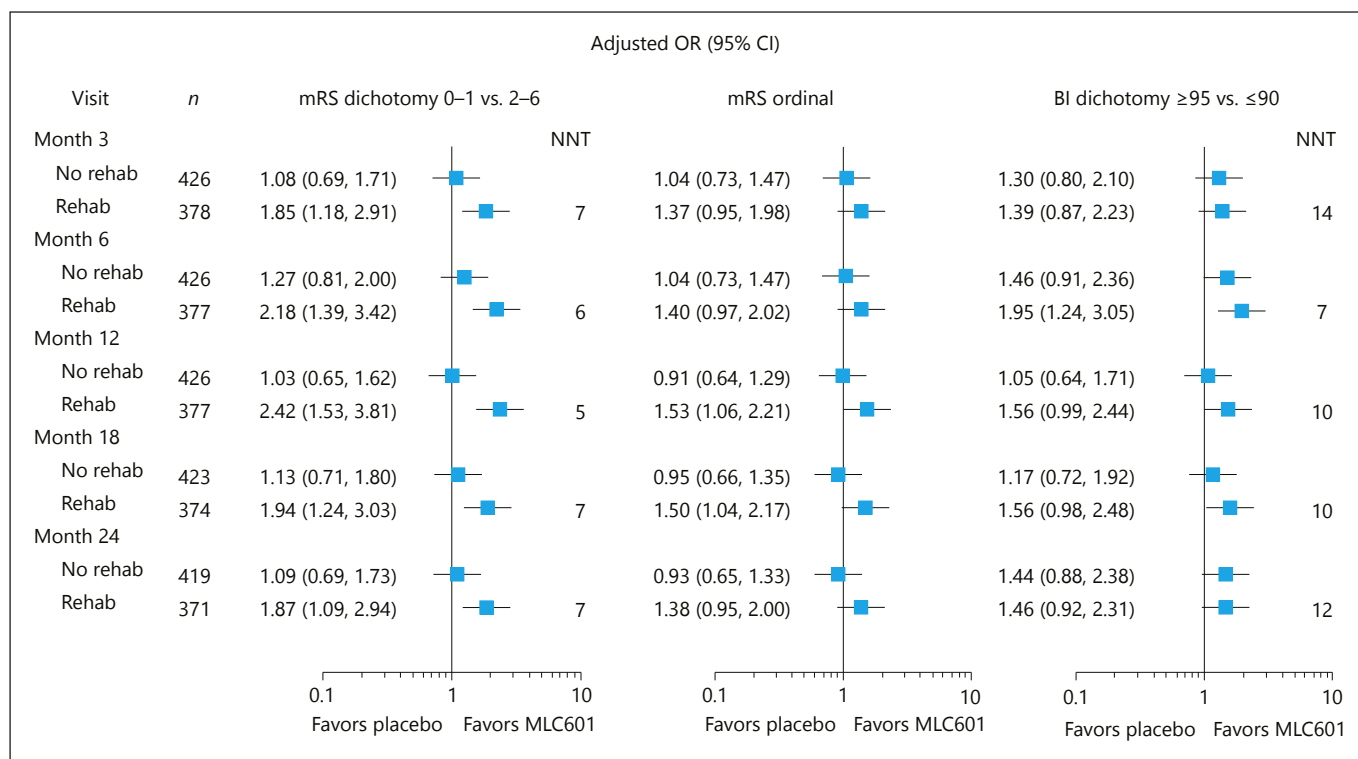
## Discussion

This analysis in subjects having received persistent rehabilitation up to M3 shows that adding MLC601 to rehabilitation increases the odds of improving functional

recovery and independence at 3 months and beyond compared to placebo in well-balanced groups at baseline, supporting a beneficial and sustained effect on brain neuro-repair processes after an acute ischemic stroke. The beneficial effect is shown through several measures (mRS dichotomy, mRS shift, and BI) and analyses showing a higher treatment effect of indicating a higher proportion of subjects attaining recovery or independence than with rehabilitation alone, this clinical benefit persisting over 2 years as supported by the stable NNT over time.

Stroke recovery is a multi-layered process and is complex [15]. Hence, it is likely that a multimodal approach may be more effective in achieving better patient outcomes, by regulating more than one endogenous neurobiological process to address the complexity of the stroke recovery process [16]. Since most post-stroke patients already undergo rehabilitation, combining a medical intervention that facilitates adaptive neuroplasticity with rehabilitation may be a logical and simple strategy for such multi-modal therapy [17].

MLC601 is a combination of various herbal and non-herbal components which has been shown to act on several biological targets involved in the ischemic cascade, in addition to its neuroprotective properties [18].



**Fig. 2.** Forest plot of analyses using modified Rankin Score (mRS) and Barthel Index (BI) at months 3–24 in CHIMES-E comparing MLC601 and placebo in subjects who received or not persistent rehabilitation up to 3 months of MLC601 treatment. NNT, number needed to treat.

**Table 2.** Outcomes at 3 months in subjects receiving Rehabilitation vs. No rehabilitation using CHIMES data

Outcome at month 3	Number	mRS dichotomy 0-1 vs. 2-6	mRS ordinal	BI Dichotomy ≥95
No Rehabilitation (MLC601 vs. placebo)	532	1.05 (0.69–1.57)	1.10 (0.80–1.51)	1.35 (0.87–2.08)
Rehabilitation (MLC601 vs. placebo)	441	1.79 (1.16–2.73)	1.31 (0.93–1.84)	1.32 (0.85–2.03)

mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale.

MLC601 has been shown in human cells in vitro and animal models to have neurorestorative properties consistent with a capacity to stimulate brain neuro-repair processes, such as neuroplasticity and neurogenesis, after ischemia and other brain injuries [7, 19]. These properties of MLC601 could enhance endogenous neural repair processes and when combined with rehabilitation, produce additional recovery benefits compared to rehabilitation alone.

In this analysis, we were able to show that MLC601 combined with rehabilitation achieved better outcome both on functional recovery and independence in activities of daily living than rehabilitation alone. The im-

portance of the first 3-month period for recovery after stroke is well known as being when most of post-stroke recovery occurs [20]. However, it has been shown that recovery is a continuing process that may take many months, the transition from functional independence to dependency from 3 months to 1 year after a stroke being significant [21]. The CHIMES-E study results have already shown that the odds of functional independence defined as mRS ≤1 were significantly increased at 6 months and persisted up to 18 months after a stroke in those treated with MLC601. In the present analysis, MLC601 benefits compared to placebo are more evident earlier and for longer in subjects receiving persistent re-

habilitation, supporting a combined effect of MLC601 with rehabilitation.

During the first 3 months, the subjects received standard stroke care and appropriate rehabilitation as prescribed by the treating physician [9]. The allocation of rehabilitation was not randomized, and the subjects without rehabilitation had significantly less severe NIHSS scores with a significantly lower risk of bad outcomes, as could be expected. This could explain why this analysis showed no difference between treatment groups in subjects without persistent rehabilitation and why the proportion of subjects with more severe stroke (NIHSS 10–14) was significantly higher in the Rehab group ( $p = 0.033$ ). The analysis, moreover, was adjusted for prognostic factors including stroke severity, hence our results suggest that the beneficial effect observed with combination of MLC601 and rehabilitation is independent of stroke severity.

#### *Limitations*

The analyses were performed post-hoc and allocation to rehabilitation was not randomized; it was based on the physician's decision. This may have been influenced by various confounding factors such as stroke severity, presumably worse outcomes, convenience, expected adherence, financial costs, and so on. This could have led to rehabilitation allowance bias. The stratification of rehab or no rehab was based on an interview so the accuracy of allocation cannot be ascertained. Detailed data on rehabilitation schedule, intensity, duration or rehab setting, whether inpatient or outpatient, was not collected. Other important variables which may contribute to ascertainment bias for example financial condition, patients with poor collaboration, family support, availability of rehabilitation centre and physical therapist, quality of care indicators were not collected in the study to enable their assessments as confounders. Patients with mild post-stroke disability and treated without rehabilitation often have undetected physical, mood, and cognitive deficits that could interfere with function. However, detailed assessment of physical function, cognition, and mood were not collected and may be a confounder as these are negative determinants on rehabilitation outcome [22, 23]. The strengths of this study are that it is based on a large multi-centre randomized placebo-controlled clinical trial, performed by experienced stroke trialists, with full blinding maintained throughout, a high follow-up rate, and is one of the few stroke trials providing long-term data.

#### **Conclusions**

Combining MLC601 with rehabilitation have shown to enhance functional recovery and independence compared to patients receiving rehabilitation only. This supports a probable beneficial effect of combining MLC601 and rehabilitation on brain neuro-repair processes after an acute ischemic stroke. Among patients receiving persistent rehabilitation up to month 3, the treatment effect of MLC601 was evident as early as M3 compared to rehabilitation alone and increased over time with a peak at 1 year.

There is a need for more data on the effect of combining rehabilitation programs with post-stroke treatments. Further research is needed to confirm the long-term beneficial effects and future trials should consider the implications of rehabilitation on demonstrating treatment effects of investigational therapies on post-stroke recovery.

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