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Frequency and Clinical Impact of Serious Adverse Events on Post-Stroke Recovery with NeuroAiD (MLC601) versus Placebo: The CHInese Medicine Neuroaid Efficacy on Stroke Recovery Study

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Keywords
Clinical trial · NeuroAiD · MLC601 · Serious adverse events · Clinical impact · Stroke

Abstract
Background: Most comparative clinical trials are designed to assess the treatment effect for efficacy endpoints, with less emphasis on the analysis of safety outcomes. However, an extensive analysis of safety data could demonstrate beneficial results in terms of effectiveness by reducing serious adverse events (SAEs), and their unfavourable clinical impact on the study population. We aimed to conduct an exploratory analysis of the CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study safety database comparing the frequency of SAEs and their clinical impacts among subjects having received MLC601 or placebo during the first 3 months post-stroke. ***Methods:*** Analyses were performed by using the safety database of the multicentre, randomised, double-blind, placebo-controlled CHIMES study of 3 months of NeuroAiD versus placebo in subjects with acute ischaemic stroke of intermediate severity in the preceding 72 h. SAEs as reported by investigators at any time-point during the 3-month study were analysed on their frequency and that of any of their outcomes (death, and life threatening, new and/or prolonged hospitalisation, disability, and medical importance, in surviving subjects), as well as their time to onset and resolution. ***Results:*** Of the 1,099 subjects in the CHIMES study, 1,087 were included in the safety analysis (MLC601 = 542) and (placebo = 545); the 12 who did not receive study treatment were excluded. There was a total of 135 subjects with SAEs (MLC601 = 60, placebo = 75). At baseline, overall, subjects with SAEs were older and had lower MMSE score. In the MLC601 group, they had higher NIHSS score, and more frequently a history of ischaemic heart disease and hyperlipidaemia. The number of SAEs per subjects was statistically significantly lower in the MLC601 group than placebo one, especially for subjects with ≥2 SAEs (6.7 vs. 29.3%; $p < 0.001$). This benefit was seen throughout the study period and during the initial hospitalisation. The main clinical impact of SAEs was an increase in hospitalisation time, reduced in the MLC601 arm with the rate of subjects hospitalised for a prolonged period being significantly threefold lower in surviving subjects (1.1 vs. 3.7%; $p < 0.01$). ***Conclusions:*** This post hoc analysis of SAEs from the CHIMES study database shows that subjects receiving a 3-month course of MLC601 experi-

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enced fewer SAEs, with lower rates of harmful clinical impacts, especially in terms of hospitalisation duration. These findings could translate to a benefit in terms of reduction of both healthcare burden and additional medical costs.

Introduction

"Primum non nocere" is a basic medical principle, originally ascribed to Hippocrates, meaning "First, do no harm" [1]. This principle should guide our therapeutic decisions for our patients, knowing that fine tuning will be necessary to aim at the best benefit-risk ratio according to disease severity, patient's clinical status, expected efficacy and potential side effects. Safety analysis plays a key role in the regulatory process of drug approval [2, 3], and the benefit assessment of drugs after approval [4]. Therefore, an important part of the clinical development of new treatments must focus on the collection and analysis of adverse events (AE), especially serious AEs ones (SAE).

Investigators and drug developers must actively guard against consequences of any philosophical dichotomy between safety and efficacy. Suboptimal efficacy can have serious adverse consequences, such as prolonged hospitalisation, complications and even death, with associated cost increases [5]. Nevertheless, usually comparative clinical trials are most designed by calculating study power and sample size mainly for efficacy purpose. Thus, randomised controlled trials are often underpowered to detect some treatment-related side effects, let alone to analyse their consequences and clinical impacts, the information provided in many publications being limited to the list of most frequent AEs during the study period [6].

A thorough analysis of safety data could demonstrate beneficial results in terms of effectiveness by reducing SAE frequency, and their unfavourable clinical impact on study population. To avoid any dichotomy between safety and efficacy, it has been recommended to analyse adverse medical events as a whole set, where efficacy and safety overlap [5]. The rationale is that fewer SAEs drives better safety and improves the treatment effect by limiting additional hurdles to obtain maximum benefit. As an example of this kind of safety/efficacy analysis, a recent retrospective study reported that mechanical thrombectomy appears to be safe and effective in anticoagulated patients, ineligible for thrombolysis, by achieving haemorrhage rates similar to those of patients not on anticoagulant therapy [7]. In the CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study conducted in subjects having experienced an ischaemic stroke in the previous 72 h, we observed at 3 months a lower frequency of SAEs with MLC601 (12%) vs. placebo (18%) [8], as well as halving of vascular events [9]. Based on these previous positive outcomes, we aimed at conducting an extensive exploratory analysis of the CHIMES study safety database. Our objective was to test the hypothesis that by reducing SAE frequency and their clinical impacts during the post-stroke recovery phase, MLC601 compared to placebo could increase the overall benefit for patients after stroke both in terms of efficacy and safety.

Methods

Study Design and Population

As previously published [10], the CHIMES study is a multicentre, randomized, double-blinded, placebo-controlled trial comparing a 3-month course of MLC601 with placebo in subjects with acute ischaemic stroke of intermediate severity in the preceding 72 h. Subjects were randomized to receive either MLC601 or matching placebo at a dose of 4 capsules 3 times daily for 3 months. Each 400 mg MLC601 capsule contained extracts from 9 herbal components (Radix astragali, Radix salviae mitorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae and Rhizoma acori tatarinowii) and 5 non-herbal components (Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensii and Cornu saigae tataricae). Study treatment was added on to standard stroke care including antiplatelet therapy, control of vascular risk factors, and appropriate rehabilitation. Any SAE occurring during the 3-month study period was recorded, with data regarding diagnosis of the event, date of onset/resolution, severity, action taken concerning study treatment, relatedness to study drug, treatment given, seriousness criteria, causality, expectedness, and outcome. All SAE were adjudicated by a committee blinded to study arm allocation.

Study Objectives

One of the objectives was to identify risk factors for SAEs. The primary objective of this analysis was to compare between treatment arms, as a safety analysis, the number of SAEs in the whole study population and in subsets of subjects with SAEs. Another main objective was to compare, as a secondary efficacy analysis, the clinical impacts of SAEs between treatment arms with respect to death, new and/or prolonged hospitalisation, life-threatening event, disability, and important medical event (IME). SAEs were classified as IME by 2 approaches: (a) by investigators at study sites based on their medical judgement; (b) according to the Medical Dictionary for Regulatory Activities (MedDRA) term list version 22.1 of European Medicines Agency, which was designed for sharing regulatory information about human medical products [11].

Table 1. Baseline characteristics of subjects with SAEs compared to those without SAE in both treatment arms

Characteristics	MLC601			Placebo		
	with SAE (n = 60)	without SAE (n = 482)	level of significance[§]	with SAE (n = 75)	without SAE (n = 470)	level of significance
Gender, female, n (%)	20 (33.3)	188 (39.0)		23 (30.7)	169 (36.0)	
Age, years, mean (SD)	65.0 (11.2)	60.9 (10.6)	**	65.6 (10.8)	60.9 (11.8)	**
BMI, kg/m^2, mean (SD)	24.3 (4.0)	24.5 (3.9)		24.9 (4.9)	24.5 (3.8)	
OTR, h, mean (SD)	42.0 (19.1)	43.8 (19.5)		42.6 (20.3)	43.1 (20.0)	
OTT, h, mean (SD)	43.2 (20.2)	45.1 (19.9)		43.8 (20.3)	44.1 (20.1)	
OTT ≥48 h, n (%)	38 (63.3)	314 (65.1)		47 (62.7)	294 (62.6)	
NIHSS, mean (SD)	9.7 (3.3)	8.6 (2.4)	*	8.8 (2.9)	8.5 (2.5)	
NIHSS score ≥10, n (%)	27 (45.0)	162 (33.6)		24 (32.0)	144 (30.6)	
MMSE, mean (SD)	19.0 (9.6)	24.7 (6.6)	***	22.2 (8.5)	24.9 (6.3)	*
Pre-stroke mRS, n (%)						
0	54 (90.0)	441 (91.5)		67 (89.3)	444 (94.5)	
1	6 (10.0)	39 (8.1)		8 (10.7)	26 (5.5)	
Risk factors, n (%)						
History of ischemic heart disease	8 (13.3)	17 (3.5)	**	7 (9.3)	29 (6.2)	
Previous myocardial infarction	5 (8.3)	9 (1.9)		6 (8.0)	14 (3.0)	
Angina	4 (6.7)	9 (1.9)		3 (4.0)	20 (4.3)	
Hypertension	52 (86.7)	389 (80.7)		60 (80.0)	381 (81.1)	
Diabetes mellitus	23 (38.3)	146 (30.3)		34 (45.3)	145 (30.9)	*
Hyperlipidaemia	39 (65.0)	222 (46.1)	**	51 (68.0)	216 (46.0)	***
BMI ≥30	6 (10.0)	31 (6.4)		10 (13.3)	37 (7.9)	
Peripheral vascular disease	0	5 (1.0)		0	3 (0.6)	
Smoking	35 (58.3)	214 (44.4)	*	36 (48.0)	210 (44.7)	
Alcohol	19 (31.7)	136 (28.2)		19 (25.3)	138 (29.4)	
Previous ischaemic stroke	7 (11.7)	42 (8.7)		7 (9.3)	42 (8.9)	
Previous haemorrhage stroke	1 (1.7)	4 (0.8)		1 (1.3)	2 (0.4)	
TIA	2 (3.3)	14 (2.9)		2 (2.7)	11 (2.3)	

[§] Level of significance for comparisons between with SAE versus without SAE subjects in each treatment arms: * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$, and blank indicates $p > 0.05$.

SAE, serious adverse event; BMI, body mass index; OTR, time from stroke onset to randomization; OTT, time from stroke onset to treatment; NIHSS, National Institute of Health Stroke Scale; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; TIA, transient ischemic attack.

The final objective was to describe and compare between treatment arms other characteristics of SAE with available data from CHIMES database in terms of outcome, time to onset and to resolution, and relationship and impact on study treatment.

Statistical Analysis

Baseline characteristics including risk factors of stroke were tabulated by treatment arm and by occurrence of SAE. Comparison of baseline characteristics between subjects with SAEs and those without SAEs was performed using the chi-square test (or Fisher's exact test if chi-square test was not appropriate) for categorical variables and 2 sample t tests for continuous variables.

Proportions of subjects in the 3 categories of number of SAEs (i.e., no SAE, 1 SAE only, and at least 2 SAEs) were compared between treatment arms using the chi-square test (or Fisher's exact test if chi-square test was not appropriate) in the whole study population and in subsets of subjects with SAEs. The same method was applied to other SAE characteristics such as death and hospitalisation that are expressed as a categorical variable. Relative risk and 95% CI were provided for binary outcome variables such as subjects with any SAE.

In analysis of individual SAEs with respect to clinical impact, OR was estimated from a logistic regression model using the Generalized Estimating Equations method to account for possible association among multiple SAEs in a subject. Time to resolution of individual SAEs was defined as time from onset of SAE to its resolution or censored at the time of death or end of follow-up if it occurred before resolution. Time to resolution of SAE was analysed using the marginal Cox model approach with a robust sandwich covariance estimate to account for possible association among multiple SAEs in a subject. Hazard ratio from the model was reported with its 95% CI together with the predicted survival curves. Time to onset of individual SAEs was compared using extended Wilcoxon rank sum test that accounted for possible association of multiple SAEs in a subject as the assumption of proportional hazards was invalid for use of the Cox model.

Table 2. Distribution of number of SAEs within individual subjects

	MLC601 (n = 542), n/m (%)	Placebo (n = 545), n/m (%)	p value
In the study population			0.002
nSAE = 0	482/542 (88.9)	470/545 (86.2)	
nSAE = 1	56/542 (10.3)	53/545 (9.7)	
nSAE ≥2	4/542 (0.7)	22/545 (4.0)	
In subjects with any SAE			<0.001
nSAE = 1	56/60 (93.3)	53/75 (70.7)	
nSAE ≥2	4/60 (6.7)	22/75 (29.3)	
In subjects surviving with any SAE			0.006
nSAE = 1	43/47 (91.5)	42/60 (70.0)	
nSAE ≥2	4/47 (8.5)	18/60 (30.0)	
In hospitalised subjects surviving with any SAE*			0.009
nSAE = 1	31/33 (93.9)	33/47 (70.2)	
nSAE ≥2	2/33 (6.1)	14/47 (29.8)	

Numbers in column of each treatment arm are number (n) and proportion (%) of subjects and the corresponding denominator (m).

* Summary includes all SAEs in subjects who were surviving during study follow-up, and had an SAE that satisfied the SAE criterion of inpatient hospitalisation and/or prolonged hospitalisation.

p values are from chi-square test (or Fisher's exact test if chi-square test is not appropriate).

"Subjects surviving" in the table above means subjects did not die during study follow-up.

SAE, serious adverse event; nSAE, number of SAEs.

Results

Of the 1,099 subjects included in CHIMES study, 1,087 were included in the safety analysis with 542 subjects in MLC601 arm and 545 in placebo arm. Twelve subjects who did not receive study treatment were excluded from this as-treated population.

A total of 135 subjects were reported as having had an SAE (MLC601 = 60, placebo = 75). As shown in Table 1, baseline characteristics of the subjects with SAE were rather well balanced within MLC601 and placebo arms, with a trend for higher proportion of subjects with SAEs in MLC601 arm having NIHSS score >10 (p = 0.085) and a higher NIHSS mean score ($p < 0.05$), and being significantly older in both treatment arms ($p < 0.01$) with a lower MMSE mean score ($p < 0.001$ and $p < 0.05$). For cardiovascular risk factors, subjects with SAE compared to those without SAE had higher frequencies of previous history of ischaemic heart disease and smoking in the MLC601 arm ($p < 0.01$ and $p < 0.05$ respectively), of diabetes mellitus in placebo arm ($p < 0.05$), and of hyperlipidaemia in both arms ($p < 0.01$ and $p < 0.001$, respectively).

As evident from our exploratory analysis, distribution of SAE numbers in individual subjects was significantly reduced in MLC601 arm in the overall study population, and in 3 subgroups of subjects with any SAE (all these subjects, those surviving, and those surviving and hospitalised; from $p < 0.01$ to $p < 0.001$). This significant reduction is mostly related to that of subjects with 2 or more SAEs (Table 2).

Among subjects with any AE, the percentage of those having SAE was lower in MLC601 arm compared to placebo one (26.1 vs. 34.4%; relative risk 0.76, 95% CI 0.57–1.01; p = 0.055). Analysis of these SAEs' clinical impact (Table 3) shows a reduced proportion of hospitalised subjects, significantly for prolonged hospitalisations (1.1 vs. 3.7%; relative risk 0.30, 95% CI 0.12–0.75; $p < 0.01$). Although not always statistically significant due to the small numbers of events in each subgroup, each individual clinical impact of SAEs was consistently lower in the MLC601 arm in terms of life threatening and IMEs, but not disability. The post hoc count of SAEs classified as IME based on the MedDRA term list was much higher than that recorded by investigators based on their own judgement without reference list. The proportion of subjects with SAEs resulting in at least 2 different impacts was reduced by more than twice in MLC601 arm compared to placebo (0.7 vs. 2.0%; p = 0.12). The evolution of SAEs was globally non-significantly different between arms, but there was a trend of higher rate of recovery with sequelae (~35%) in placebo arm (42.7 vs. 31.7%; p = 0.19).

Table 3. Clinical impacts of SAEs

	MLC601 (n = 542)		Placebo (n = 545)		RR (95% CI)	p value
	subjects, n (%)	events, n	subjects, n (%)	events, n		
All patients with						
Any AE (AE or SAE)	230 (42.4)	461	218 (40.0)	507	1.06 (0.92–1.22)	0.41
Any SAE	60/542 (11.1)	64	75/545 (13.8)	98	0.80 (0.59–1.11)	0.18
Any SAE in patients with any event (AE + SAE)	60/230 (26.1)	64	75/218 (34.4)	98	0.76 (0.57–1.01)	0.055
Patients surviving with						
>1 SAE	47 (8.7)	51	60 (11.0)	78	0.79 (0.55–1.13)	0.20
>2 SAEs (different disease and/or organ)	4 (0.7)	8	18 (3.3)	36	0.22 (0.08–0.66)	0.004
Deaths	13 (2.4)		15 (2.8)		0.87 (0.42–1.81)	0.71
SAE outcome in subjects with >1 SAE	60 (100.0)		75 (100.0)			
Recovered	27 (45.0)	29	36 (48.0)	44	0.94 (0.65–1.35)	0.73
Recovered with sequelae	19 (31.7)	19	32 (42.7)	34	0.74 (0.47–1.17)	0.19
Ongoing	3 (5.0)	3	3 (4.0)	3	1.25 (0.26–5.97)	1.00
Death	13 (21.7)	13	15 (20.0)	17	1.08 (0.56–2.10)	0.81
Relatedness to study treatment						
Not related	36/60 (60.0)	37	45/75 (60.0)	55	1.00 (0.76–1.32)	1.00
Unlikely related	22/60 (36.7)	22	29/75 (38.7)	35	0.95 (0.61–1.47)	0.81
Possibly related	3/60 (5.0)	3	4/75 (5.3)	4	0.94 (0.22–4.03)	1.00
Probably related	1/60 (1.7)	1	1/75 (1.3)	1	1.25 (0.08–19.6)	1.00
Unknown	1/60 (1.7)	1	2/75 (2.7)	3	0.63 (0.06–6.73)	1.00
Impact on study treatment						
None	33/60 (55.0)	34	46/75 (61.3)	57	0.90 (0.67–1.20)	0.46
Temporarily interrupted	9/60 (15.0)	9	11/75 (14.7)	14	1.02 (0.45–2.31)	0.96
Permanently discontinued	20/60 (33.3)	21	24/75 (32.0)	27	1.04 (0.64–1.69)	0.87
Clinical impact of SAE in subjects surviving with						
New and/or prolonged hospitalisation[#] (a)	33 (6.1)	35	47 (8.6)	61	0.71 (0.46–1.08)	0.11
In-patient hospitalisation only	27 (5.0)	29	33 (6.1)	37	0.82 (0.50–1.35)	0.44
Prolonged hospitalisation only	6 (1.1)	6	20 (3.7)	23	0.30 (0.12–0.75)	0.006
Both	0	0	1	1		ns
Life-threatening event (b)	5 (0.9)	5	9 (1.7)	11	0.56 (0.19–1.66)	0.29
Disability (c)	9 (1.7)	9	6 (1.1)	6	1.51 (0.54–4.21)	0.43
Important medical event according to						
Investigator judgement (d)	7 (1.3)	7	14 (2.6)	15	0.50 (0.20–1.24)	0.13
MedDRA term list (e)	41 (7.6)	43	55 (10.1)	68	0.75 (0.51–1.10)	0.14
Subjects surviving with						
>1 SAE impact*	47 (8.7)	56	59 (10.8)	93	0.80 (0.56–1.15)	0.23
SAE having >2 SAE impacts*	4 (0.7)	9	11 (2.0)	29	0.37 (0.12–1.14)	0.12
>1 SAE and SAE-IME MedDRA-impact**	47 (8.7)	92	60 (11.0)	146	0.79 (0.55–1.13)	0.20
SAE having >2 SAE-IME MedDRA-impacts**	37 (6.8)	79	46 (8.4)	126	0.81 (0.53–1.23)	0.32

Numbers in column of each treatment arm are number (n) and proportion (%) of patients with a characteristic, unless otherwise specified.
[#] Subjects may have multiple events with new and/or prolonged hospitalisation and counted once.
* SAE impacts according to investigator judgement: (a) + (b) + (c) + (d).
** SAE considered IME according to MedDRA term list – impacts: (a) + (b) + (c) + (e).
p values are from chi-square test (or Fisher's exact test if chi-squared test is not appropriate).
"Subjects surviving" in the table above means patients did not die during study follow-up.
AE, adverse event; CI, confidence interval; SAE, serious AE; RR, relative risk; IME, important medical event; MedDRA term list, medical dictionary for regulatory activities term list from European Medicines Agency (EMA); ns, non significance.

Times to onset and to resolution of SAEs are detailed in online supplemental Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000506070). Overall, SAEs appear about 10 days later and resolve significantly quicker in MLC601 arm, for those inducing a prolonged hospitalisation both for individual SAEs by onset (7 vs. 20 days; $p = 0.03$) as shown in Figure 1 and for first SAEs by onset (7 vs. 18 days; $p = 0.04$).

Discussion

Our exploratory analysis shows that among subjects with SAEs, those receiving MLC601 had fewer SAEs than those in placebo arm. This reduction was observed both in the whole CHIMES study population, all those with any AE or SAE, and those surviving with SAE being hospitalised or not. In addition, most clinical im-

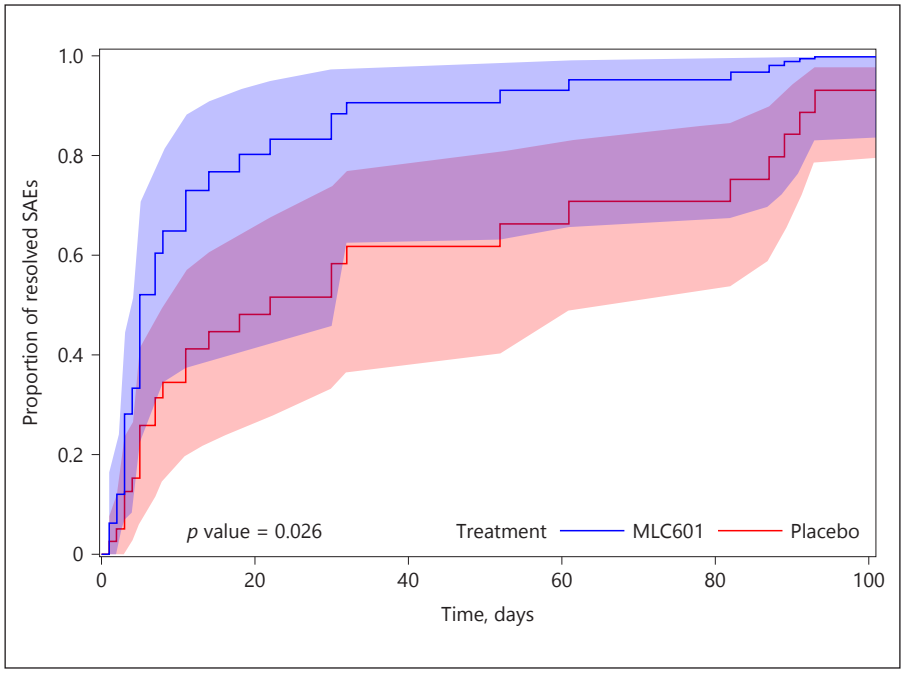

Fig. 1. Time to resolution of individual serious adverse events (SAE) by onset inducing prolonged hospitalisation in hospitalised subjects surviving with any SAE. Wald test of hazard ratio estimate in the Cox regression model.

pacts associated with SAEs were reported in fewer subjects receiving MLC601 than placebo. The main clinical impact of SAEs was an increase in hospitalisation time, reduced in MLC601 arm, with the rate of subjects hospitalised for a prolonged period being significantly threefold lower. Our analysis also shows that time to resolution of SAEs is reduced in MLC601 arm both for individual and first SAEs by onset in hospitalised surviving subjects. Concerning SAE outcome, most subjects recovered in both arms, however, with one-third more subjects having recovered with sequelae in placebo arm. To properly assess real treatment benefit, an approach similar to ours recommended using survival time methods accounting for time dependencies and follow-up duration, not only for time-to-event of efficacy endpoints, but also for that of SAEs and their impact, especially in the case of multiple events in single patients, as in our study [12]. Thus, we applied survival time methods in our new analysis of onset and resolution time of SAEs, which clearly indicates a trend for late onset and significantly more rapid resolution of SAEs as illustrated with "survival" curves in hospitalised subjects receiving MLC601.

The main driver for acute care costs is length of stay in hospital [13, 14]. Studies showed that initial hospitalisation cost for stroke is highly correlated with length of stay, the bulk of cost being attributable to stroke unit stay, increasing with most severe stroke subtypes. The beneficial effects observed in this study of fewer SAEs with quicker and better resolution, and shorter hospitalisation time may reduce the burden on healthcare team and the direct medical costs associated with managing such events in addition to those of standard post-stroke treatments for [15]. Our percentages of subjects affected by SAE impact on hospitalisation might seem low and raise queries about their clinical or economic relevance. However, by applying these reduction rates to millions of stroke survivors each year, this represents hundreds of thousands of SAEs and millions of days of hospitalisation avoided for our patients.

While safety concerns mainly relate to SAEs, less serious but unpleasant side effects are likely to affect quality of life and willingness to continue treatment, which may affect the patient's future [16]. Some prognostic factors may predict some of these complications as it was reported for various post-stroke conditions [17–22]. In our study, more severe stroke, advanced age and the presence of some vascular risk factors increase the risk of SAEs. Appropriately targeted preventative measures would reduce this risk [23]. Interventions to reduce delirium, cardiopulmonary arrest and mortality, drug AEs, infections and falls are helpful.

The CHIMES study has already shown that baseline characteristics such as advanced age, stroke severity, and female gender, portended a poor prognosis for recovery. In these subjects at risk of poor recovery,

the relative level of recovery was enhanced by MLC601 [24, 25]. This is consistent with our finding in this study that there were fewer SAEs among subjects receiving MLC601.

Study limitations are as follows. This exploratory analysis was post hoc, and the trial was not originally powered to investigate SAEs. The number was small in some subcategories. Classification of SAEs according to MedDRA term list was done post hoc. Although the study required that all subjects receive standard stroke care, the choice of specific therapies to control medical and social risk factors in each subject was left to the treating physician. Nevertheless, the CHIMES study was a well-monitored, large, double-blinded, randomized trial in which SAEs were hence blindly adjudicated.

Conclusions

This post hoc and exploratory analysis of SAEs from CHIMES study database shows that subjects receiving a 3-month course of MLC601 experienced less SAEs, with lower rates of harmful clinical impacts, especially in terms of hospitalisation duration. These findings could represent a benefit in terms of reduction of both burden and additional costs. They also suggest the need to invest in further research to better identify patients at risk of SAE and interventions that have a real impact on patient safety.

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Appendix

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