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Long-Term Outcomes of the Spinal Cord Injury Assessing Tolerability and Use of Combine Rehabilitation and NeuroAID (SATURN STUDY)

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Abstract

Background: Spinal cord injury (SCI) is a devastating neurological disorder that affects thousands of individuals each year. Recent advances in research have given us greater understanding of the molecular and cellular events in SCI.The latest frontier in research involves neuroprotection, repair and regeneration. This paper aims to evaluate the effects of the initial 6-month treatment with MLC601/MLC901 on long term outcomes at 12 months,18 months and 24 months.

Methods: The study was an open label, prospective, cohort trial of MLC601/MLC901 (NeuroAiD) in subjects with moderate to severe SCI. Patients age was 18 to 65 years old, and the SCI occurs within 3 days and 4 weeks. Each received MLC601/MLC901 for 6 months in addition to standard care and rehabilitation. Key endpoints were safety, American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade and AIS motor scores at month 6 (M6).

The protocol and the primary results of the 6th month period were previously published. The primary result showed safety and potential role of MLC601/MLC901 in moderate to severe spinal cord Injury. Outcomes of the long-term follow up was assessed up to 24 months.

Results: Long term follow-up after 6-month treatment showed durability of improvement in total motor, sensory and SCIM score .The improvement was maintained until 12, 18 and 24 months.

Conclusion: The long-term outcomes further provided evidence in the safety and potential role of MLC601/MLC901 in SCI. This findings should help plan a study design for a randomized controlled trial.

Keywords: Spinal Cord Injury; NeuroAiD; MLC901; Neuroregeneration; ASIA motor score; ASIA Sensory score; Clinical trial

Introduction

Spinal cord injuries remain a devastating disease with functional and neurologic sequalae requiring multimodal therapeutic approaches. Treatment remains supportive which mainly focuses on preventing further injury including surgery and medications[1]. Current understanding of SCI pathophysiology and neuronal recovery involving neuroprotective, immunomodulatory and neuro-regenerative are necessary to formulate appropriate treatment modalities to improve SCI recovery[2]. Currently, researchers are focussing on the development of effective neurorenegerative properties in moderate to severe SCI[3].

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MLC901 (NeuroAiD II) is a Traditional Chinese Medicine (TCM) with 9 herbal components (Radix Astragali, Radix Salviae miltiorrhizae, Radix Paeoniae rubra, Rhizoma chuanxiong, Radix Angelicae sinensis, Carthamus tinctorius, Semen persica/Prunus persica, Radix Polygalae, Rhizoma acori tatarinowii). MLC901 is a simplified formulation of MLC601 (NeuroAiD I). MLC601 contains 9 herbal and 5 non-herbal components and has extensive historical use in human. The herbal components of MLC601 and MLC901 are the same. The similarity of the two products MLC601 and MLC901 is based upon preclinical work by Michel Ladzunski et al. [4,5]. The combination of the multiple herbal compounds produces the multimodal mechanism of action of neuroprotection and neurorepair. It demonstrated in vitro neuronal proliferation and neurite outgrowth and in vivo neurogenesis in animal study[6]. Treatment of MLC901 in ischemic mice model stimulates angiogenesis by significantly increasing the capillary density and BrdU-reactive endothelial cell in ischemic borders and increase in the Vascular Endothelial Growth Factor (VEGF) There was also improvement in neurological function in behavioural test performed among injured mice given MLC901[7]. Similar safety and benefit/risk profile observed for the 2 products in the extensive clinical experience with MLC601 and MLC901.

Both demonstrated to enhance neurological recovery and extensively studied in stroke [8,9,10] and traumatic brain injury with promising clinical and functional outcome[11].

MLC601/MLC901 has neuroprotective effects in neuronal and brain injuries as well as positive effects on functional recovery after stroke. We aimed to evaluate the safety and efficacy among subjects with moderate to severe SCI.

The Study protocol[12] and the primary result of an exploratory study[13] were previously published. Briefly, the study was an open label, prospective cohort trial of MLC601/MLC901 (NeuroAiD) in subjects with moderate to severe spinal cord injury (SCI). The results showed safe use and potential role of MLC601/MLC901 in moderate to severe spinal cord Injury.

Methodology

The result of the primary outcome has been published and may refer to complete listing of the eligibility criteria and methodology. A total of 30 patients were enrolled. Patient received MLC601, 4 capsule 3x a day or MLC901, 2 capsule 3x a day for 6 months with the standard care and rehabilitation as prescribed by the physician. The AIS grade, AIS motor score, AIS sensory score, and occurrence medical events were ascertained at month 1,3,6,12,18 and 24 months. Compliance assessment was done at month 1,3, and 6.

Results

The long-term outcomes confirmed the potential benefit of MLC601/MLC901 in moderate to severe spinal cord injury. Baseline characteristics were detailed in the primary result publication. The 24th month study flow is shown in (Figure 1).

The MLC601/MLC901 was given for six months together with the standard care, and follow up to 24 months. On the long term follow up, secondary endpoints were AIS grade, AIS motor scores, AIS sensory scores, SCIM (Spinal Cord Independence Measure Outcomes) at 1, 3, 6, 12, 18, and 24-months including compliance to NeuroAiD at 1, 3, and 6 months.

At Month 6, conversion to a more functional grade was seen in 25 % (5/20) for AIS A patients and 50% (5/10) conversion for AIS grade B. This improvement was consistent and maintained up to 18 and 24 months for AIS grade A. For AIS grade B there was a higher percentage of conversion to a better grade at 24 months (Table 1; Figure 2).

The median AIS total motor score improved significantly from 50 at baseline to 54 at M6, with the median change from baseline reported to be 9.0 (IQR: 0-44.5), P 0.00050 (Table 2).The change in motor score from baseline to Month 6 was statistically significant (P<0.005).The peak of improvement of the median motor score was maximal at 6 months, slight decline at 12 months then reached the plateau state at 18 and 24 months (Figure 3).There was no reversal of benefit after stopping the treatment at 6 months.

The most significant improvement in the total sensory score was at month 6.The total sensory score improved maximally at 6 months, slight decrease at 12 months then improved at 18 months then plateaus at 24 months (Table 2,Figure 4).

Functional recovery was assessed using the SCIM. (Figure 5).The score improved consistently across all timepoint and is clinically significant at month 3, month 12, and month 24.

There were no delayed side effects noted up to 24 months.

The compliance was presented in terms of the missed doses. At month 1 the percentage of patient who never missed dose was (88%), at month 3 and month 6, 70 % and 46.47 % of patients never missed a dose respectively.

Discussion

In the present study, favourable motor functional recovery was observed in patients who were given MLC601/MLC901 for 6 months. Furthermore, the higher motor scores were present at various timepoints, suggesting clinically meaningful improvement in neurological outcome of those treated with MLC601/MLC901.

The long-term follow up showed the consistency of findings between AIS conversion, motor, sensory and SCIM score. The median improvement of motor and sensory score

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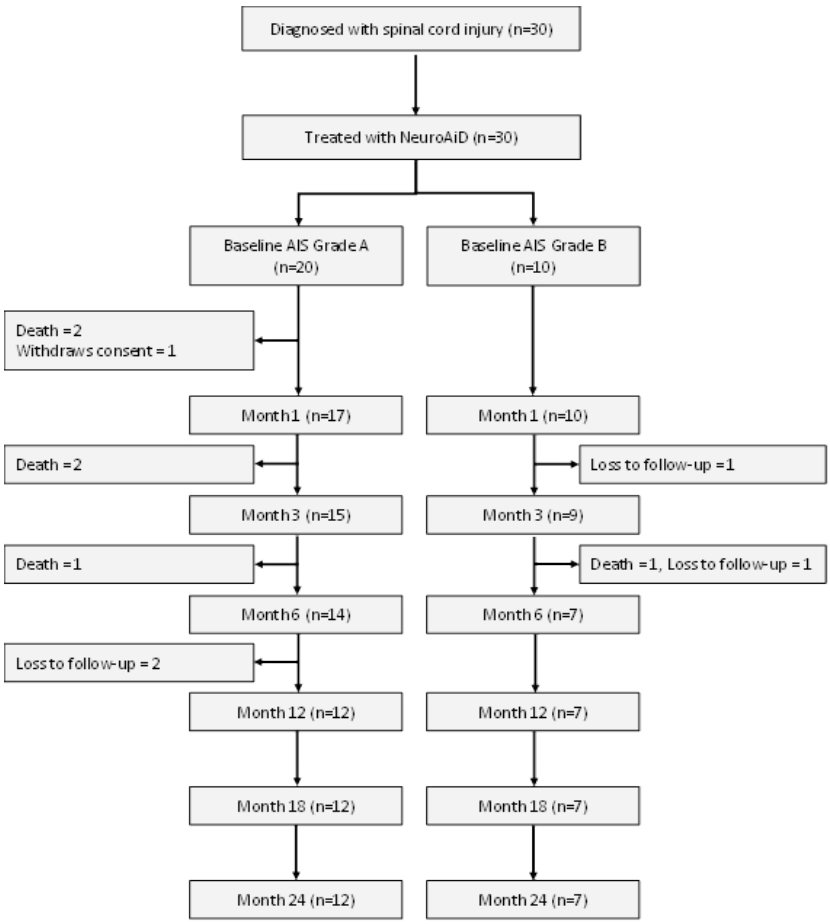

Figure 1: Consort diagram of patient flow.

Table 1: Improvement in AIS grade compared to baseline (Treated patients)

Parameter	Neuro AiD (N=30)	95% CI $	P-value $
Baseline AIS Grade			
A	20 (66.7)		
B	10 (33.3)		
Total	30 (100.0)		
Patients achieving Better Grade Compared to Baseline			
Month 1 (N=30)	10 (33.3)	(17.29, 52.81)	0.068
Month 3 (N=30)	10 (33.3)	(17.29, 52.81)	0.068
Month 6 (N=30)	10 (33.3)	(17.29, 52.81)	0.068
Month 12 (N=30)	10 (33.3)	(17.29, 52.81)	0.068
Month 18 (N=30)	10 (33.3)	(17.29, 52.81)	0.068
Month 24 (N=30)	11 (36.7)	(19.93, 56.14)	0.144
Patients with Baseline Grade A achieving Grade B or Better Compared to Baseline*	NeuroAiD	95 % CI $	p value $
Month 1 (N=20)	6 (30.0)	(11.89, 54.28)	0.074
Month 3 (N=20)	5 (25.0)	(8.66, 49.10)	0.025
Month 6 (N=20)	5 (25.0)	(8.66, 49.10)	0.025
Month 12 (N=20)	5 (25.0)	(8.66, 49.10)	0.025
Month 18 (N=20)	5 (25.0)	(8.66, 49.10)	0.025
Month 24 (N=20)	5 (25.0)	(8.66, 49.10)	0.025
Patients with Baseline Grade B achieving Grade C or Better Compared to Baseline&			
Month 1 (N=10)	4 (40.0)	(12.16, 73.76)	0.527
Month 3 (N=10)	5 (50.0)	(18.71, 81.29)	> 0.999
Month 6 (N=10)	5 (50.0)	(18.71, 81.29)	> 0.999
Month 12 (N=10)	5 (50.0)	(18.71, 81.29)	> 0.999
Month 18 (N=10)	5 (50.0)	(18.71, 81.29)	> 0.999
Month 24 (N=10)	6 (60.0)	(26.24, 87.84)	0.527

AIS -American Spinal Injury Association(ASIA) Impairment Scale

CI- Confidence Interval

Missing values are imputed by LOCF (Last Observation Carried Forward) except for death

$ 95 % Confidence Interval and Two sided P values are derived from exact binomial test

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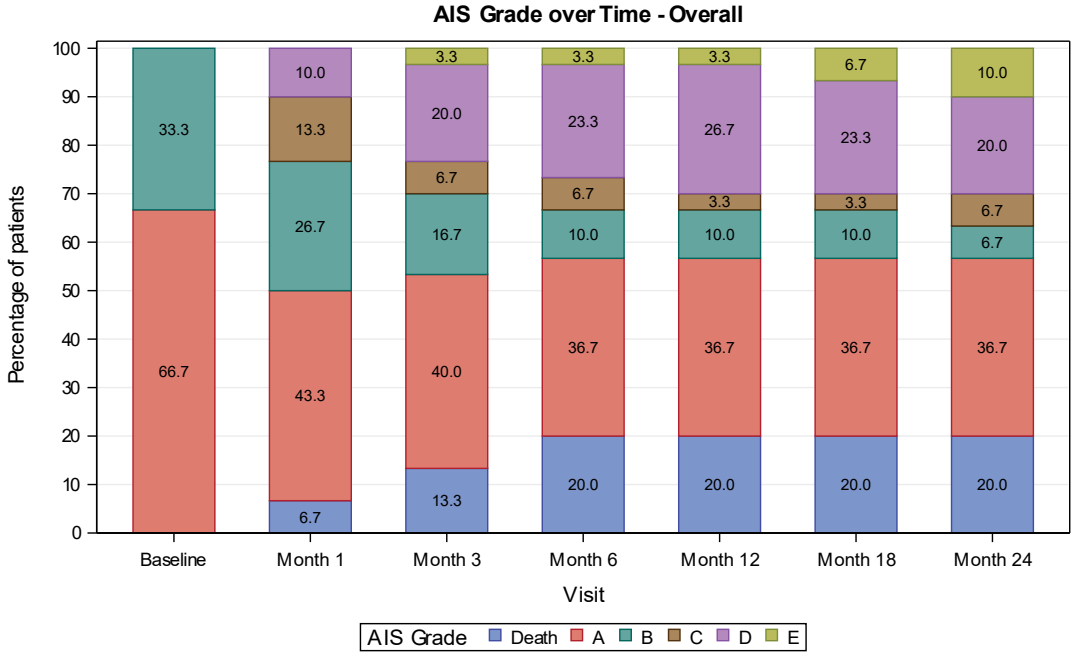

Figure 2: Conversion of AIS impairment grades

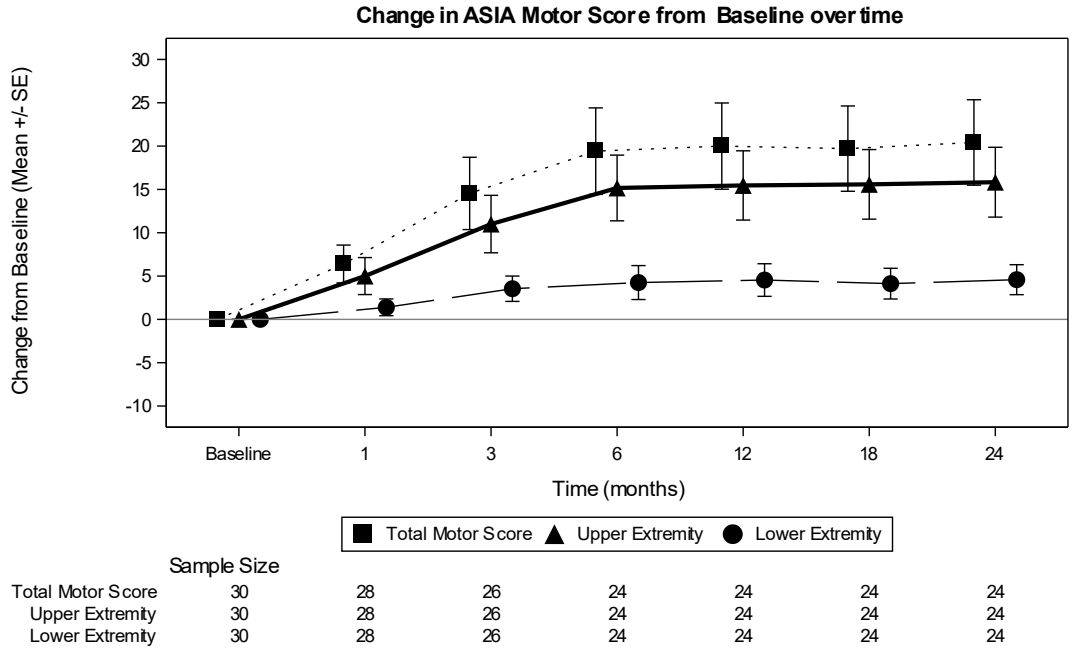

Figure 3: Change in AIS Motor Score from Baseline over time

peaked at 6 months and beyond 6 month the improvement was durable reaching the plateau state at 18 to 24 months. There was no reversal of benefit after stopping the treatment at month 6, meaning the recovery gained in 6 months continued to be seen in patients at 24 months. It may be possible that longer treatment duration could lead to further improvement. There were no delayed side effects noted at 24 months.

Spontaneous recovery in SCI of varying extent do occur even without treatment. According to published data, the rate of motor recovery after SCI is rapid during the first three months and motor improvement is almost complete by 9 months but ultimately plateaus at 12-18 months after SCI. In view of the likelihood that recovery of function following treatments will be concentrated close to the level of injury, it would be very useful to present some of the existing trial data in a format which shows recovery of function relative to distance below the neurologic level or whether recovery occurred within or beyond the Zone of partial preservation

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Table 2: Summary of Mean and Median at All Time Points and Change from Baseline in American Spinal Injury Association (ASIA) International Standard for Neurological Classification of Spinal Cord Injury Total Motor and Sensory Score and Spinal Cord Independence Measure Outcomes.

	Time point	Raw values		Change from Baseline	
Scale		Mean SD	Median (IQR)	Median (IQR)	p values
Total Motor Score	Baseline	35.7 (20.0)	50 (20,50)		
	Month 1	43.4 (24.0)	50 (29,50)	0 (0,9)	0.0007
	Month 3	60.5 (27.2)	50 (50,70)	0.5(0,31)	0.0004
	Month 6	59.5 (26.7)	54(50,81)	9 (0,44)	0.0005
	Month 12	60.1 (26.3)	50 (50,85)	8(0,41)	0.0001
	Month 18	59.8 (26.9)	50 (48,83)	10(0,42)	0.0003
	Month 24	60.5 (27.2)	50 (50,83)	11(0,43)	0.0002
AIS Sensory Subscore					
	Baseline	61(26)	68(42,80)		
	Month 1	69 (24)	74 (46,88)	4(0,15)	0.053
	Month 3	72 (26)	74 (48,94)	3(0, 19)	0.073
	Month 6	78 (23)	80(66,94)	8(0,27)	0.005
	Month 12	74 (25)	76 (48,98)	6 (-4,25)	0.006
	Month 18	76 (29)	80 (56,98)	6 (0,24)	0.022
	Month 24	75 (24)	80 (56,90)	6 (-7,24)	0.049
Total SCIM Score					
	Baseline				
	Month 1	34 (20)	33 (15,49)		
	Month 3	43 (21)	41 (24,60)	4 (-0.5, 15)	0.018
	Month 6	47 (20)	48(28,63)	9 (2,20)	0.06
	Month 12	52 (18)	53 (39,65)	14 (2,23)	0.001
	Month 18	53 (23)	56 (33,68)	19 (1,29)	0.003
	Month 24	54 (25)	50 (33,69)	16 (1,32)	0.002

AIS (ASIA Impairment Scale) ; SCIM (Spinal Cord Independence Measure)

$ p values are calculated based on Wilcoxon signed rank test, missing values are imputed by LOCF except for death

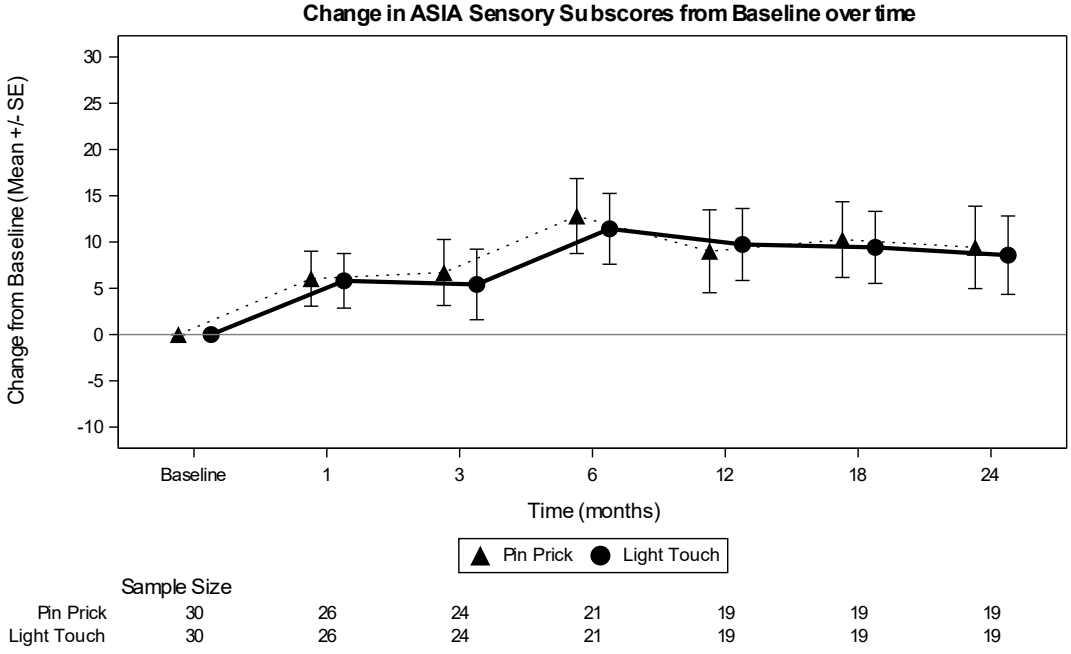

Figure 4: Change in AIS Sensory Subscore from Baseline over time

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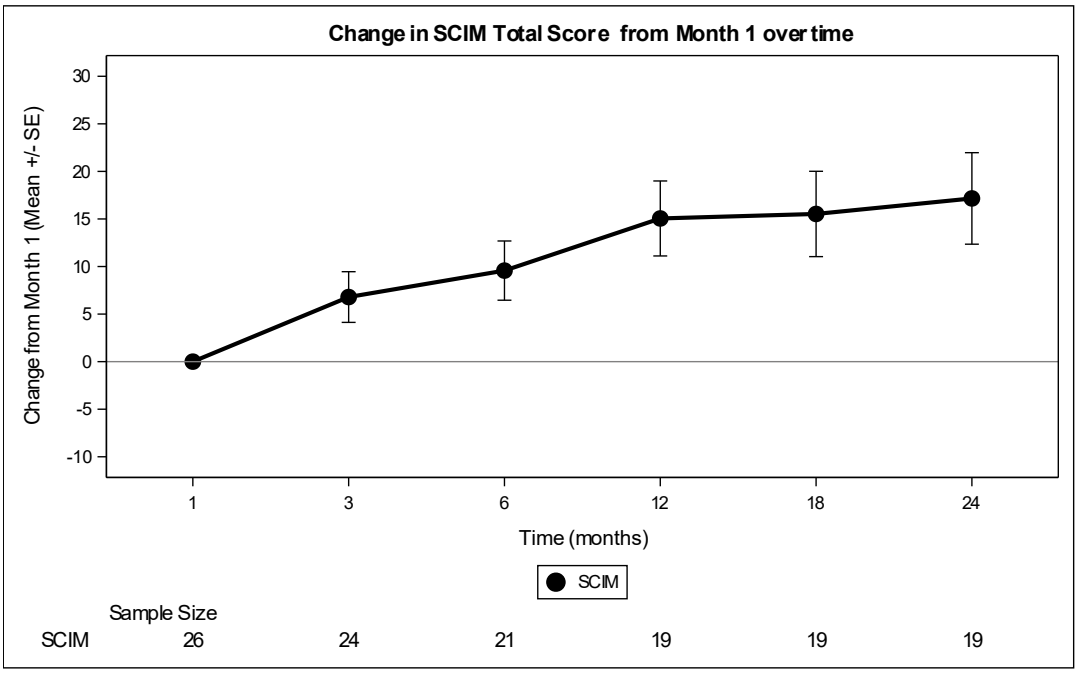

Figure 5: Change in SCIM Total Score from Month 1 over time

(ZPP) which may differentiate treatment effect and spontaneous recovery[14]. In one study by Waters et al, the change in AIS motor score for sensorimotor complete (AIS A) patients within initial two years after SCI showed that the most rapid improvement occurs within the first 6 months after SCI and is essentially maximal after 12 months[15]. In many studies AIS sensory examination often provided somewhat variable results within individual patients.

It is difficult to get a sufficient number of subjects to be able to analyse the effects of the new agent in SCI. The strength of this study is the 24 months follow up at a large health care facility with trained study investigators. This is longer as compared to the 12 months recommended follow up for SCI patients [16].

In the absence of control arm and the likelihood of spontaneous recovery, it is highly recommended to conduct a clinical trial with a six-month follow-up, but may be worth exploring the effect of treatment of longer than 6 months. We believe this study is important and will contribute the body of knowledge in treating SCI and does suggest a role for therapeutic neuromodulation in SCI patients.

Conclusion

The long-term outcomes further add evidence in the safety use and potential role of MLC601/MLC901 in SCI. This findings should help plan a study design for a randomized controlled trial.

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Conflict of Interest

The authors have no conflict of interest

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