Supplementary Online Appendix

Supplement to: Creamer M, et al: Intrathecal baclofen therapy versus conventional medical management for severe post-stroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS). Submitted to *JNNP*.

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APPENDIX 1: SECONDARY & ADDITIONAL EFFICACY OUTCOME MEASURES

Table S1: Details of secondary and additional outcome measures

SECONDARY OUTCOMES	
Safety	▪ Number of adverse events (AEs), including adverse drug reactions (ADRs), unexpected ADRs, adverse device effects (ADEs), unexpected ADEs, serious adverse events (SAEs), serious adverse drug reactions (SADRs), serious adverse device effects (SADEs), suspected unexpected serious adverse reactions (SUSARs), events related to trial/implant procedure. ▪ Vital signs (temperature, systolic and diastolic blood pressure, and pulse). ▪ Inpatient hospitalisations.
Efficacy	▪ Change in the average Ashworth Scale[1] score in affected upper extremities (wrist flexors, elbow flexors, elbow extensors, shoulder abductors, and shoulder adductors) from baseline to Month 6. ▪ Changes in the functional independence measure (FIM)[2] total score, motor sub-score, cognition sub-score, and 6 FIM domains from baseline to Month 6. ▪ Proportion of high-level functional patients (HLP) and low-level functional patients (LLP) and proportion of LLP converting to HLP. ▪ Change in the average 10 metre timed walking test[3] from baseline to Month 6 (HLP only). ▪ Changes in the Numeric Pain Rating Scale[4] scores (actual/least/worst spasticity-related or spasm-related pain) from baseline to Month 6. ▪ Proportion of patients achieving the therapeutic goal (Goal Attainment Scale[5]) at Month 3 and Month 6. ▪ Proportions of patients/caregivers who are satisfied with the therapy at Month 6. ▪ Healthcare resource utilisation (treatment use, concomitant medication and non-drug therapy use, healthcare contacts, hospitalisations).
Quality of Life	▪ Change in the EQ-5D-3L utility score and EQ-5D-3L-VAS from baseline to Month 6. [6] ▪ Changes in the SF-12 PCS and MCS summary scores from baseline to Month 6.[7] ▪ Change in the Stroke Specific – Quality of Life[8] summary score from baseline to Month 6.
ADDITIONAL OUTCOME	
Efficacy[a]	▪ Change in the Fugl-Meyer (FM)[9] total score and FM subdomains (motor, sensation, balance, joint range, and joint pain) from baseline to Month 6.

a: Assessment of sensorimotor recovery with the FM assessment was not listed as an objective in the CIP (error of omission) although it was included in the list of efficacy assessments and assessment schedule tables for both treatment arms. Consequently, analysis of this outcome as an additional objective was specified in the statistical analysis plan.

APPENDIX 2: ORAL ANTISPASTIC MEDICATIONS

Data for oral medications taken during the study by patients in the CMM arm are shown in **Table S2**. During the randomised period, the most frequently taken medications were oral baclofen (23/29 patients; 79.3%) and tizanidine (6/29; 20.7%). All other medications were each taken by one or two patients.

Table S2: Oral medications and daily dose for patients in the CMM arm (N=29 patients)

Drug Name (generic)	Number of patients	Daily dose (mg)				
		Mean	SD	Median	Min	Max
Baclofen	23	37.2	25.9	30.0	5.0	100.0
Tizanidine	6	6.3	3.3	6.0	2.0	12.0
Gabapentin	2	300.0	0.0	300.0	300.0	300.0
Tolperisone	2	300.0	150.0	300.0	150.0	450.0
Clonidine	1	0.4		0.4	0.4	0.4
Pregabalin	1	75.0		75.0	75.0	75.0
Tramadol	1	100.0		100.0	100.0	100.0

APPENDIX 3: ANALYSIS OF INDIVIDUAL FIM DOMAINS

Table S3: Summary of analysis of the change in individual FIM domains from baseline to Month 6 between ITB therapy and CMM arms (intention-to-treat population)

Individual FIM Domain		Change in FIM domain score from baseline to Month 6	
		ITB (N=31)	CMM (N=29)
Self-care score	N	25	26
	Mean (SD)	1.28 (4.60)	-1.27 (5.33)
	Median (min, max)	0.00 (-9.0, 11.0)	0.00 (-13.0, 10.0)
	p-value	0.0964	
Sphincter control score	N	25	26
	Mean (SD)	0.40 (1.38)	0.08 (1.72)
	Median (min, max)	0.00 (-2.0, 5.0)	0.00 (-5.0, 4.0)
	p-value	0.7776	
Transfers score	N	25	26
	Mean (SD)	0.28 (3.10)	0.19 (3.27)
	Median (min, max)	0.00 (-6.0, 10.0)	0.00 (-7.0, 7.0)
	p-value	0.7755	
Locomotion score	N	25	26
	Mean (SD)	0.24 (2.77)	0.04 (2.79)
	Median (min, max)	0.00 (-4.0, 6.0)	0.00 (-6.0, 7.0)
	p-value	0.9461	
Communication score	N	25	26
	Mean (SD)	0.16 (2.97)	-0.27 (1.95)
	Median (min, max)	0.00 (-5.0, 12.0)	0.00 (-6.0, 6.0)
	p-value	0.3776	
Social cognitive score	N	25	26
	Mean (SD)	0.32 (1.95)	-1.35 (3.89)
	Median (min, max)	0.00 (-4.0, 5.0)	0.00 (-11.0, 7.0)
	p-value	0.1144	

All p-values are for comparison of change from baseline to Month 6 between groups using the Wilcoxon test.

Calculation was based on LOCF imputation using data for Month 3 assessment in patients for whom Month 6 data was not available. Patients with data missing for both Month 3 and Month 6 were excluded from the analysis.

APPENDIX 4: SERIOUS ADVERSE EVENTS

In the present study, serious adverse events (SAEs) were defined as those events that met any of the following criteria: resulted in patient death; was life-threatening; required inpatient hospitalisation or prolongation of an existing hospitalisation; resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect. A total of 59 SAEs were reported, of which 35 events met at least one of the aforementioned criteria: 19 events in 9/25 (36%) patients in the ITB-I group and 16 events in 6/35 (17%) patients in the CMM+non-implanted group.

In addition, other medically significant conditions were to be considered serious as appropriate, such as important medical events that may not have been immediately life-threatening or resulted in death or hospitalisation, but may have jeopardised the patient or required intervention to prevent one of the previously listed outcomes. A total of 44 of 59 SAEs were classed as medically significant, of which 24 events were classed as medically significant only: 16 events in 8/25 (32%) patients in the ITB-I group and 8 events in 6/35 (17%) patients in the CMM+non-implanted group).

The overall rate of treatment-emergent SAEs was higher in the ITB-I group (34 events in 12/25 [48%] patients) compared to the CMM+non-implanted group (24 events in 10/35 [29%] patients) (**Table S4**). No individual PT was reported as an SAE by more than two patients in either group. Overall, the most common treatment-emergent SAE was urinary tract infection, reported in 3 patients (more frequently (one event in 1/25 [4%] patients in the ITB-I group, and five events in 2/35 [6%] patients in the CMM+non-implanted group). Other SAEs reported for more than one patient in total include implant site infection, urinary retention, and device dislocation (each two events in 2/25 [8%] patients in the ITB-I group only), and epilepsy (one event in each treatment group). Other PTs were reported by no more than one patient overall.

Table S4: Treatment-emergent serious adverse events by primary System Organ Class and Preferred Term

System Organ Class, Preferred Term	ITB-I (N=25)	CMM+non-implanted (N=35)	ALL (N=60)
All treatment-emergent SAEs	**12 (48.0%) [34]**	**10 (28.6%) [24]**	**22 (36.7%) [58]**
Infections and infestations	**4 (16.0%) [5]**	**3 (8.6%) [6]**	**7 (11.7%) [11]**
Urinary tract infection	1 (4.0%) [1]	2 (5.7%) [5]	3 (5.0%) [6]
Implant site infection	2 (8.0%) [2]	0	2 (3.3%) [2]
Cystitis	1 (4.0%) [1]	0	1 (1.7%) [1]
Pharyngitis	0	1 (2.9%) [1]	1 (1.7%) [1]
Pneumonia bacterial	1 (4.0%) [1]	0	1 (1.7%) [1]
Nervous system disorders	**6 (24.0%) [6]**	**3 (8.6%) [3]**	**9 (15.0%) [9]**
Epilepsy	1 (4.0%) [1]	1 (2.9%) [1]	2 (3.3%) [2]
Cerebrovascular accident	0	1 (2.9%) [1]	1 (1.7%) [1]
Dizziness	1 (4.0%) [1]	0	1 (1.7%) [1]
Hemiparesis	1 (4.0%) [1]	0	1 (1.7%) [1]
Intracranial hypotension	1 (4.0%) [1]	0	1 (1.7%) [1]
Muscle spasticity	1 (4.0%) [1]	0	1 (1.7%) [1]
Normal pressure hydrocephalus	1 (4.0%) [1]	0	1 (1.7%) [1]
Transient ischaemic attack	0	1 (2.9%) [1]	1 (1.7%) [1]
Renal and urinary disorders	**2 (8.0%) [2]**	**1 (2.9%) [4]**	**3 (5.0%) [6]**
Nephrolithiasis	0	1 (2.9%) [3]	1 (1.7%) [3]
Urinary retention	2 (8.0%) [2]	0	2 (3.3%) [2]
Hydronephrosis	0	1 (2.9%) [1]	1 (1.7%) [1]

System Organ Class, Preferred Term	ITB-I (N=25)	CMM+non-implanted (N=35)	ALL (N=60)
General disorders and administration site conditions	**4 (16.0%) [6]**	**0**	**4 (6.7%) [6]**
Device dislocation	2 (8.0%) [2]	0	2 (3.3%) [2]
Device occlusion	1 (4.0%) [1]	0	1 (1.7%) [1]
Implant site effusion	1 (4.0%) [1]	0	1 (1.7%) [1]
Oedema peripheral	1 (4.0%) [1]	0	1 (1.7%) [1]
Pain	1 (4.0%) [1]	0	1 (1.7%) [1]
Injury, poisoning and procedural complications	**2 (8.0%) [2]**	**1 (2.9%) [2]**	**3 (5.0%) [4]**
Alcohol poisoning	1 (4.0%) [1]	0	1 (1.7%) [1]
Fall	0	1 (2.9%) [1]	1 (1.7%) [1]
Post-traumatic pain	0	1 (2.9%) [1]	1 (1.7%) [1]
Suture related complication	1 (4.0%) [1]	0	1 (1.7%) [1]
Musculoskeletal and connective tissue disorders	**2 (8.0%) [2]**	**2 (5.7%) [2]**	**4 (6.7%) [4]**
Arthralgia	1 (4.0%) [1]	0	1 (1.7%) [1]
Mobility decreased	0	1 (2.9%) [1]	1 (1.7%) [1]
Muscular weakness	1 (4.0%) [1]	0	1 (1.7%) [1]
Plantar fasciitis	0	1 (2.9%) [1]	1 (1.7%) [1]
Cardiac disorders	**1 (4.0%) [3]**	**0**	**1 (1.7%) [3]**
Diastolic dysfunction	1 (4.0%) [1]	0	1 (1.7%) [1]
Mitral valve stenosis	1 (4.0%) [1]	0	1 (1.7%) [1]
Supraventricular tachycardia	1 (4.0%) [1]	0	1 (1.7%) [1]
Psychiatric disorders	**1 (4.0%) [1]**	**1 (2.9%) [2]**	**2 (3.3%) [3]**
Mental disorder	0	1 (2.9%) [2]	1 (1.7%) [2]
Depression	1 (4.0%) [1]	0	1 (1.7%) [1]
Gastrointestinal disorders	**3 (12.0%) [3]**	**0**	**3 (5.0%) [3]**
Constipation	1 (4.0%) [1]	0	1 (1.7%) [1]
Faecaloma	1 (4.0%) [1]	0	1 (1.7%) [1]
Gastritis	1 (4.0%) [1]	0	1 (1.7%) [1]
Eye disorders	**0**	**1 (2.9%) [2]**	**1 (1.7%) [2]**
Cataract	0	1 (2.9%) [1]	1 (1.7%) [1]
Diabetic retinopathy	0	1 (2.9%) [1]	1 (1.7%) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (4.0%) [1]**	**1 (2.9%) [1]**	**2 (3.3%) [2]**
Lymphoma	0	1 (2.9%) [1]	1 (1.7%) [1]
Osteochondroma	1 (4.0%) [1]	0	1 (1.7%) [1]
Skin and subcutaneous tissue disorders	**2 (8.0%) [2]**	**0**	**2 (3.3%) [2]**
Ingrowing nail	1 (4.0%) [1]	0	1 (1.7%) [1]
Skin ulcer	1 (4.0%) [1]	0	1 (1.7%) [1]
Vascular disorders	**1 (4.0%) [1]**	**1 (2.9%) [1]**	**2 (3.3%) [2]**
Hypertension	0	1 (2.9%) [1]	1 (1.7%) [1]
Hypotension	1 (4.0%) [1]	0	1 (1.7%) [1]
Respiratory, thoracic and mediastinal disorders	**0**	**1 (2.9%) [1]**	**1 (1.7%) [1]**
Pneumonia aspiration	0	1 (2.9%) [1]	1 (1.7%) [1]

Data presented are number of patients (% of patients) and [number of AE reports].

Appendix References

1 Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner* 1964;192:540-2.

2 Granger CV, Cotter AC, Hamilton BB, et al. Functional assessment scales: A study of persons after stroke. *Arch Phys Med Rehabil* 1993;74(2):133-8.

3 Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: Reference values and determinants. *Age Ageing* 1997;26(1):15-9.

4 Farrar JT, Young JP, Jr., LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94(2):149-58.

5 Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. *Community Ment Health J* 1968;4(6):443-53.

6 Euroqol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208.

7 Ware J, Jr., Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33.

8 Williams LS, Weinberger M, Harris LE, et al. Development of a stroke-specific quality of life scale. *Stroke* 1999;30(7):1362-9.

9 Fugl-Meyer AR, Jaasko L, Leyman I, et al. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med* 1975;7(1):13-31.