Transcutaneous Electrical Spinal Stimulation (tSCS) for Improving Upper Limb Function in People with MS

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Current disease-modifying therapies aim to prevent the development of new lesions; unfortunately, there are no current FDA-approved therapies to promote Central Nervous System (CNS) repair mechanisms. Thus, strategies to promote functional recovery from lesion-related deficits in adults with multiple sclerosis remain an unmet need. This proposal seeks to remedy this significant gap in MS care. 21

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Patients with MS (McDonald criteria 2017) with moderate to severe upper-limb disability defined as 9HPT in the dominant hand/functional hand > 33.3 sec (range: 33.3-240 sec) 22

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1.0 TRIAL OUTLINE

Study Title	Transcutaneous Electrical Spinal Stimulation (tSCS) for Improving Upper Limb Function in People with MS
Study Registration	TBD
Study Category	Interventional
Phase	Pilot study
Background & Rationale	The ability to efficiently use their hands is critical for maintaining activities of daily living (ADLs), a crucial unmet need for people with MS (PwMS). Recent clinical trials in patients with spinal cord injury have shown excellent safety and provided evidence of efficacy that tSCS associated with occupational therapy can improve the upper limb (UL) function and the ability to perform ADLs. Therefore, we propose to test the efficacy of tSCS in a pilot study in PwMS with moderate to severe UL disability.
Study Design	Double-blind, parallel, randomized, two arms, sham-controlled study in patients with MS and with significant disability of the upper limbs treated with tSCS and occupational therapy
Objective(s)	To assess the safety and efficacy of tSCS as add-on to standard rehabilitation in MS patients with moderate to severe UL disability
Outcome(s)	1. Primary endpoint: differences in the nine-hole peg test (9-HPT) affected hand in the tSCS treated vs. sham groups by the end of treatment (V3 vs V5) Secondary endpoints: 2. Percentage of responders: 20% difference on the 9HPTd (minimal clinically important difference (MCID)) from baseline to end of the study 3. Change in the 9HPT dominant and non-dominant hand from baseline to end of the study 4. Change in the Action Research Arm Test (ARAT) from baseline to end of the study 5. Change in the modified Ashworth Scale (mAS) for spasticity assessment from baseline to end of the study 6. Hand strength measured by Grip and Pinch force dynameters from baseline to end of the study 7. Change in the NeuroQOL Upper Extremity function from baseline to end of the study 8. Change in the Modified Fatigue Impact Scale (MFIS) from baseline to end of the study

	9. Change in Global Impression of change (GIC) from baseline to end of the study Safety and Tolerability 1. presence of serious adverse events 2. Retention rate 3. % sessions attended
Inclusion / Exclusion Criteria	Inclusion: Patients with MS and moderate to severe UL disability defined as 9HPT affected hand ≥ 33.4 sec; 21 to 65 years old Exclusion: patients with relevant comorbidities, pacemakers or metal implants
Measurements & Procedures	1. tSCS 2. Occupational Therapy 3. Clinical scales and PROs
Study Product / Intervention	tSCS is a non-invasive electric stimulation system that has shown good tolerability and signs of efficacy for improving UL disability
Controls	Sham (fictitious stimulation) will be used as control arm
Number of Participants & Rationale	N=60 (30:30) Rationale: accepting an alpha risk of 0.05 and a beta risk of 0.1 in a two-sided test, 10 subjects are necessary in each group to recognize as statistically significant a minimum difference of 10 units on the 9HPT scale between any pair of groups assuming that 2 groups exist. The common deviation is assumed to be 5.5. It has been anticipated a drop-out rate of 10%.
Study Duration:	24 months 6 months recruitment, 9 months randomized phase, 6 months OLE, 3-month analysis and clinical scientific report
Timelines:	● First Patient First Visit (FPFV): January 1st, 2025 ● Last Patient Last Visit (LPLV): December 30th 2026
Study Schedule:	Patients in Spain are recruited from the three MS centers (Hospital del Mar, Hospital Clínic and Hospital Sant Pau) in Barcelona and treated in a single therapy center at Hospital del Mar located closely to all of them. Patients in the Netherlands are recruited at the Rijndam center, Erasmus Medical Center. Run-in period (6 weeks with occupational therapy) Double-Blinded period: 6 weeks for safety and efficacy assessments

	Open Label Extension (6 weeks) for safety and durability of efficacy
Study Center:	Hospital del Mar (HMar); Hospital Clinic of Barcelona (HCB); Hospital Sant Pau (HSP), all in Barcelona, Spain; Rijndam center, Erasmus Medical Center (EMC)
Statistical Analysis Plan	The primary and secondary endpoints will be assessed using linear mixed-effects models (LME). These models will include the outcome measure as the dependent variable, and treatment group, time, and their interaction as independent variables, with random intercepts for participant and site to account for the longitudinal and clustered nature of the data. Populations : 1) Intention to treat population; 2) Per protocol population: patients that completed 70% of the therapeutic sessions

A list of abbreviations used in this document can be found in Appendix 12.3.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a double-blinded, parallel, sham-controlled study in PwMS and with significant disability of the upper limb (UL). Participants are exposed to a 6-week run-in period with standard occupational therapy and then randomized to 6 weeks of tSCS or sham combined with ongoing occupational therapy. After completion of the double-blind period, sham-treatment participants will be offered an additional 6 weeks open-label extension (OLE) where they receive active tSCS combined with occupational therapy. Participants in the original active group will be followed with no additional stimulation or occupational therapy to assess the durability of effects. The duration of the run-in, active treatment and extended follow (6 weeks each) are defined based in the previous results from a similar therapy for SCI.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

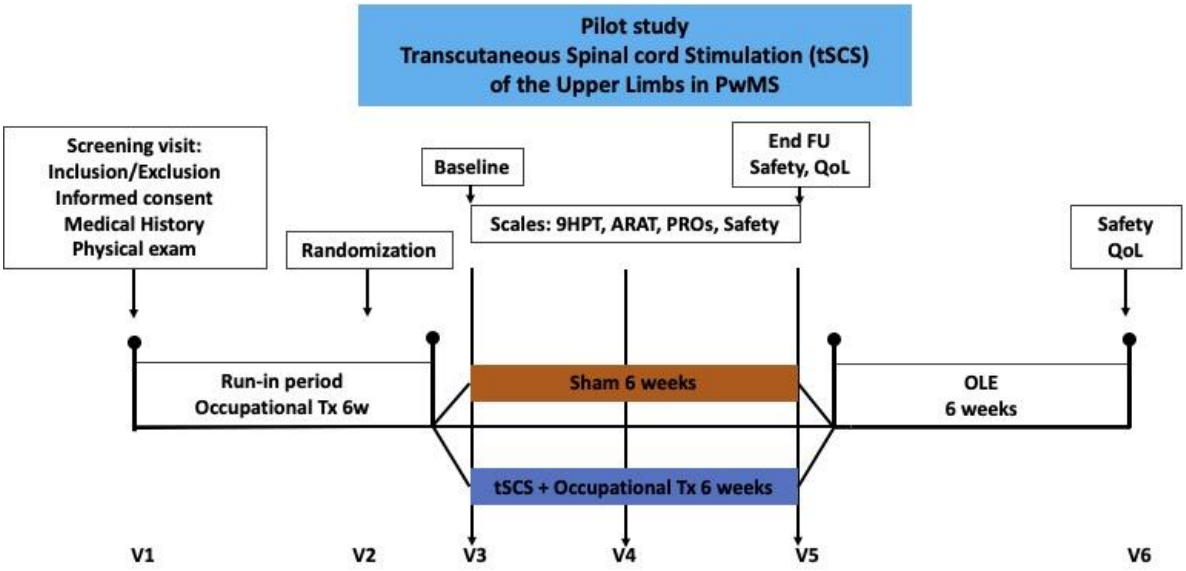

Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Co- Primary Objective(s) & Hypothesis(es)

Objectives:

• Objective 1. To assess the safety and tolerability of tSCS in PwMS.

• Objective 2. To assess the preliminary efficacy of tSCS on relevant clinical endpoints for PwMS, including patient-reported outcomes. This will be assessed by the differences in the

nine-hole peg test (9-HPT) affected hand in the tSCS treated vs. sham groups by the end of treatment (V3 vs V5)

Hypothesis:

We hypothesize that cervical tSCS combined with therapy will be tolerable and feasible in PwMS and enhance functional recovery of the upper extremity when compared to occupational therapy alone.

3.2 Key Secondary Objective(s) & Hypothesis(es)

Objectives:

1. Percentage of responders: 20% difference on the 9HPTd (minimal clinically important difference (MCID)) from baseline to end of the study
2. Change in the 9HPT dominant and non-dominant hand from baseline to end of the study
3. Change in the Action Research Arm Test (ARAT) from baseline to end of the study
4. Change in the modified Ashworth Scale (mAS) for spasticity assessment from baseline to end of the study
5. Hand strength measured by Grip and Pinch force dynameters from baseline to end of the study
6. Change in the NeuroQOL Upper Extremity function from baseline to end of the study
7. Change in the Modified Fatigue Impact Scale (MFIS) from baseline to end of the study
8. Change in Global Impression of change (GIC) from baseline to end of the study

Hypothesis: Our hypothesis is that tSCS treatment of the cervical cord combined with occupational therapy is safe and efficacious for treating people with MS with moderate to severe upper limb (hands) disability. Recent multi-site clinical trials in patients with spinal cord injury (SCI) have shown excellent safety and efficacy of tSCS associated with occupational therapy to improve UL functioning (NCT04697472). Therefore, this relevant evidence support moving this therapy directly to people with MS (PwMS) with moderate to severe UL disability.

3.3. Exploratory endpoints

None

Hypothesis: NA

3.4. Safety endpoints

Safety and Tolerability Objectives:

1. **Adverse Events (AEs) and Serious Adverse Events (SAEs):**
   All adverse events, regardless of severity or relatedness to the intervention, will be collected and documented throughout the study period. This includes both serious and non-serious adverse events. Serious adverse events will be defined according to ICH-GCP guidelines as any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

2. **Discontinuations and Reasons for Discontinuation:**
   Participant retention will be assessed by monitoring the number of participants who discontinue the study prior to its completion. The reasons for discontinuation (e.g., adverse events, lack of efficacy, personal decision, protocol deviations) will be recorded systematically.
3. **Retention Rate:**
   The retention rate will be defined as the percentage of participants who complete the study intervention and all study visits relative to the total number of participants initially randomized.
4. **Attendance Rate:**
   The percentage of scheduled intervention sessions that each participant attends will be recorded to assess adherence and tolerability.

Hypothesis: We hypothesize that tSCS will be safe and well tolerated in PwMS, with a low incidence of serious adverse events and a high retention rate.

4. BACKGROUND & RATIONALE

4.1 Background

4.1.1 Therapeutic Background

Multiple sclerosis (MS) is a relapsing and/or progressive disease characterized by lesions comprised of demyelination and axonal loss throughout the brain and/or spinal cord[1]. Current disease-modifying therapies aim to prevent the development of new lesions; unfortunately, there are no current FDA-approved therapies to promote Central Nervous System (CNS) repair mechanisms. Thus, strategies to promote functional recovery from lesion-related deficits in adults with multiple sclerosis remain an unmet need.

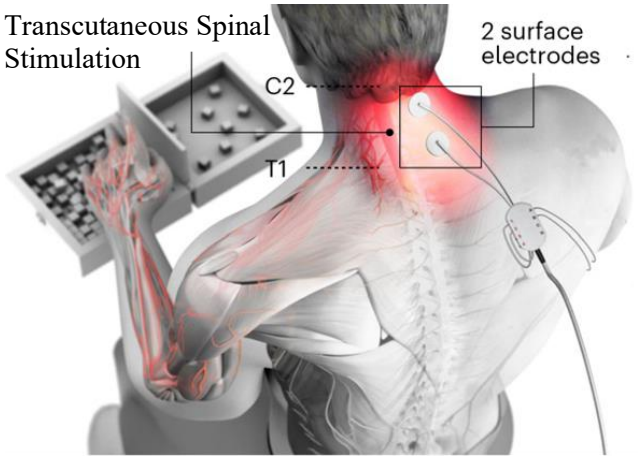

Figure 2: Transcutaneous electrical spinal stimulation is applied to the skin surface over the cervical spinal cord. In our preliminary studies of a person with MS, and our extensive studies of people with chronic spinal cord injury, this transcutaneous spinal stimulation substantially improves hand strength and function.

Electrical spinal cord stimulation is a neuromodulation technique that has been used to amplify sensorimotor recovery after a wide variety of CNS disorders, including MS, traumatic spinal cord injury (SCI), cerebral palsy, dystonia, stroke, and traumatic brain injury[2]. Historically, implantable epidural electrical stimulators were used, but despite initial promising results, the requirement of surgically implantable hardware and lack of understanding of the mechanism of action limited its use[3]. Most recently, however, we

have helped to pioneer new methods of non-invasive transcutaneous spinal cord stimulation[4, 5] (tSCS; Figure 2).

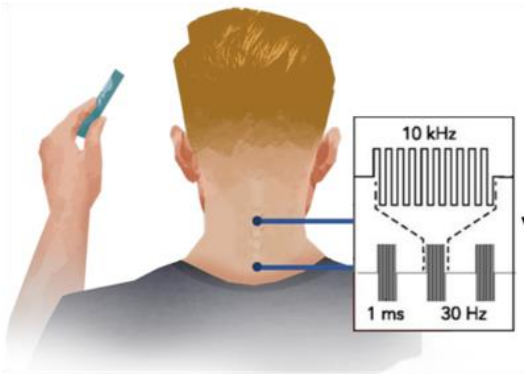

Figure 3: Transcutaneous spinal stimulation applied via electrodes placed above and below a cervical spinal injury. A 10 kHz carrier frequency fills the 1ms stimulus pulses delivered at 30 Hz, allowing 5-fold more current to be delivered to the skin over the spinal cord and improve hand function.

We are using a 10 kHz overlapping frequency to apply skin-surface stimulation (Figure 3). This high-frequency waveform allows the application of 5-fold greater stimulation intensities through the skin 6-8, which effectively reaches the spinal cord without causing discomfort[4-7, 9]. Thus, tSCS now permits administration of effective and well-tolerated, high stimulation intensities via removable electrodes placed on the skin over the vertebrae. While our tSCS protocols are less spatially specific than implanted epidural stimulation, both activate the dorsal sensory roots as they enter the spinal cord[3, 10-12]. Activation of sensory afferent fibers provides direct excitation of motor neurons via mono-and poly-synaptic reflexes to improve strength and function[4-6, 9]. Stimulation likely also activates ascending sensory and other interneuron structures within the spinal cord to improve sensation and reduce spasticity without the need for surgical implantation[5, 6].

We have demonstrated that our method of tSCS is well-tolerated and promotes significant and meaningful recovery of upper extremity function after chronic traumatic spinal cord injury[4, 6, 13-15]. For example, a prospective, open-label cross-over studies showed that non-invasive tSCS combined with functional task training improved upper extremity function in adults with SCI compared to functional task training alone, even after motor complete injury, and when administered up to 12 years after initial injury (Figure 4)[4].

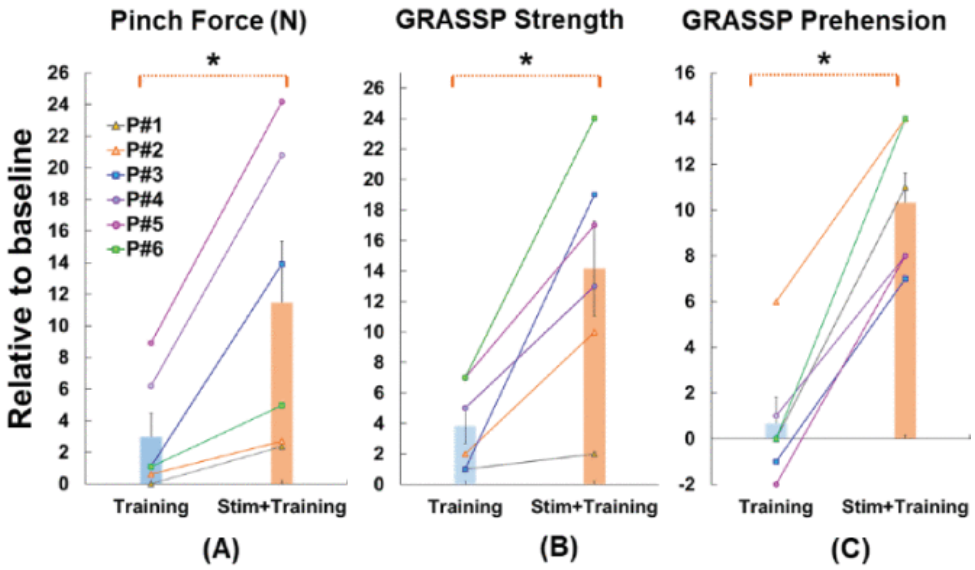

*Figure 4: Stimulation improved hand and arm function, which was sustained for 3-6 months in participants with cervical spinal cord injury. All six participants improved hand function during transcutaneous stimulation paired with training. Stimulation combined with training led to greater improvements than training alone in bilateral (A) pinch force, (B) Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP test), and (C) GRASSP quantitative prehension. Improvements that occurred during stimulation paired with training were maintained for at least 3 to 6 months of follow-up. *: $p < 0.05$; NS: $p > 0.05$.*

Strikingly, these gains were maintained for all 6 participants at least 3-6 months beyond stimulation, as long as could be measured. Also notable was the finding that benefits from this study extended beyond hand function, as some participants noted improvements in bladder function and reduction in spasticity. Improvements in psychological well-being, and self-care scores were also captured.

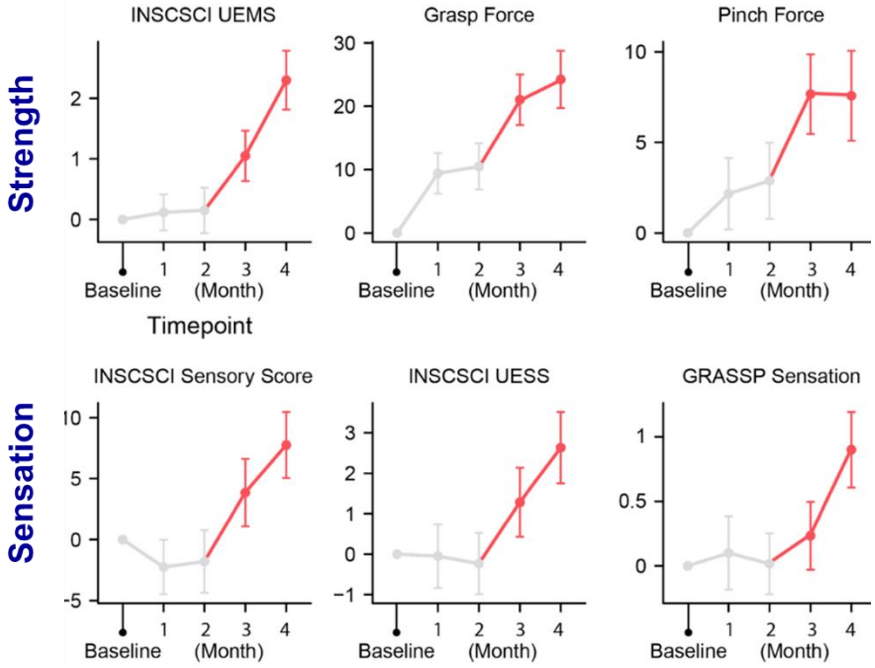

Figure 4. tSCS improves strength and function in 60 people with SCI. Our pivotal of tSCS began with 8 weeks of therapy alone (grey data points and lines), followed by 8 weeks of transcutaneous spinal stimulation combined with therapy (red data points and lines). While participants either reached a plateau or showed no improvement with therapy alone, subsequent tSCS led to significant improvements in strength and sensation, with 90% of participants improving in strength or function outcomes. Strength measures included ISNCSCI

Upper Extremity Motor Score (UEMS), hand grasp force, and finger-tip pinch force. Sensory outcomes were ISNCSCI Sensory Score, Upper Extremity Sensory Score (UESS) and monofilament finger-tip sensation in the GRASSP test.

We then led a pivotal, multi-site trial of 60 participants with traumatic SCI and demonstrated the safety and efficacy of tSCS for arm and hand function in chronic tetraplegia[5] (Figure 4). Following 8 weeks of tSCS combined with hand therapy, 90% of participants improved in either strength or function outcomes. Seventy-two percent of participants improved in both strength and function (the primary endpoint). Sensation also improved following tSCS by more than 9 points on the gold-standard clinical ISNCSCI total sensory score, compared to an equal number of sessions of therapy alone. These results are currently under review by the FDA following a do-novo submission by ONWARD Medical, for potential device approval in early 2024.

We are beginning to test tSCS for people with multiple sclerosis (PwMS) and observing impressive results in our first participant (see preliminary data below). Although the lesions in MS are distributed throughout the brain and spinal cord, there is strong evidence to suggest that spinal stimulation, and tSCS in particular, will be similarly effective for PwMS as those with SCI[4-7, 9, 16], stroke[17], and children with cerebral palsy[18-20], based on the mechanisms of action of tSCS.

Evidence is accumulating that the combination of tSCS and intensive functional task training (therapy) promotes recovery via the following mechanisms (outlined in Figure 5). tSCS directly activates sensory afferent pathways via the dorsal or posterior spinal roots[3, 10-12]. Sensory afferent activation then provides trans-synaptic, sub-threshold excitatory input to the lower motor neurons within the spinal cord[21]. This sub-threshold input is believed to raise the motor neuron's baseline level of excitability, which allows spinal cord motor neuron pools to be activated by the remaining, but weak, descending motor pathways from the brain22. Thus, by raising the lower motor neuron's level of excitability to a sufficient sub-threshold level, descending volitional control of movement can be restored[23]. Continued active participation in rehabilitation training can then promote further reorganization of the spinal networks and strengthen the remaining intact but weak synaptic connections[24-26].

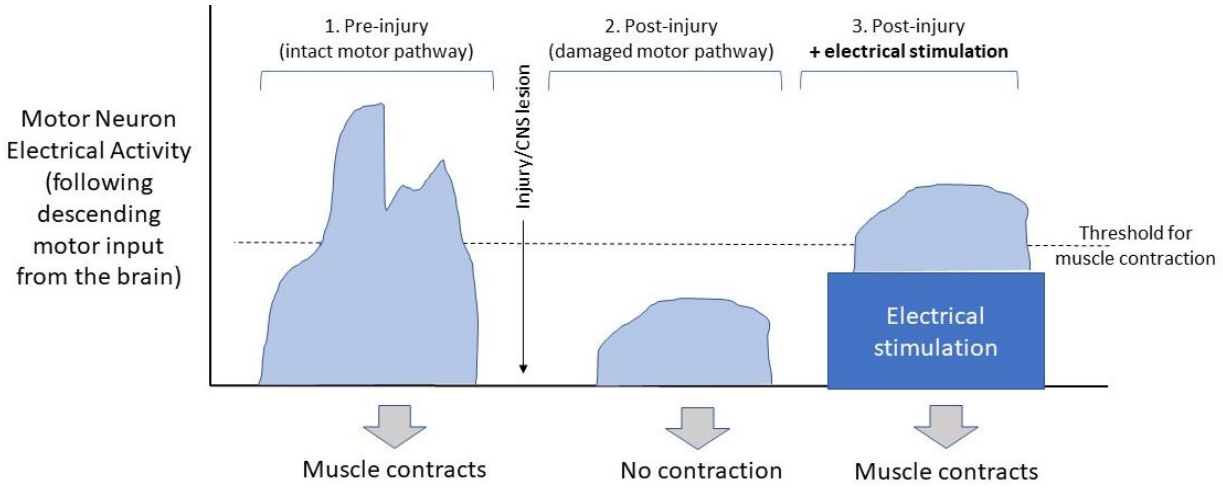

Figure 5. A schematic of the mechanism by which spinal cord stimulation enables voluntary movement after damage to descending motor tracts from SCI or MS. **1.** In the intact nervous system, a voluntary effort can readily elevate the level of excitability of the lower motor neuron to exceed the motor threshold and activate a muscle contraction; **2.** Following nervous system injury or demyelination, descending motor tracts from the brain are less effective in allowing an individual to initiate movement. There is some electrical activity from remaining intact fibers, but the level of excitability is insufficient to reach motor threshold. Hence, no movement occurs; **3.** In the case of nervous system injury or demyelination + electrical stimulation, spinal stimulation raises the level of excitability to a sub-threshold level; this can enable the weak but remaining descending input from the brain to exceed the motor threshold. Voluntary movement is restored and enables participation in therapy which leads to further neuroplasticity.

The mechanisms of tSCS suggest it may be very effective for persons with multiple sclerosis. Multiple Sclerosis (MS) is a chronic, inflammatory demyelinating condition characterized by multiple lesions disseminated throughout the brain and spinal cord. Thus, weakness may occur due to inadequate motor output from the brain, similar to stroke and cerebral palsy. Weakness in MS may also result from axon conduction failure in signals passing through the spinal cord, as in spinal cord injury.

There are notable similarities between MS and SCI as well as dissimilarities. Chronic spinal cord lesions in each condition are characterized by demyelination, axonal loss, and chronically activated microglia[27, 28]. The list of resulting symptoms and functional impairments are remarkably similar: motor weakness, sensory impairment, spasticity, neuropathic pain, and neurogenic bowel/bladder are highly prevalent in both conditions[29, 30]. Therefore, similar to SCI, we hypothesize that spinal stimulation in people with MS has the potential to bring lower motor neurons closer to the threshold, allowing weak but descending input from the brain to initiate movement (Figure 5).

Although most of the research on SCS has been conducted in humans, the beneficial effect of tSCS in animal models of SCI and MS has also been demonstrated. SCS has shown the ability to restore the functioning of spinal cord circuits that were disconnected from central control with functional (locomotor and pain reduction) improvements in the animals[31-34]. In experimental autoimmune encephalomyelitis, SCS reduces CNS inflammation[35] and promotes the release of neuroprotective genes such as BDNF[36].

Although transcutaneous spinal cord stimulation has not been well-studied in PwMS, electric stimulation has been applied peripherally to the nerve supply of weak muscles (e.g., foot extensors) to restore function and prevent muscle atrophy in PwMS[37-39]. Existing data

on epidural spinal cord stimulation in MS also shows promise: a 2021 systematic review concluded that spinal cord stimulation was likely efficacious for MS-related motor impairment, neuropathic pain, and neurogenic bladder, although all available studies used only surgically implanted devices and were only retrospective in nature[40].

Less is known about the efficacy of transcutaneous SCS in MS, which highlights the novelty of our proposal. One prior study demonstrated that the application of single-session transcutaneous lumbar spinal cord stimulation without therapy is feasible in MS and demonstrated short-term improvements in mobility, postural control and spasticity[41]. An important proof-of-concept study in MS, functional gains from this single session of transcutaneous lumbar spinal cord stimulation lasted 2 hours post-intervention.

To our knowledge, the proposed study will be the first to investigate the ability of repeated transcutaneous cervical spinal cord stimulation combined with occupational therapy on longer-term recovery of upper extremity function, which is identified as a high priority by the MS community[42, 43].

An alternative to electrical spinal cord stimulation is transcranial magnetic stimulation (TMS), which has shown some promise in PwMS[44]. Here, however, we propose to use tSCS instead of TMS based on the wider efficacy demonstrated in SCI by tSCS, the latest improvement of the tSCS technology to non-invasively activate the spinal cord without pain or discomfort. We believe that the direct effects of spinal cord electric stimulation on sensory axons which in turn enable movement is the ideal treatment for PwMS, given their partial preservation of cortical and spinal cord circuits. Our encouraging preliminary data, combined with the demonstrated safety and efficacy of tSCS in SCI, compels us to test non-invasive spinal stimulation as a treatment to improve hand function for PwMS.

This application aims to conduct a pilot clinical trial to demonstrate the safety and preliminary efficacy of tSCS and to inform the design of pivotal trials aimed at obtaining regulatory approval for the indication of treating people with MS with moderate to severe upper limb disability. We model this approach after our recent proof-of-concept4, 6 and then multi-site clinical trial 5 in people with SCI where we have demonstrated the safety and efficacy of tSCS combined with intensive occupational therapy to improve upper extremity functioning The results of this pivotal trial, combined with our strong preliminary data, supports moving this therapy directly to PwMS with moderate to severe upper limb disability.

Preliminary Results

Preliminary data from a participant with secondary progressive MS, EDSS 8.0 (indicating high baseline disability) provides confidence that transcutaneous spinal cord stimulation will benefit patients with MS. This participant required caregiver assistance for many activities of daily living (ADLs), including transfers, dressing, grooming, bathing and feeding, due to bilateral (left>right) upper extremity weakness. Prior to enrollment in our preliminary study, this participant had been working with a local occupational therapist but had transitioned to monthly maintenance therapy visits after reaching a plateau in functional recovery.

Upon enrollment in our study, this participant with MS underwent two assessment visits one week apart, during which their baseline function was assessed. Subsequently, they completed 10 intervention visits consisting of transcutaneous spinal cord stimulation (tSCS) combined with occupational therapy for hand and arm function as previously described[1]. Treatments occurred 3 times per week for 60-minutes each session.

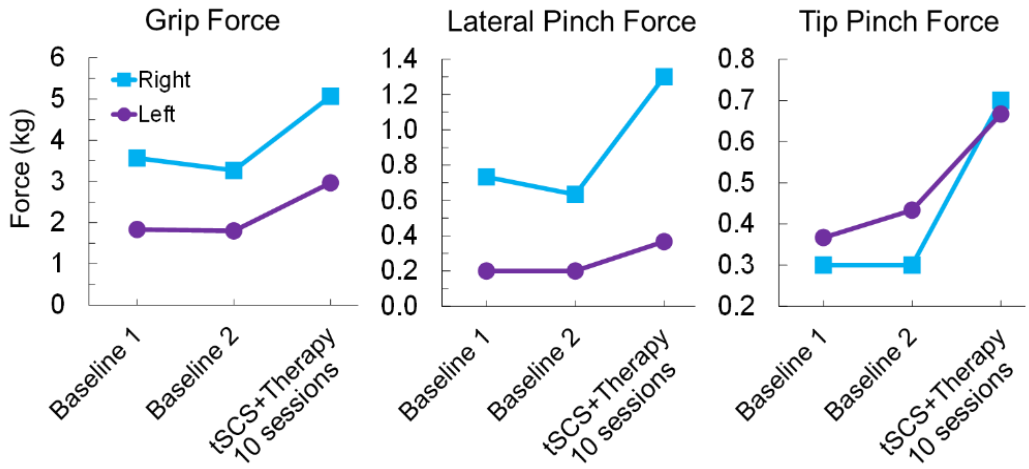

Figure 6. **Transcutaneous spinal cord stimulation (tSCS) + occupational therapy led to notable improvements in strength.** The average improvement of grip force in the right and left hand were 55%, lateral pinch force was 86%, and tip pinch force was 100% following 10 intervention sessions. Grip force, lateral pinch force, and tip pinch force were measured by precise digital dynamometers.

Following 10 visits tSCS and occupational therapy, the participant improved substantially in hand strength, upper extremity function, and spasticity. Specifically, grip force, lateral pinch force, and tip pinch force increased by 55-100% in both hands due to the intervention (**Figure 6 and 7**).

Due to muscle weakness and spasticity, this participant's gross upper limb movements, coordination, and finger opening were severely restricted. The hand and arm function and dexterity progressively improved throughout 10 sessions of tSCS combined with hand and arm therapy (**Figure 7**).

Figure 7. Starting from the very first session, tSCS combined with hand and arm therapy gradually enhanced gross upper extremity movements, pinch and grip performance, and hand dexterity.
From left to right, (**a**) limited movement and dexterity at baseline/first few sessions and (**b**) gradual improvement in right upper limb coordination; left gross manual dexterity; and left arm range of motion; and reduction in left flexor spasticity by tSCS combined with therapy.

Figure 7. **Patient with SPMS hand performance before (A) and after (B) tSCS therapy.**

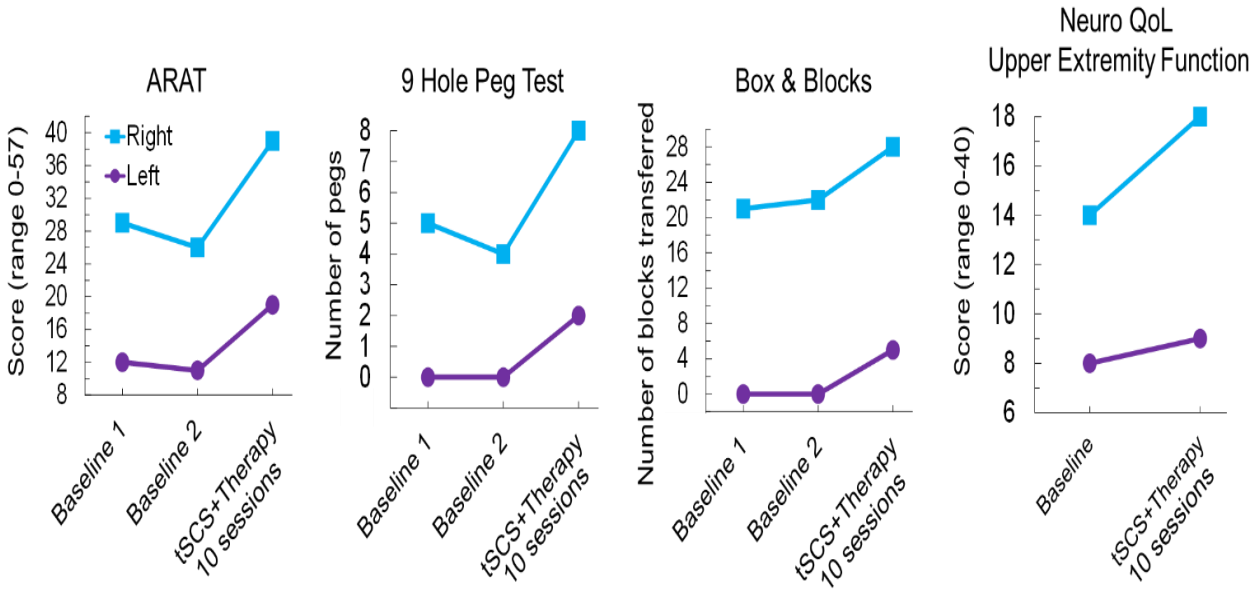

Figure 8. **Dexterity, functional movement capacity, and coordination of the upper extremities showed rapid and clinically meaningful improvements after 10 sessions with Transcutaneous Spinal Cord Stimulation (tSCS) combined with occupational therapy.** The functionality of the hand and arm were tested by the Action Research Arm Test (ARAT, a measure of upper extremity coordination, dexterity, and functioning), 9-Hole Peg Test (a measure of finger dexterity), and Box & Blocks Test (a measure of gross manual dexterity Our participant showed an improvement exceeding the 15-20% threshold. While the MCID for the ARAT and Box and Blocks Test has not been established for MS. Notably, our participant's improvements in both tests surpassed these benchmarks by only 10 sessions with tSCS. Patient-reported upper extremity function was also captured by Quality of Life in Neurological Disorders (NeuroQoL) Upper Extremity Function Questionnaire (a self-report of health-related quality of life in for adults with neurological disorders).

These hand strength gains were mirrored by improvements in upper extremity function measured by the Action Research Arm Test, a measure of upper extremity coordination, dexterity, and functioning[2], 9-Hole Peg Test (9HPT), a measure of finger dexterity[3], and Box & Blocks Test, a measure of gross manual dexterity[4] (**Figure 8**).

Note that due to fatigue and physical limitations, this participant was unable to complete the 9HPT, and therefore their score is recorded as the total number of pegs placed in 90 seconds. This reflects the participant's significant baseline disability. Even their left upper extremity, which was more severely impaired at baseline, demonstrated gains following as few as 10 tSCS intervention sessions. At baseline, the participant was unable to transfer any blocks during the Box & Blocks test or place any pegs during 9HPT with their left upper limb; however, after 10 intervention sessions, they developed the ability to independently perform these tasks using their left upper extremity. Importantly, the intervention also led to subjective improvements in upper extremity function, as evidence by increased scores on the Quality of Life in Neurological Disorders (NeuroQoL) Upper Extremity Function Short Form Questionnaire[5] (**Figure 8d**), a patient-reported outcome developed with support from the National Institute of Neurologic Disorders and Stroke to assess health-related quality of life in individuals with neurologic conditions, including MS.

The participant also experienced a reduction in spasticity following only 10 sessions of tSCS + hand therapy (**Figure 9**). The Modified Ashworth Scale score evaluates spasticity in 16

joint movements of the upper extremities. Muscle resistance during each movement is scored on a scale of 0-4, where 0 is not spasticity, and 4 is complete rigidity. For simplicity of presentation, we sum the scores for all 16 movement, for a range of 0-64 points[1] . We observed a 3-6 point reduction in spasticity in both upper limbs (**Figure 8**). The participant reported that reduced spasticity led to improvement in daily activities and a reduction in their spasticity-related shoulder pain.

Most importantly, all outcomes were measured in the absence of tSCS. Therefore, the measured functional gains persisted after only 10 sessions of tSCS, suggesting they will easily translate to better function during daily activities outside of stimulation and therapy sessions.

In addition to the above improvements, the participant reported high satisfaction with the treatment, and felt sessions were painless and easy to tolerate (**figure 10**).

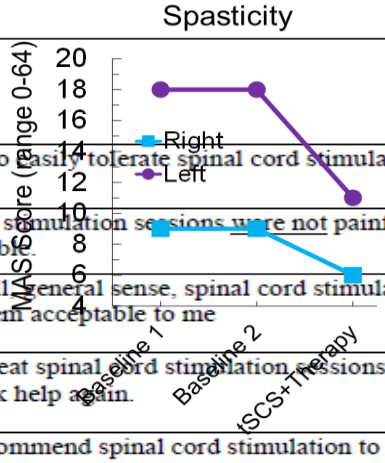

Figure 9. Notable reduction in upper extremity spasticity facilitated the participant's daily activities and alleviated their spasticity-related shoulder pain. Lower scores indicate less spasticity/better outcome. MAS; Modified Ashworth Scale.

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
1. I was able to easily tolerate spinal cord stimulation sessions.	X				
2. Spinal cord stimulation sessions were not painful or uncomfortable	X				
3. In an overall general sense, spinal cord stimulation sessions seem acceptable to me	X				
4. I would repeat spinal cord stimulation sessions if I were to seek help again.	X				
5. I would recommend spinal cord stimulation to a friend, if he [illegible]	X				
6. I would like to see more research on spinal cord stimulation trials for people with multiple sclerosis	X				

	Very Satisfied	Satisfied	Neutral or no preference	Dissatisfied	Strongly Dissatisfied
1. How satisfied are you overall with the study treatment?	X				

Figure 10. Participant found transcutaneous spinal cord stimulation tolerable, painless, and highly satisfactory. Participant answered the acceptability of intervention questionnaire after 10 sessions of therapy + transcutaneous spinal cord stimulation. The questionnaire consisted of 7 questions relating to tolerability and acceptability of the intervention, answered on a Likert scale, as shown above.

After the 10 intervention sessions were completed, the participant provided the following positive feedback:

"My left hand was curled all the time before I started stimulation sessions. Now, I am able to extend my fingers without needing a stretch."

"My left shoulder was bothering me a lot. Now, the pain is gone, which is a big benefit of spinal cord stimulation."

> *"I can raise my right arm much easier than before and can touch the top of my head now, which was not possible before. I can also raise and extend my left arm higher than before."*

Positive feedback was also noted by the participant's local occupational therapist post-intervention. Throughout the pilot trial, the participant did not participate in any sessions with this local therapist. However, after the pilot trial intervention was completed, this local therapist (who had no connection to the study or study team) re-evaluated this participant and noted the following positive effects:

> *" (the participant) demonstrated significant improvement in functional use of right hand today, as well as ADL and progress towards goals. She also demonstrates gains in psychological wellness, including motivation, initiation and self-efficacy."*

We are very encouraged by the significant gains after only 10 intervention sessions in this participant and anticipate continued improvement with further sessions. Importantly, these gains were seen in a participant who had been undergoing occupational therapy (without tSCS) in the community but who had plateaued in their progress. The proposed randomized clinical trial is needed to rigorously test whether tSCS combined with therapy can lead to functional gains when directly compared to occupational therapy alone in PwMS.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Current disease-modifying therapies aim to prevent the development of new lesions; unfortunately, there are no current FDA-approved therapies to promote Central Nervous System (CNS) repair mechanisms. Thus, strategies to promote functional recovery from lesion-related deficits in adults with multiple sclerosis remain an unmet need. This proposal seeks to remedy this significant gap in MS care.

4.2.2 Rationale for Stimulation Protocols Selection/Regimen

The tSCS non-invasive spinal stimulation utilizes two modulated frequencies: (1) base frequency and (2) overlapping frequency. The base frequency is 30 Hz, whereby 1ms pulses are delivered 30 times per second Figure 12 right). Within each pulse, an overlapping frequency of 10kHz is deployed to permit about 5-fold more current to be delivered for the same level of cutaneous sensation under the electrodes. This 10 kHz overlapping frequency is adapted from kilohertz-frequency muscle stimulation, permitting high-amplitude stimulation on the skin surface without discomfort. Thus, stimulation applied on the surface of the skin can reach the spinal cord dorsal roots to activate spinal networks. The rationale for the 10 kHz overlapping frequency is that high-frequency waveforms can selectively block unmyelinated C-fibers in the skin[50, 51], and stimulation may penetrate more deeply due to the lowering of the tissue impedance [4, 6, 52]. We have observed substantial improvements in hand and arm function without inducing discomfort under the electrodes in our studies of more than 70 people with spinal cord injury[4-6].

4.2.2.1 Rationale for the Use of Sham

In order to assess the efficacy of the therapy in clinical outcomes, comparison between active and sham treatment is required. Using sham or placebo for 6 weeks is accepted for patients with MS. In order to encourage participation and fulfill patients' expectations, sham treated patients will be offered an additional 6 weeks open-label extension (OLE) where they receive active tSCS combined with occupational therapy.

4.2.2.2 Rationale for Healthy Control

No healthy control group is required.

4.2.2.2 Starting Stimulation Protocols for This Trial

The base frequency is 30 Hz, whereby 1ms pulses are delivered 30 times per second Figure 12 right). Within each pulse, an overlapping frequency of 10kHz is deployed to permit about 5-fold more current to be delivered for the same level of cutaneous sensation under the electrodes.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary endpoints: the 9HPT is the accepted outcome for UL assessment in MS.

Secondary endpoints: In addition to the 9HPT, the ARAT, MAS, NeuroQOL, MFIS, and GIC are standard scales used in patients with MS

4.2.3.2 Safety Endpoints

The safety and tolerability of tSCS will be assessed throughout the study via Adverse Event reporting, and vital signs will be assessed at every trial visit.

4.3 Benefit/Risk

Participants in this study are patients with MS with severe disability involving UL (and most likely with severe lower limb disability, being restricted to a wheelchair) or having significant ambulation limitations). tSCS is not invasive, is well tolerated and is a minimal-risk device. As a result, the risk/benefit should be highly beneficial for the participants.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with MS (McDonald criteria 2017) with moderate to severe upper-limb disability defined as 9HPT in the dominant hand/functional hand > 33.3 sec (range: 33.3-240 sec)

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be between 21 to 65 years of age (inclusive) on the day of signing informed consent.
2. Have MS (McDonald criteria 2017) with moderate to severe upper-limb disability defined as 9HPT in the dominant hand/functional hand > 33.3 sec (range: 33.3-240 sec)
3. Any type of disease modifying therapy is allowed and should be stable in the last 3 months.
4. Not having received corticosteroids previous month.
5. Each subject must sign the informed consent form, in accordance with local requirements, after the scope and nature of the investigation have been explained to the subject, and before Screening assessments.
6. Based on the investigator's judgment, the subject should:
    a. Be able to speak, read, and understand the language of the trial staff and the informed consent form;
    b. Possess the ability to respond verbally to questions, follow instructions, and complete study assessments.
    c. Be able to adhere to the stimulation protocol and visit schedules.
7. Women of child-bearing potential* must have a negative urine pregnancy test before the inclusion in the study and agree to use highly effective contraceptive methods during the study. Highly effective contraceptive methods will include intrauterine device, implant, patch or pill, bilateral tubal occlusion, vasectomized partner and sexual abstinence.

* A woman will be considered of childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as 0 menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post- menopausal state in women not using hormonal

contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject has:

1. Any condition or therapy impairing trial participation and assessments
2. The presence of a relapse or use of IV steroids for any reason 3 months prior to screening visit.
3. Severe systemic diseases or history of cancer or hereditary familiar cancer.
4. Clinically relevant concomitant disease: cardiac, gastrointestinal, hepatic, pulmonary, neurological, renal or other major disease.
5. Pregnant or breastfeeding women.
6. Drug or alcohol abuse.
7. Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at screening.
8. Ongoing known bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), positive hepatitis B surface antigen or hepatitis C antibody tests at screening.
9. Patients with a known history of syphilis or tuberculosis or test positive for syphilis (positive rapid plasma regain, RPR) or tuberculosis (positive skin test) at screening. Active or latent tuberculosis (TB).
10. Dementia or severe psychiatric, cognitive or behavioral problems or other comorbidity that may interfere with the compliance to the protocol.
11. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study.
12. Participation in other experimental studies within the previous 90 days prior to screening visit.
13. Patients having a pacemaker or other metal implants.

5.2 Trial Treatment(s)

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Therapeutic regimen Selection: tSCS stimulation protocols

The tSCS non-invasive spinal stimulation utilizes two modulated frequencies: (1) base frequency and (2) overlapping frequency. The base frequency is 30 Hz, whereby 1ms pulses are delivered 30 times per second Figure 12 right). Within each pulse, an overlapping frequency of 10kHz is deployed to permit about 5-fold more current to be delivered for the same level of cutaneous sensation under the electrodes. This 10 kHz overlapping frequency is adapted from kilohertz-frequency muscle stimulation, permitting high-amplitude stimulation on the skin surface without discomfort. Thus, stimulation applied on the surface

of the skin can reach the spinal cord dorsal roots to activate spinal networks. The rationale for the 10 kHz overlapping frequency is that high-frequency waveforms can selectively block unmyelinated C-fibers in the skin[6, 7], and stimulation may penetrate more deeply due to the lowering of the tissue impedance [1, 8, 9]. We have observed substantial improvements in hand and arm function without inducing discomfort under the electrodes in our studies of more than 70 people with spinal cord injury[1, 8, 10].

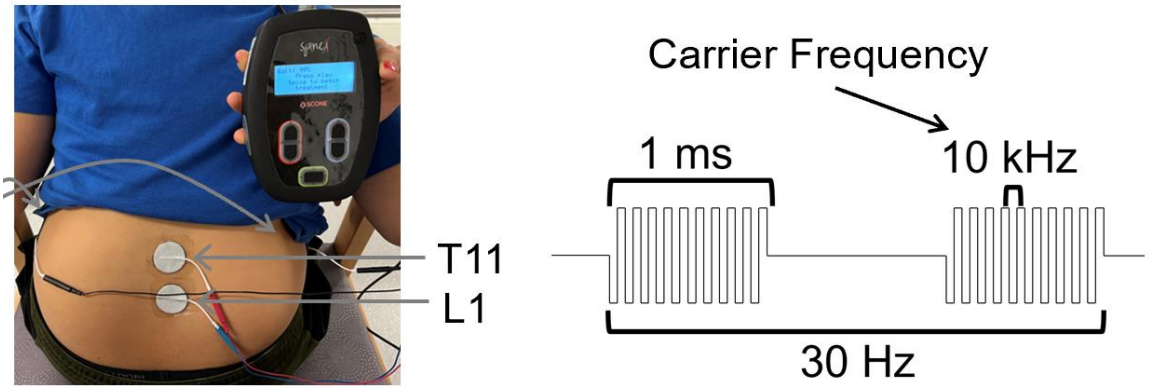

Figure 12: (Left) SpineX device attached to two skin-surface electrodes for a child with cerebral palsy. (Right) Stimulation waveform with 10 kHz carrier frequency superimposed on each 1ms pulse, delivered 30 times per second to activate the spinal cord without discomfort from the surface of the skin.

Based on the protocol[11], stimulation waveforms are configured as monophasic or biphasic based on the configuration that leads to the most robust facilitation of arm and hand movements. The intensity of the stimulation is increased gradually (e.g., 5 mA steps) until the increase in muscle tone began to interfere with movement coordination or is judged uncomfortable by the participant. Treatment is performed with amplitudes of stimulation just below the motor threshold and adjusted as needed for the remainder of the therapy sessions as in prior studies[1, 8, 10].

5.2.2 Timing of Therapeutic Regimen Administration

The treatment will be administered 6 weeks in conjunction with standard occupational therapy.

5.2.3 Trial Blinding/Masking

Patient and physician will be blinded. For participants who randomize to the sham stimulation condition, the presence of active stimulation treatment will be concealed by using a sham stimulation that begins with the same stimulation waveforms and amplitudes used for treatment, but gradually reduces the stimulation current to zero over the first two minutes of each session. All participants will be instructed that they will most likely accommodate to the stimulation and not perceive it after several minutes. The treating researcher will be unaware of the patient allocation. An independent investigator informed of the therapeutic arm will prepare the device to administer treating stimulation or sham

and will record such assignment for each treating visit in a secured file not available for the treating researcher.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms: stim and sham. Subjects will be assigned randomly in a 1:1 ratio to either tSCS or sham.

5.4 Stratification

Randomization will be stratified by center.

5.5 Concomitant Treatments (Allowed)

Patients will be allowed to take their therapy prescribed for MS and any other comorbidity.

Treatments specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any treatment specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Principal Investigator. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator and the subject.

5.6 Rescue Treatments & Supportive Care

No rescue or supportive treatments are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

Not required.

5.7.1 Diet

Subjects should maintain their usual diet throughout the duration of the trial.

5.7.2 Use of Alcohol, Caffeine, and Tobacco

The site should advise subjects that alcohol should NOT be consumed during the study. The site should advise subjects to limit their alcohol intake as follows:

Refrain from consuming any alcohol for at least 24 hours prior to the study.

The site should advise subjects to limit their tobacco use as follows:

Refrain from the equivalent of >15 cigarettes a day during the study, and

Refrain from smoking during the study

5.7.3 Activity

NA

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures are provided in Section 7.1.4 – Other Procedures.

Table 1 provides reasons why a subject must be discontinued from treatment but may continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 1 Discontinuation Scenarios

Reason for Discontinuation Scenario	Action
The subject or legal representative (such as a parent or legal guardian) withdraws consent.	Discontinuation from Treatment and Trial
The subject has a medical condition or personal circumstance which, in the opinion of the investigator, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinuation from Treatment and Trial
The subject is no longer able to participate in the trial or is not compliant with trial-related procedures.	Discontinuation from Treatment and Trial
The subject takes a prohibited treatment during the trial.	This deviation should be documented and consulted regarding the management of the subject.
Subjects who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior may meet discontinuation criteria.	Please refer to Section 7.1.2.2.11, 7.2.3.2 and the ECI guidance document for details.

Discontinuation from treatment is “permanent.” Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.9 Subject Replacement Strategy

No subject replacement is intended.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial, or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Table 2 Trial flow chart

Visit Number	1	2	3-6	7
Visit Title	**Screening**	**Randomization Baseline**	**Double blinded assessment**	**OLE**

Scheduled Week/Day	Day 0	Day 42	Days 42-61-84	Day 126
Scheduling Window by Days:	±2	±3	±3	±5
Administrative Procedures				
Informed Consent – Subject	X			
Inclusion/Exclusion Criteria	X			
Subject Identification Card	X			
Medical History	X			
Prior Medication Review	X			
Randomization		X		
Monitor Trial Device Compliance		X		
Clinical Procedures/Assessments				
9HPT		X	X	X
ARAT		X	X	X
mAS		X	X	X
NeuroQOL		X	X	X
MFIS		X	X	X
GIC		X	X	X
Safety		X	X	X

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. Documented consent from each subject (referred to as subject consent) will also be obtained by the investigator or qualified designee.

7.1.1.1.1 General Informed Consent

Consent will be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the respective signed and dated consent forms (subject consents) will be given to the subject and subject before participation in the trial.

The initial subject informed consent forms, any subsequent revised written informed consent forms and any written information provided to the subject will receive the Ethic Committee of the Hospital del Mar approval/favorable opinion in advance of use. The

subjects will be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form(s) or addendum to the original consent form(s) that captures the subject's dated signature.

Relevant clinical or MRI findings will be disclosed to the patient and refer for appropriate care.

Specifics about a trial and the trial population will be added to the consent form template(s) at the protocol level. Informed consent(s) will adhere to the ethics Committee requirements, applicable laws and regulations.

7.1.1.2 Inclusion/Exclusion Criteria

If it is determined that the subject does not meet the inclusion/exclusion criteria at visits, the subject will be withdrawn from the study.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site (Hospital del Mar) contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Treatments Review

7.1.1.5.1 Prior Treatments

The investigator or qualified designee will review any prior therapeutic drug or neurostimulation use, in advance to visit 2, and record prior treatment taken by the subject within 30 days before starting the trial.

7.1.1.5.2 Concomitant Treatments

The investigator or qualified designee will record treatment(s), if any, taken by the subject during the trial. Any changes to treatment(s) (i.e., dose, frequency) will also be recorded. If the subject reports taking any prohibited treatments during the study, this will be recorded as a study deviation. Concomitant treatments will not be changed during the study, without first consulting the investigator, except in cases of medical emergencies or other obvious exceptions. Please see Section 5.5 for more details.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization numb

7.1.1.8 Trial Compliance (Treatment)

During stimulation visits, administration of tSCS therapy will be witnessed by the investigator and/or trial staff. Accounting of trial treatment will be conducted as specified in the Trial Flow Chart.

7.1.1.9 Interactive Voice Response System/Integrated Web Response System

The investigator or designee will call/log into IVRS/IWRS as specified in the Trial Flow Chart. Upon confirmation of a subject's eligibility at Visit 2, the investigator or designee will call IVRS or log into IWRS to randomize the subject. Subjects who do not meet eligibility criteria at Visit 4 will be screen-failed in IVRS/IWRS. For all randomized subjects, the investigator or designee will continue to call/log into IVRS/IWRS as per the Trial Flow Chart. For completed or discontinued subjects, the investigator or designee will make the final call/web action into IVRS/IWRS at their last trial visit. For additional information, please refer to Section 5.3.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Assessments/Examinations

7.1.2.1.1 Neurological Examination (Neuro Exam)

A complete physical examination (PE), including a neurological exam, will be performed by a primary investigator or sub-investigator. This examination will also be performed in the event of early discontinuation. The following body systems should be included in these exams:

7.1.2.1.3 Vital Signs

Body Temperature: Body temperature will be measured with an oral or tympanic thermometer. The same method (e.g., oral, or tympanic, ºC) should be used for all measurements for each individual subject and should be the same for all subjects throughout the trial.

Heart Rate (HR), Blood Pressure (BP) and Respiratory Rate (RR): Subjects should be resting **for at least 10 minutes** prior to having vital sign measurements obtained. The **same position** should be used for all measurements for each individual subject and should be the same for all subjects throughout the trial. The correct size of the blood pressure cuff and the correct positioning on the subject's arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual, or automated) should be used for all measurements for each individual subject and should be the same for all subjects throughout the study.

Vital signs will be assessed also after the tSCS sessions for identifying any adverse effect.

7.1.2.1.4 Body Height/Weight

Height (cm/in) and body weight (kg/lbs.) will be collected and recorded. Measurements should be recorded to the nearest centimeter/inch and kilogram/pound. Body weight data will be collected without shoes and with heavy clothing (such as coats) removed. Body weight should be performed on the same scale for the same individual throughout the study.

7.1.2.2 Neurological and Cognitive exam

At baseline and by end of the visit 2 (stimulation) a neurological exam (as defined in section 12.6) will be administered for identifying CNS related adverse events.

7.1.2.2.2 Measurements of Upper-Limb Function

The Nine-hole peg test (9HPT) has been validated as the assessment of the hand function for MS[46], with 15 to 20% defined as the minimal clinically important difference. In order to capture the upper-limb functioning we will include the Action Research Arm Test for motor function. The smallest real difference/minimal detectable change is defined as 5.7 points for the ARAT54 and 5.5 points for the Box and Blocks Test in stroke55. The Asworth scale will be used for assessing spasticity and the NeuroQOL Upper Extremity function as a PRO relevant for upper-limb dysfunction. In addition we will include a validated scale for fatigue in MS such as the MFIS and a global scale such as GIC for identifying additional effects of PROs.

7.1.3 Laboratory Procedures/Assessments

No laboratory procedures are planned.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial during visit 2 (before completing the three planned stimulations), all applicable activities scheduled for the end of visit 2, as outlined in Section 6.0 Trial Flow Chart, will be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal will be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the treatment arm used by a subject in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study arm, the reason thereof, etc., in the medical chart etc., before unblinding is performed. Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update arm disposition. If the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

If unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and principal investigator notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Domiciling

NA

7.1.4.4 Calibration of Critical Equipment

Not required for the SCONE device.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Visits

Each visit should be performed as noted in the Trial Flow Chart. For visits that require additional explanations, please see those specific visits below.

7.1.5.1.1 Visit 1: Screening

At Visit 1, subjects who provide informed consent will undergo a series of diagnostic and safety assessments to determine if they are eligible for the trial. A designated subject must also consent to participate and will be asked to complete certain assessments throughout the trial. Subjects planning to undergo elective procedures during the study (known prior to trial start) should not proceed until such procedures have been completed.

At the screening visit, medical history, use of drugs, alcohol, caffeine, smoking will be recorded. If the subject fulfills the inclusion criteria and signs the informed consent, the patient will then be exposed to a 6-week run-in period with standard occupational therapy.

7.1.5.1.2 Visit 2: Baseline

Patients will be randomized to either treatment or sham stimulation and assigned a code. Before starting stimulation, the researcher will conduct a vital signs and neurological examination. Then, the patient will be subjected to the first tSCS stimulations (a 30 min stimulations).

7.1.5.1.3 Visit 3-5: Stimulation Visits

At each visit the patient will be reassessed for vital signs. After the completion of each session period. 9HPT will be assessed the last day of stimulation for each session period.

7.1.5.1.2 Visit 13, 14 and 29: end of DBP, onset and end of OLE

During such visits, vital signs, and neurological exam and 9HPT will be conducted.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a medical device treatment and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether considered related to the medicinal product or protocol specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Product includes any device, diagnostic agent, pharmaceutical product, biological product, or protocol-specified procedure, whether investigational (including sham or active comparator treatment) or marketed, manufactured by, licensed by, provided by, or distributed by the vendor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from inadequate therapeutic regimen (whether accidental or intentional), from abuse and from withdrawal.

Electronic reporting procedures can be found in the electronic data capture (EDC) entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Over-treatment for this Protocol and Reporting of Over-treatment

In this trial, an over-treatment is any therapeutic regimen of higher intensity or of longer duration than the specified therapeutic regimen to be administered in a calendar day (accidental or intentional). If an adverse event(s) is associated with ("results from") the over-treatment, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met. If the therapeutic regimen meeting the protocol definition of over-treatment is taken without any associated clinical symptoms or abnormal laboratory results, the over-treatment is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional over-treatment without adverse effect."

All reports of over-treatment with and without an adverse event must be reported by the investigator within 24 hours either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capturing (EDC) entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation

Female participants may screen for this study if:

- They are surgically sterile [have had a hysterectomy (uterus removed), bilateral oophorectomy (ovaries removed), or tubal ligation at least 6 months prior]
- They are of post-menopausal age and have not had a menstrual period for 12 months
- They have a vasectomized partner (performed at least 6 months prior) who has been documented to no longer produce sperm
- They are using a highly effective method of contraception to avoid pregnancy throughout the study and for 30 days after you complete this study.

Examples of acceptable forms of highly effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception plus use of a condom for your male partner.
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS) plus use of a condom for your male partner.
3. True abstinence: When this is in line with your preferred and usual lifestyle

NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), condoms alone or double barrier are not acceptable methods of contraception.

Male participants must ensure a condom is used for all sexual intercourse as well as following the acceptable methods of contraception listed above for your female partner and ensuring that they are used for the entire duration of the study, and for at least 90 days after you complete this study.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

7.2.3 Immediate Reporting of Adverse Events

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any therapeutic regimen or during any use of the product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 3 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours for weekly days or 72 days over the weekend if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, sham treatment or a procedure. The 24 hours for the site starts when the site becomes aware of the SAE. SAEs not reported will be considered a major protocol deviation.

For the time beginning at treatment allocation through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the product, must be reported within 24 hours either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the product that is brought to the attention of the investigator at any time outside of the time specified in the previous paragraph also must be reported immediately.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 . Events of Clinical Interest (during the stimulation visit 2 (in the 1h after each stimulation)

1. Agitation – daytime or nighttime
2. Confusion or cognitive impairment - daytime or nighttime

Regarding items #1 and 2 above, agitation, confusion or cognitive impairment should be considered an ECI if in the investigator's opinion an acute worsening from baseline has occurred, or there is an unusual or atypical presentation of symptoms for a given subject.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 3. The investigator's assessment of causality is required for each adverse event. Refer to Table 3 for instructions in evaluating adverse events.

7.2.5 Management and Reporting of Adverse Events

All adverse events (AEs), regardless of their severity or relationship to the investigational product, will be systematically assessed, recorded, and reported as follows:

- **Detection**: Investigators will actively monitor participants for any signs or symptoms of adverse events during study visits and treatment sessions.
- **Assessment**: A qualified physician investigator will assess each AE for severity, seriousness, causality, and expectedness according to protocol guidelines and regulatory standards (ICH-GCP).
- **Reporting**:
    - All serious adverse events (SAEs) must be reported to the sponsor within **24 hours** of awareness via the electronic data capture (EDC) system or by paper form if needed.
    - Non-serious AEs will be documented in the case report forms (CRFs) and summarized during regular safety reviews.
- **Follow-up**: All AEs will be followed until resolution, stabilization, or until an adequate explanation is available.
- **Pregnancy and lactation**: Although not considered AEs, any pregnancy or lactation event during the study must also be reported promptly according to protocol procedures.

These procedures are designed to ensure participant safety and regulatory compliance throughout the study.

Table 3 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (SAE) is any adverse event occurring at any Therapeutic regimen or during any use of product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Hospital del Mar neurosciences product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable within 24 hours to meet certain local requirements); **or**	
	Is associated with an over-treatment (whether accidental or intentional). Any adverse event associated with an over-treatment is considered a serious adverse event for collection purposes. An over-treatment that is not	

	associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action Taken	Did the adverse event cause the product to be discontinued?	
Relationship to Product	Did the product cause the adverse event? The determination of the likelihood that the product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the p product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacological effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal products)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to the Product (continued)	**The following components are to be used to assess the relationship between the product and the AE (continued)**	
	Dechallenge	Was the product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If not, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the product; (3) the trial is a single-Therapeutic regimen drug trial); or (4) product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If not, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-Therapeutic regimen drug trial); or (3) product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE PRODUCT, OR IF RE-EXPOSURE TO THE PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the product or drug class pharmacology or toxicology?
The assessment of the relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a**

	product relationship).
Yes, there is a reasonable possibility of product relationship.	There is evidence of exposure to the product. The temporal sequence of the AE onset relative to the administration of the product is reasonable. The AE is more likely explained by the product than by another cause.
No, there is not a reasonable possibility of product relationship	Subject did not receive the product OR temporal sequence of the AE onset relative to administration of the product is not reasonable OR the AE is more likely explained by another cause than the product. (Also entered for a subject with over-treatment without an associated AE.)

7.2.5 Investigator Responsibility for Reporting Adverse Events

All Adverse Events will be reported to the Ethical Committee of Hospital del Mar and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Linear mixed-effects models will be used to test the association between treatment arm and all primary and secondary endpoints. These models will include an outcome measure as the dependent variable, treatment assignment, time of measurement, and their interaction as independent variables and a random intercept for participant and site to account for the longitudinal and clustered nature of the data. If imbalances exist in baseline characteristics between treatment groups, sensitivity analyses will be conducted by including the covariate in the mixed-effects models as an independent variable to determine the impact it may have on the desired association. For the primary outcome, the interaction between treatment assignment and the 6 weeks follow-up will be assessed, with statistical significance indicating a difference in the change in 9-HPT is present between treatment groups at V5. All other time points and outcome measures will be treated as secondary. These analyses will be conducted following the intention to treat principle. Additional exploratory analyses will be conducted on the per protocol population defined as those who completed at least 70% of therapeutic sessions.

Table 4 Statistical analysis plan

Study Design Overview	Transcutaneous Electrical Spinal Stimulation (tSCS) for Improving Upper Limb Function in People with MS
Treatment Assignment	Active stimulation: tSCS Sham: stimulations using a non-active electric stimulation
Analysis Populations	Intention to treat Per Protocol
Primary Endpoint(s)	Differences in the nine-hole peg test (9-HPT) affected hand in the tSCS treated vs. sham groups by the end of treatment (V3 vs V5)
Key Secondary Endpoints	1. Percentage of responders: 20% difference on the 9HPTd (minimal clinically important difference (MCID)) from baseline to end of the study 2. Change in the 9HPT dominant and non-dominant hand from baseline to end of the study 3. Change in the Action Research Arm Test (ARAT) from baseline to end of the study 4. Change in the modified Ashworth Scale (mAS) for spasticity assessment from baseline to end of the study

	5. Hand strength measured by Grip and Pinch force dynameters (Figure 10) 6. Change in the NeuroQOL Upper Extremity function from baseline to end of the study 7. Change in the Modified Fatigue Impact Scale (MFIS) from baseline to end of the study 8. Change in Global Impression of change (GIC) from baseline to end of the study
Exploratory endpoints	
Statistical Methods for Key Efficacy Analyses	Linear mixed-effects models will be used to test the association between treatment arm and all primary and secondary endpoints.
Statistical Methods for Key Safety Analyses	Descriptive statistics
Interim Analyses	No interim analysis for efficacy or safety is planned for this study.
Multiplicity	Not planned
Sample Size and Power	Sample size: n=60 For a large, standardized effect size (Cohen's d=0.8), with a sample size of 52 (26 in each arm) we would have greater than 80% power to detect a significant difference in 9HPT between treatment arms using a two-sample t-test and a two-sided significance level of 0.05. Assuming a common standard deviation of 5.5, this corresponds to a difference of 4.4 units between treatment groups. Allowing for a conservative attrition rate of 15% (our previous trial in SCI with a similar design had 10% attrition[4-6]), we plan on enrolling 60 participants. Furthermore, as our proposed analysis is a linear mixed-effects model, we anticipate greater efficiency resulting in a slightly higher power. Reimbursement of travel expenses will be used to promote retention.

8.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Principal Investigator (Pablo Villoslada, HMar) and the biostatistician of the study (Agustin Conesa, HMar).

8.3 Hypotheses

Objectives and hypotheses of the study are stated in Section 3.

8.4 Analysis Endpoints

Key efficacy and safety endpoints that will be evaluated for within- and/or between-tSCS protocols are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1. Efficacy Endpoints

Rationale for the key efficacy endpoints is given in Section 4.2.3.1 and an initial description of the efficacy measures is included in Section 7.1.2.2. In general, if a baseline value exists for a particular efficacy measure, then the change from baseline in that value will be evaluated.

Primary Endpoint

Differences in the nine-hole peg test (9-HPT) affected hand in the tSCS treated vs. sham groups by the end of treatment (V3 vs V5)

Secondary Endpoint

1. Percentage of responders: 20% difference on the 9HPTd (minimal clinically important difference (MCID)) from baseline to end of the study
2. Change in the 9HPT dominant and non-dominant hand from baseline to end of the study
3. Change in the Action Research Arm Test (ARAT) from baseline to end of the study
4. Change in the modified Ashworth Scale (mAS) for spasticity assessment from baseline to end of the study
5. Hand strength measured by Grip and Pinch force dynameters (Figure 10)
6. Change in the NeuroQOL Upper Extremity function from baseline to end of the study
7. Change in the Modified Fatigue Impact Scale (MFIS) from baseline to end of the study
8. Change in Global Impression of change (GIC) from baseline to end of the study

8.4.2 Safety Endpoints

Presence of serious adverse events (together with items of special attention)

An initial description of the safety measures is included in Sections 7.1.2.1, 7.1.2.2.10 and 7.1.3. Safety and tolerability will be assessed by statistical and clinical review of the following data collected throughout the study: adverse experiences (AEs), and treatment-emergent suicidality. The primary time for safety analyses is Visit 2; Safety endpoints are classified into 2 tiers (see Statistical Methods for Key Safety Analyses in Section 8.1 for Tier definitions).

Tier 1 Safety Endpoints include (the proportion of subjects with):

1. Any AE
2. Any Serious AE
3. Any treatment-Related AE
4. Any Serious and treatment-Related AE
5. Discontinuation due to AE

Tier 2 Safety Endpoints include:

1. Specific AEs, SOC AEs or PDLCs which have incidence in all 3 subjects.

8.5 Analysis Populations

8.5.1 Safety Analysis Population

The safety population will be used for the analysis of safety data in this study. The safety population consists of all subjects who received at least 1 stimulation protocol of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they received for the analysis of safety data using the safety population. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment received.

At least 1 vital sign measurement obtained after at least 1 stimulation protocol of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

Safety and tolerability will be assessed by statistical and clinical review of the following data collected throughout the study: adverse experiences (AEs). Safety will be evaluated with doses combined; selected safety analyses will be performed for doses separately.

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered as Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons.

Membership in Tier 1 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 2.

Summary statistics for baseline, on-treatment, and change from baseline values will be provided by the treatment group in table format.

See Table 5 for a classification of safety endpoints as Tier 1, or 2 and the corresponding analysis strategy for each endpoint.

Table 5 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value§	95% CI for Treatment Comparison§	Descriptive Statistics
Tier 1	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 subjects in 1 of the treatment groups)		X	X

Tier 2	Specific AEs, SOCs or PDLCs [‡] (incidence <4 subjects in all the treatment groups)			X

[2] Adverse Event (AE) references refer to both Clinical and Laboratory AEs.
[3] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoint
[4] P-value and CI for safety endpoints based upon Miettinen & Nurminen method
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.1 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.1.1 Demographic and Baseline Characteristics

Demographic variables (e.g., age, gender, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analysis

No interim analyses for efficacy or safety are planned for this study

8.8 Multiplicity

Not planned.

8.9 Sample Size and Power Calculations

Sample size

Sample size: n=60

Power for the primary hypothesis

For a large, standardized effect size (Cohen's d=0.8), with a sample size of 52 (26 in each arm) we would have greater than 80% power to detect a significant difference in 9HPT between treatment arms using a two-sample t-test and a two-sided significance level of 0.05. Assuming a common standard deviation of 5.5, this corresponds to a difference of 4.4 units between treatment groups. Allowing for a conservative attrition rate of 15% (our previous trial in SCI with a similar design had 10% attrition4-6), we plan on enrolling 60 participants. Furthermore, as our proposed analysis is a linear mixed-effects model, we anticipate greater efficiency resulting in a slightly higher power. Reimbursement of travel expenses will be used to promote retention.

8.10 Subgroup Analyses

An exploratory sex-stratified analysis will be conducted to assess potential differences in safety and efficacy outcomes between male and female participants. Although the study is not powered to detect sex-specific effects, this analysis aims to provide additional insights into potential sex-related variations in treatment response.8.11 Compliance (Treatment Adherence)

Summary statistics will be provided on percent compliance by treatment for all subjects included.

8.12 Extent of Exposure

The total number of days each subject received a particular total daily stimulation protocol will be identified and then summarized (as subject counts and percentages)

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

No drugs are being tested in this study

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms that information furnished to the investigator will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Ethical Committee, or regulatory authority representatives may consult and/or copy trial documents to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules, and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

10.1.4 Confidentiality of Ethics Committee Information

The principal investigator is required to record the name and address of the Ethics Committee that reviews and approves this trial.

10.2 Compliance with Financial Disclosure Requirements

The investigator/subinvestigator(s) agree to provide his/her financial interests to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form.

10.2.1 Compliance with Ethical Principles and Medical Device Regulation

This study will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, as adopted by the 75th World Medical Assembly, Helsinki, Finland, October 2024, and any subsequent revisions.

In addition, the study will comply with all applicable regulatory requirements, including the Regulation (EU) 2017/745 on medical devices, specifically concerning clinical investigations involving medical devices.

The protocol, informed consent forms, and any other relevant study documentation will be reviewed and approved by an independent Ethics Committee prior to initiation. All participants will provide written informed consent before any study-related procedures are performed.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations, is provided in Section 12.1 Hospital del Mar Neurosciences Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, Ethics Committee review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the regulatory agencies.

Trial documentation will be promptly and fully disclosed by the investigator upon request and shall be made available at the trial site upon request for inspection, copying, review

and audit at reasonable times from any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested because of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

10.4 Compliance with Trial Registration and Results Posting Requirements

The principal investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to EUDRA (http://eudragmdp.ema.europa.eu) or ClinicalTrials.org (http://www.clinicaltrials.gov) or other local registries. Hospital del Mar researchers will review this protocol and submit the information necessary to fulfill these requirements. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under EMA clinical trials directive or other locally mandated registries are that of the investigators and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the principal investigator agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial may be intended for publication, even if terminated prematurely. Publication may include any or all the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The principal investigator will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. Hospital del Mar researchers will post a synopsis of trial results for approved products on EUDRA or Clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered, or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the researchers will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be considered to determine authorship if contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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12. APPENDICES

12.1. List of Abbreviations and Definition of Terms

AE	Adverse Experience
ASaT	All Subjects as Treated
βhCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Scale
DEGs	Data Entry Guidelines
ALS	Amyotrophic Lateral Sclerosis
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FSH	Follicle-stimulating Hormone
TPS	Transcranial Pulse Stimulation
GCP	Good Clinical Practice
HR	Heart Rate

IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Review Committee
IRB	Institutional Review Board
kg	Kilogram
NCS	Not Clinically Significant
PDLC	Pre-Defined Limit of Change.
PE	Physical Examination

SAC	Scientific Advisory Committee
SAE	Serious Adverse Experience
SAP	Statistical Analysis Plan
SD	Standard Deviation
SES	Standardized Effect Size
SOC	System Organ Class

SOP	Standard Operating Procedure
SAP	Statistical Analysis Plan
ULN	Upper Limit of Normal

12.2. MS Diagnosis Criteria

The diagnosis of MS according to the McDonald criteria requires:

Clinical Presentation	Additional data needed for MS diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • MRI or, • Two or more MRI-detected lesions consistent with MS plus positive CSF or, • Further clinical attack at a different site later
One attack; objective clinical evidence for two or more lesions	Dissemination in time, demonstrated by: • MRI or, • Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; CIS)	Dissemination in space, demonstrated by: • MRI or, • Two or more MRI-detected lesions consistent with MS plus positive CSF and Dissemination in time, demonstrated by: • MRI or, • Second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1-year disease progression (retrospectively or prospectively objectively determined) and two of the following: • Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) • Positive spinal cord MRI (two focal T2 lesions) • Positive CSF

12.3 General Neurological Exam

The General Neurological Examination will be performed at the timepoint(s) specified in the protocol flow chart.

Note to the investigator: If at any time abnormalities are observed in the General Neurological Exam, the Investigator should do additional examinations as needed based on his or her medical judgment.

The **General Neurological Examination** includes all of the modules listed below, ***with the exception of Module 1,*** and is intended to be a general screening examination and sufficient for this study and subject population.

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and acuity
B. II, III – Pupil Size and Reactivity
C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)
    1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus
D. V – Facial Sensation, Jaw Strength
E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)
F. VIII – Auditory Acuity (assessed using a bed-side screening test eg by rubbing fingers on each side of subject's head or by whispering numbers)
G. IX – Gag reflex
H. X – Swallow
I. XI – Shoulder shrug
J. Tongue Protrusion (midline)

Score: left and right (except for G, H, J)

Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone
    1. Ask the volunteer to relax.
    2. Flex and extend the volunteer's elbows and knees (bilaterally).
    3. There is a small, continuous resistance to passive movement.
    4. Observe for involuntary movements (eg, tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

        Score: left and right

        Grade: **NORMAL, INCREASED or DECREASED**
B. Muscle Strength

1. Ask the subject to stand up from sitting without using hands *Grade:* ***NORMAL, IMPAIRED*** **and describe abnormality**
2. Test proximal limb strength by having the volunteer flex and extend the knees and elbows against your resistance.

   Test bilaterally and compare 1 side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity
3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer's feet; finger abduction and handgrip strength against your resistance.

   Test bilaterally and compare 1 side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

C. Pronator Drift
1. Ask the volunteer to hold both arms straight forward with, palms up and eyes closed for ~10-15 seconds as tolerated; watch for how well the arm position is maintained.
2. Instruct the volunteer to keep both arms still while you tap them briskly downward. The volunteer should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

   Score: left and right

   Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 4 - REFLEXES

A. Biceps

B. Knee

Note: *Other deep tendon reflexes may be tested at Investigator's discretion (eg elbow, wrist or Achilles tendon)*

Score: left and right

Grade: **NORMAL, INCREASED, DECREASED or ABSENT**

C. Babinski

Score: left and right

Grade: **NORMAL or ABNORMAL**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

   Reminder: If the rapid alternate movements are disturbed, the subject will be asked to strike his hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place. (This test is impaired in cerebellar disease, extra pyramidal disease and upper MN weakness.)

B. Point-to-Point Movements

1. Ask the volunteer to touch your index finger and their nose alternately several times. Move your finger about as the volunteer performs this task.

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

   Reminder: If the point-to-point testing is disturbed, the subject will be asked to place 1 heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides. (Impaired tests indicate cerebellar disease.)

C. Romberg

1. Ask the volunteer to stand with both feet together and eyes closed for 20 to 30 seconds without support.
2. Be prepared to catch the volunteer if they are unstable.

   Grade: **NORMAL or IMPAIRED**

D. Gait

1. Ask the volunteer to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

   Grade: **NORMAL or IMPAIRED and describe abnormality**

2. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

   Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 6 - SENSORY

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.

B. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

C. Temperature: warm or cool object touched to skin of forearms and legs, bilaterally.

D. Vibration: tuning fork vibration detection in hands, feet bilaterally. E. Position sense: perception of thumb and toe movement, bilaterally.

F. Stereognosis: (identify common objects placed in hand, eg, coin, key).

Score: left and right

Grade: **NORMAL OR IMPAIRED and describe abnormality (for each A to F)**

12.4 Predefined Limits of Change Criteria

Predefined Limits of Change Criteria for Vital Signs, Weight, and Temperature

Measurement	Criteria
Systolic blood pressure	≥180 mm Hg and ≥20 mm Hg increase from baseline
	≤ 90 mm Hg and ≥ 20 mm Hg decrease from baseline
Diastolic blood pressure	≥105 mm Hg and ≥15 mm Hg increase from baseline
	≤ 50 mm Hg and ≥ 15 mm Hg decrease from baseline
Pulse	≥120 bpm and ≥15 bpm increase from baseline
	≤ 50 bpm and ≥ 15 bpm decrease from baseline
Orthostatic blood pressure	>20 mm Hg systolic sitting to standing after treatment (but not in baseline)
Weight	≥7 % increase from baseline
	≥7 % decrease from baseline
Temperature	≥101°F and ≥2°F increase from baseline (≥38.3°C and ≥1°C increase from baseline)

13.0 SIGNATURES

13.1 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	