High-frequency rTMS targeting lower motoneuron circuits in SMA: interim safety, tolerability and efficacy results from STIM-SMA (NCT06977269)

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Introduction

Lower motoneuron insufficiency is a leading cause of functional limitations in spinal muscular atrophy (SMA) [1]. We hypothesize that controlled motoneuron activation may "train" or enhance compensatory mechanisms and increase neuronal viability. To test this hypothesis, we applied high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) to deliver a targeted, precise dose of motoneuron activation. Since not all SMA patients have access to recently developed disease-modifying therapies [2], and even when available, treatment effects may be modest [3,4], an rTMS-based approach could extend meaningful benefit to a broader SMA population. This study is conducted under STIM-SMA (NCT06977269) - an interventional, open-label trial designed to evaluate the safety and tolerability of HF-rTMS in individuals aged ≥12 years with 5q-SMA, supported by the CSMA foundation.

Methods

To report interim safety, feasibility, and early changes in prespecified functional outcomes, complete datasets from 9 participants were analyzed at an early data cutoff. The first participant started the intervention on 14th of May 2025, and the last completed the final examination on 20th of September 2025.

All patients underwent HF-rTMS targeting the limb areas of the primary motor cortex, delivered at a frequency >5 Hz and an intensity of 90–100% of the resting motor threshold, over 10 sessions.

Participants were aged 12–24 years (mean 17.44 ± 4.77 years). Three participants had SMA type III and the remainder had type II; two were female and seven were male.

SMA type	Age	Sex	ΣΔ*	HFMSE			RULM			MFM			6MWT	
				Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After
II	24	M	7	3	3	0	10	12	+2	15	20	+5	N/A	N/A
II	15	M	2	3	3	0	21	21	0	21	23	+2	N/A	N/A
II	15	M	3	2	2	0	18	19	+1	20	22	+2	N/A	N/A
II	23	M	0	0	0	0	2	2	0	3	3	0	N/A	N/A
II	15	M	5	6	6	0	23	25	+2	23	26	+3	N/A	N/A
II	12	F	3	7	7	0	21	22	+1	26	28	+2	N/A	N/A
III	15	M	4	63	63	0	42	42	0	85	89	+4	missed	missed
III	24	F	0	59	59	0	35	35	0	83	83	0	missed	missed
III	16	M	6	42	44	+2	29	30	+1	54	57	+3	87	104

Table 1. Participant characteristics and functional outcome changes. **HFMSE** = Expanded Hammersmith Functional Motor Scale (O'Hagen et al., 2007); **RULM** = Revised Upper Limb Module (Mayhew et al., 2013); **MFM** = Motor Function Measure (Bérard et al., 2005); **6MWT** = Six-Minute Walk Test (Paul Enright, 2003).
*__ΣΔ__ = sum of changes across all scales.

Safety and Tolerability of Low Motoneuron Stimulation Via Transcranial Magnetic Stimulation in Spinal Muscular Atrophy (STIM-SMA)

Recruiting

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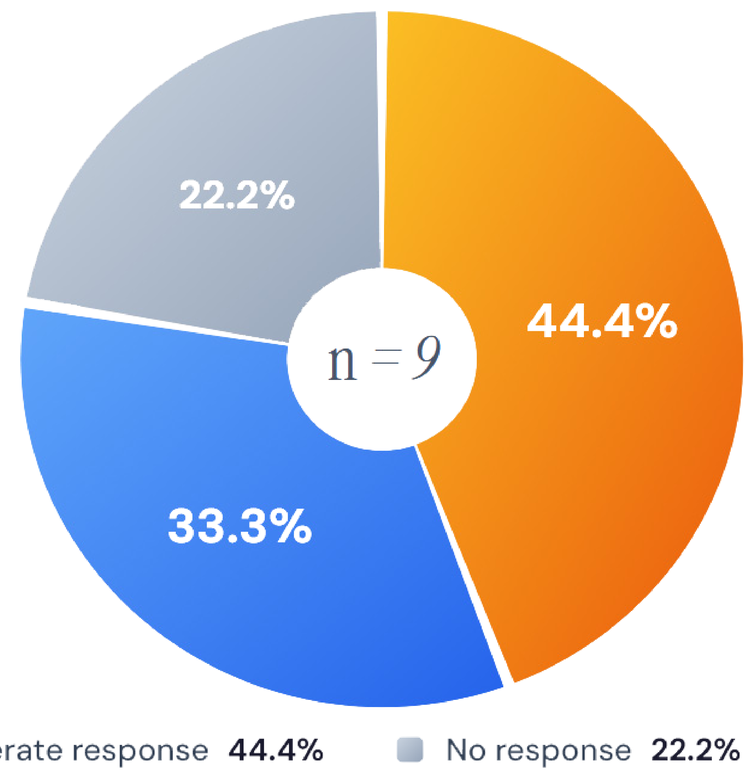

Figure 1. Treatment responders vs non-responders proportion. According to Tab.1 patients with ∑Δ score <=2 are considered as non-responders, response >2 and <6 is considered as moderate, >=6 is strong response.

Results

Safety: No adverse events were observed. One participant experienced a mild respiratory infection at the very beginning of the intervention, which did not affect daily activities. There were no discontinuations, interruptions, or protocol deviations.

Exploratory functional outcomes: With the exception of two cases, all participants demonstrated at least a 1-point improvement on either the MFM or RULM after two weeks of treatment. One participant achieved a 2-point improvement on the HFMSE. No improvement was observed in the strongest participant (type III female) and the weakest participant (type II male). Nevertheless, the weakest participant reported high satisfaction due to positive autonomic changes and a subjective sense of improved endurance.

Treatment perception: By the end of 2025, two participants from this cohort had voluntarily undergone a 2nd treatment course, despite the requirement for two lumbar punctures (performed for biomarker measurement). An additional four participants expressed a strong intention to repeat treatment once safer war conditions are restored in the trial site region.

Conclusions

Interim findings demonstrate that HF-rTMS is feasible, safe, and well-tolerated in individuals with SMA. Seven of nine participants showed meaningful functional gains across multiple validated scales after just two weeks of treatment. These early results, combined with high participant satisfaction and willingness to repeat the intervention, support continued investigation of HF-rTMS as a potential adjunctive or standalone approach for SMA. Ongoing enrollment with greater participant heterogeneity will help define the magnitude and durability of benefit and identify the most responsive target population.

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