Clinical Data and Real World Evidence Supports US Marketing Authorization of

Cranial Nerve Neuromodulation Device for Patients With MS

Helius MEDICAL

PoNS®

Multiple sclerosis (MS) is a chronic, progressive, neurologic, inflammatory, autoimmune disease of the central nervous system caused by demyelination and dysfunction of axons, resulting in a disruption of central control of motor function.[1]

Walking impairment is a clinical hallmark in individuals with MS.[2] It is a primary factor in assessing the progression of MS disease and in diminishing a patient's overall quality of life, independence, and personal productivity.[2] Walking impairment disrupts gait, as evidenced by a reduction in gait speed, altered cadence, reduced stride length, an increased time spent on double-limb support, or a combination of these effects, often in association with a loss of balance. Most people experience their first symptoms of MS between the ages of 20 and 40 years, and the disease occurs more frequently in women.[1] It is estimated that walking assistance will be needed by approximately 40% of individuals with MS within 15 years of disease onset.[2]

> *"Walking impairment is...a primary factor in assessing the progression of MS disease and in diminishing a patient's overall quality of life, independence, and personal productivity."*

Given that the pathogenesis of MS is the result of an interaction between the immune and the central nervous systems, clinicians have a range of targets for therapeutic interventions, which may act both additively and synergistically.[3]

Therapeutic interventions for the treatment of gait disturbance among MS patients include rehabilitation therapy, pharmacological management, and exercise and increased physical activity. The optimal form of exercise intensity, frequency, duration, and maintenance necessary to manage the progression of balance and gait dysfunction in MS has not yet been established through randomized clinical trials.[4]

2 clinical evaluations of the effect of targeted physical therapy with and without cranial nerve non-invasive neuromodulation (CN-NINM) have been conducted on the walking ability of people with mild to moderate symptoms of MS with symptomatic gait dysfunction.[5,6,7]

CN-NINM delivers multiple electrical stimuli to the tongue using the Portable Neuromodulation Stimulator (PoNS®) that can be used in the clinic and at home. Studies have shown that the tongue can be used as an effective interface for sending electrical signals to the to the central nervous system through the cranial nerves.[8]

Portable Neuromodulation Stimulator (PoNS®)

3 independent data sets show improvements in walking ability in people with mild to moderate symptoms of MS.

- Tyler, et al. evaluated the effect of targeted physical therapy, with versus without use of an active PoNS® device, on walking ability in subjects with MS who presented with dysfunctional gait[5]
- Leonard, et al., evaluated the impact of neuromodulation associated with use of the PoNS device, in combination with a cognitive and physical rehabilitation program, on the working memory, gait, balance, and concomitant changes in the brain of MS patients[6]
- To supplement the Tyler, et al. and Leonard, et al. MS studies, Helius conducted a retrospective analysis of real-world data collected with the PoNS in MS patients in clinical rehabilitation settings in Canada[7]

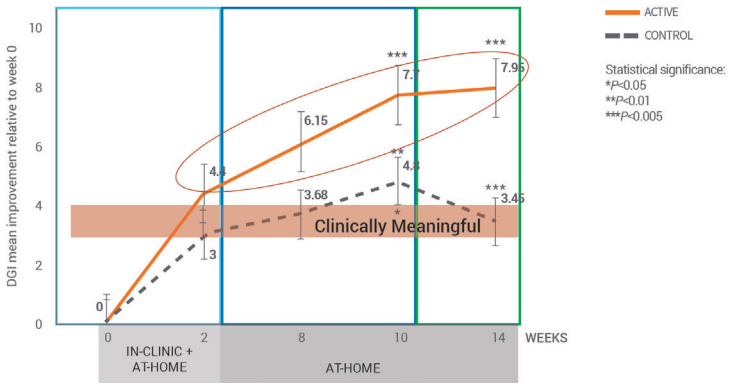
Tyler et al, investigated the use of targeted physical therapy with and without cranial nerve non-invasive neuromodulation (CN-NINM) on the walking ability of people with mild to moderate MS with symptomatic gait dysfunction.[5]

Twenty individuals (males and females) with identified gait deficits with any type of MS (Expanded Disability Status Scale [EDSS] scores 3.0-6.0) were randomized into 2 treatment groups: 10 used an active CN-NINM device (PoNS), and 10 used a placebo device. Each participant received 2 weeks of twice-daily gait training in the clinic while using the PoNS, followed by 12 weeks of the same daily routine at home. The active and placebo devices were physically identical, but patients in the active group could adjust the PoNS stimulus level whereas patients in the control group received a fixed stimulus that was so low it could not be perceived.

The groups were similar across age and EDSS scores. There was a difference between the groups for mean number of years with a diagnosis of MS (P=0.01) and for baseline Dynamic Gait Index (DGI), although the latter did not reach statistical significance (at Week 14, P = 0.745).

The study results showed that patients in the active group achieved both statistically significant (P<0.05) and clinically significant DGI improvements (increase of at least 4 points) by the 6-week test point, and these improvements continued through the 14-week test point. The difference between groups was statistically significant P value beginning at 6 weeks, with the active group improving more than double the placebo group by the 14-week test point.

> *"The study results showed that subjects in the active group achieved both statistically... and clinically significant DGI improvements..."*



The raw DGI data from this study show that 100% of active group patients and 90% of placebo group patients exhibited some improvement between baseline and 14-week scores. The major difference was the magnitude of both the individual and mean group change between the 2 treatment groups. On average, the active group improved by 7.95 points, while the placebo group exhibited a mean change of 3.45 points.

ACTIVE GROUP IMPROVED
7.95

PLACEBO GROUP IMPROVED
3.45

Leonard et al. investigated the effects of the PoNS device in combination with intensive cognitive and physical rehabilitation.[6]

A group of fourteen subjects with MS were randomized to either a PoNS Stimulation Group (n=7; active group) or a Sham Stimulation Group (n=7; Sham Group). Each group received intensive working memory training and physical rehabilitation. Outcome measures included Functional magnetic resonance imaging (fMRI) using motor imagery and working-memory tasks, sensory organization tests (SOT), motor performance measures, and neuropsychological assessment.[6]

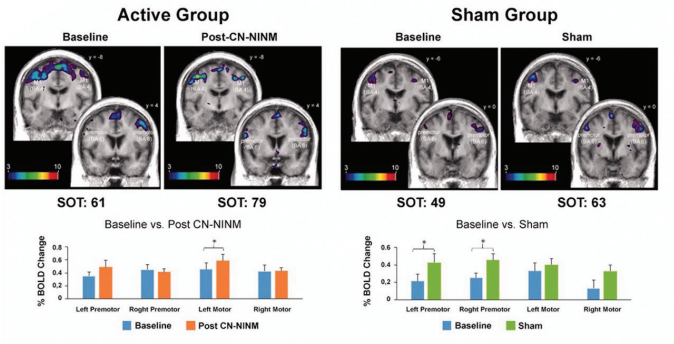
Pre- and post-training gait imagery fMRI showed task-related activations in bilateral premotor and motor regions for both groups. A significant increase in blood oxygen level-dependent (BOLD) signal was identified in the left motor cortex for the active group after training as compared to before, whereas in the control group a significant increase in BOLD signal was only seen in bilateral premotor regions.

Both groups showed a trend for improvement over time in the SOT, but this was more consistent for the active group, which also showed a statistically significant improvement ($p<0.001$) between baseline and Week 14 [where the control group did not reach statistical significance ($p<0.006$)].

> *"Both groups showed a trend for improvement over time in the SOT, but this was more consistent for the active group..."*

On the SOT, the active group showed a statistically significant improvement from baseline, and over 17 points difference on average from the sham group which did not show a statistically significant improvement.

Mean DGI scores at Week 14 increased modestly from 18.29 to 19.57 in the active group, versus increasing from 14.29 to 15.57 in the control group.



SOT ACTIVE GROUP IMPROVED

17 POINTS

To supplement the Tyler, et al. and Leonard, et al. MS studies, Helius conducted a retrospective analysis of real-world evidence data analysis (RWE) collected with the PoNS in 42 MS patients in clinical rehabilitation settings in Canada.[7]

Data from all 42 MS patients treated with the PoNS in the March 4 – December 31, 2019, were included in the RWE effectiveness analysis.[7]

In the real-world evidence dataset, 36/42 MS patients reached a 4.75-point and over 5-point (20/42) mean improvement in Functional Gait Assessment at Week 14.

Week 14, the mean DGI improvement was 4.75 points. In addition, the median improvement was 5 points – above the accepted threshold for clinical significance – and 83.3% of patients improved at least 2 points.

The RWE effectiveness data demonstrates clinically and statistically significant improvements in gait for MS patients using PoNS as reflected in improved FGA total scores. The homogeneity of treatment effect was demonstrated for an extensive set of baseline characteristics including gender, age category, years with MS, type of MS, prior PT status, and use of various medications. The effectiveness evidence from the RWE-based assessment is relevant and reliable and supports that use of the PoNS as an adjunct to supervised therapeutic exercise is likely to improve gait function in MS more than supervised therapeutic exercise alone.[7]

WEEK 14: MEAN DGI IMPROVEMENT

4.75

The results of these clinical evaluations demonstrate that noninvasive electrotactile stimulation, when combined with targeted physical therapy, can significantly improve clinical symptoms of gait dysfunction in individuals with MS.[6,7,8]

PoNS therapy is well tolerated with no reported serious device-related AEs in the clinical studies.

The FDA assessed the safety and effectiveness of the PoNS device and in March 2021, authorized marketing of the device indicated for use as a short- term treatment of gait deficit due to mild to moderate symptoms of MS.[1]

Indication

The PoNS device is indicated for use as a short-term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program for adults 22 years of age and over by prescription only.

Contraindications

The PoNS device delivers electrical stimulation directly to the surface of the tongue. Precautions for use are similar to those for transcutaneous electrical nerve stimulation (TENS).

Electrical stimulation SHOULD NOT be used

- If there is an active or suspected malignant tumor
- In areas of recent bleeding or open wounds
- In areas that lack normal sensation

The PoNS has not been tested on, and thus should not be used by, individuals who are pregnant.

Do not use the PoNS if you are sensitive to nickel, gold, or copper.

References

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