REH08

# Translingual Neurostimulation by Portable Neuromodulation Stimulator System as a New Rehabilitation Therapy for Improving Gait in People With Multiple Sclerosis

Antonella Favit-VanPelt, MD, PhD[1]; Kim Skinner, PT, DPT[1]; Greg Maislin, PhD[2]; Nicole Strachan, BHK, MSc. P.Kin[1]; and Lola Abhulimen, MBA[1] — [1]Helius Medical Technologies, Newtown, PA; [2]Biomedical Statistical Consulting, Wynnewood, PA

## Introduction

- Although gait impairment is a disabling symptom in MS leading to reduced mobility and impacting quality of life, current interventions (eg, rehabilitation therapy and pharmacological management) only marginally improve gait function.[1–3]
- Translingual neurostimulation (TLNS) delivered by a portable neuromodulation stimulator system promotes neuromodulation by stimulating the trigeminal (CN-V) and facial (CNVII) nerves exciting a natural flow of neural impulses to the brainstem (pons Varolii and medulla) and cerebellum.[4]
- Recent studies have shown that noninvasive activation of cranial nerves by TLNS when combined with therapeutic exercise programs can modulate neural pathways involved in gait and balance to improve function.[5–9]

## Objectives

- To assess the effect of TLNS (Portable Neuromodulation Stimulator [PoNS®]), in combination with a supervised therapeutic exercise program, to improve gait deficit in persons with MS—based on real-world evidence (RWE) data collected at clinical rehabilitation settings and pooled analysis of RWE data and data from 2 previous RCTs.[5,10]

## Methods

*RWE Data*

- The RWE dataset was gathered from 4 Canadian rehabilitation clinics that integrated TLNS (PoNS) as an adjunct to a supervised therapeutic exercise program to treat gait deficit in patients with MS between March 4, 2019 and December 31, 2019.
  - All patients treated within this date range are included in the analyses regardless of the completeness of the data in order to avoid selection bias.
- Gait performance assessment was determined using the Functional Gait Assessment (FGA),[11] a 10-item clinical gait test scored on a 4-level (0–3) ordinal scale; scores range from 0–30, with lower scores indicating greater impairment.
  - FGA measurements were made during patient care visits: Week 0 (baseline), Week 2, Week 8, and Week 14.
  - Values over time and changes from baseline are summarized by mean (SD), median, minimum, and maximum values and 95% confidence intervals (CI) for the mean score and mean improvements; primary endpoint is mean change from baseline to Week 14.
  - Paired *t*-tests were employed to evaluate the mean improvements from baseline at each subsequent time point based on observed data.

### PoNS® Therapy Rehabilitation Program

| | Daily Training Schedule | |
|---|---|---|
| Morning Session | Warm-up Exercises with PoNS | 10 min |
| | Balance Training with PoNS | 20 min |
| | Gait Training with PoNS | 20 min |
| | Breathing and Awareness Training with PoNS | 20 min |
| Break | | 3–4 hours |
| Afternoon Session | Balance Training with PoNS | 20 min |
| | Movement Control Exercises without PoNS | 20 min |
| | Gait Training with PoNS | 20 min |
| Break | | |
| Evening Session | Breathing and Awareness Training with PoNS | 20 min |

*RWE Data*

- The primary analysis of the RWE was based on a mixed model for repeated measures (MMRM),[12] both to account for missing data over time and to ensure that variability in baseline FGA scores did not result in substantial bias.
  - The MMRM assumed an unstructured covariance matrix that allows variances and pairwise covariances to vary over time; parameters of the MMRM were estimated using SAS Proc Mixed.
  - MMRMs were used to evaluate values over time as well as changes from baseline including baseline as covariate.
  - For mean changes, *t*-tests derived from the MMRM were used to determine nominal significance levels; distributions of improvements were evaluated graphically using a cumulative distribution function.
- Heterogeneity of improvements in gait deficit in the real-world clinical setting were evaluated across a number of clinical factors (gender, age category, race/ethnicity, years with MS category, type of MS, Expanded Disability Status Scale (EDSS) category, prior physical therapy (PT), and medication use), with modeling approaches similar to those used in the overall analyses.

*Pooled Analysis of RWE and RCT Data*

- In the 2 previous RCTs, gait improvement was assessed using the Dynamic Gait Index (DGI),[13] an 8-item test scored on a 4-level (0–3) ordinal scale; scores range from 0–24, with lower scores indicating greater impairment.
  - Seven of the 8 items on the DGI are also included within the 10-item FGA.
- In order to pool the RWE data with data from the RCTs, an adjusted DGI score was derived by summing the 7 scores from the tasks the two measures have in common and multiplying by 8/7; this "adjusted" 7-item DGI, therefore, has the same overall scores range as the 8-item DGI.
- A similar MMRM model was used to characterize expected improvements in gait from baseline to Week 14 in order to provide a summary of expected improvements in DGI over time using the largest possible sample size.
- An additional responder analyses was performed to summarize the number and percentage of patients achieving improvement based on DGI categorical response.

## Results

*Demographic and Baseline Characteristics*

- The RWE analysis included 42 patients with a mean age of 55.4 years, mean duration of MS of 18.6 years, and mean EDSS score of 5.5. (**Table 1**)
  - Median age stratified by gender was 57.5 years (range: 39–72) for females (n = 28) and 51.0 years (range: 32–72) for males (n = 14).
- While the previous RCTs restricted eligible patients to those with EDSS scores ranging from 3.0 to 6.0, the RWE dataset included a broader ranger of EDSS scores.
  - Patients in the RWE sample had a mean EDSS score of 5.5 (range: 1.0–6.5), with a mean duration of MS of 18.6 years (range: 4–45 years).

### Table 1. Baseline and Disease Characteristics

| Characteristic* | RWE Sample (N = 42) |
|---|---|
| **Gender** | |
| Female | 28 (66.7%) |
| Male | 14 (33.3%) |
| **Age** | |
| Total RWE sample, mean (SD) | 55.4 (11.0) |
| **Age Category** | |
| <50 | 14 (33.3%) |
| 50 to 64 | 17 (40.5%) |
| ≥65 | 11 (26.2%) |
| **Race/Ethnicity** | |
| Caucasian | 38 (90.5%) |
| Hispanic | 2 (4.8%) |
| Afro-Caribbean | 1 (2.9%) |
| Indian | 1 (2.9%) |
| **Years with MS** | |
| Total RWE sample, mean (SD) | 18.6 (9.5) |
| 0–10 | 11 (26.2%) |
| 11–20 | 16 (38.1%) |
| 21–30 | 11 (26.2%) |
| 31–45 | 4 (9.5%) |
| **Type of MS, n (%)** | |
| Primary Progressive | 6 (20.7%) |
| Relapsing/Remitting | 9 (31.0%) |
| Secondary Progressive | 14 (48.3%) |
| Missing | 13 |
| **EDSS** | |
| Total RWE, mean (SD) | 5.5 (1.3) |
| Mild | 2 (5.0%) |
| Moderate | 21 (52.5%) |
| Moderate Severe | 17 (42.5%) |
| Missing | 2 |
| **Prior PT** | |
| Yes | 34 (85.0%) |
| No | 6 (15.0%) |
| Missing | 2 |
| **Medications†** | |
| Disease modifying | 7 (17.9%) |
| Symptom moderating | 13 (33.3%) |
| Gait dysfunction | 8 (20.5%) |
| Neuropsychotropic | 3 (7.7%) |
| Other medications | 16 (41.0%) |
| Missing | 3 |

*Values are number (percent) unless otherwise noted.
†Subjects can have more than one type of medication. Thus, the sum of percentages can exceed 100%.

*Efficacy: FGA in RWE Dataset*

*MMRM for FGA Values Over Time*

- Using all available data from 42 MS patients, the MMRM estimated mean improvement from baseline to Week 14 in the FGA was 4.63 (95% CI: 3.61 to 5.65). (**Table 2**)
  - Estimated mean improvements from baseline in FGA score based on the random effects model were statistically significant at all subsequent time points (**Figure 1**) and were similar to mean improvements based on the observed data.
  - Notably, the estimated mean improvement at Week 14 of 4.63 is above the minimum detectable change (MDC) for stroke patients (4.2 points)[14] and people with other specific neurological disease (4 points)[15] and above the minimum clinically important difference (MCID) in community-dwelling older adults (4 points).[16] The MDC and MCID on the FGA have not been reported for patients with MS.
  - The percentage of patients who achieved at least a 4-point improvement in the FGA increased over time and was 58.3% at Week 14. (**Figure 2**)

### Table 2. MMRM for FGA Total Score Over Time and Change From Baseline

**Least Square Means From Random Effects Model for Repeated Measures**

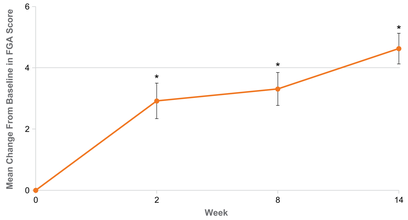
| Visit | Mean (Standard Error) | 95% CI | P-value |
|---|---|---|---|
| Week 0 (Baseline) | 10.19 (0.97) | 8.24–12.14 | <0.0001 |
| Week 2 (Progress) | 13.12 (1.07) | 10.96–15.28 | <0.0001 |
| Week 8 (BenchMark) | 13.49 (1.12) | 11.23–15.75 | <0.0001 |
| Week 14 (Discharge) | 14.88 (1.01) | 12.84–16.91 | <0.0001 |

**Changes From Baseline Estimated From MMRM**

| Visit | Estimate (Standard Error) | 95% CI | P-value |
|---|---|---|---|
| Week 2 (Progress) | 2.92 (0.58) | 1.74–4.10 | <0.0001 |
| Week 8 (BenchMark) | 3.31 (0.54) | 2.22–4.40 | <0.0001 |
| **Week 14 (Discharge)*** | **4.63 (0.50)** | **3.61–5.65** | **<0.0001** |

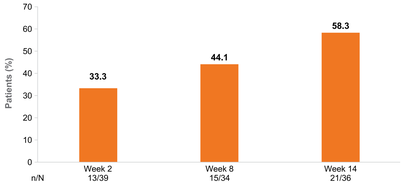
*Primary endpoint of RWE analysis.

### Figure 1. RWE Patients: Difference in Least Squares Means in FGA Score From Baseline




*P<0.0001 vs baseline.
Solid line indicates clinically significant change (≥4 points) for older adults, stroke patients, and people with other specific neurological disease. The FGA MDC for MS has not been reported.

### Figure 2. Percentage of RWE Patients With FGA Improvements ≥4 Points Over Time




*Efficacy: FGA in RWE Dataset*

*Observed Data for FGA Values Over Time*

- Mean improvements in FGA total scores based on observed data were highly statistically significantly at all follow-up time points (paired t-test *P*<0.0001). (**Table 3**)
- Mean improvement in FGA at Week 14 was 4.75 (95% CI: 3.66 to 5.84).
- Median improvement was 5 points, and 83% of patients an improvement of ≥2 points. (**Figure 3**)

*Stratified Analysis*

- Homogeneity of treatment effect was demonstrated for an extensive set of baseline characteristics including gender, age category (<50, 50 to 64, ≥65), years with MS category (0–10, 11–20, 21–30, 31–45), type of MS (primary progressive, relapsing/remitting, secondary progressive), prior PT status, and use of various medications.
  - Patients with an EDSS category of moderately severe appeared, on average, to have smaller, yet still statistically significant, improvements compared to subjects with an EDSS category of moderate disease; mean improvement from baseline to Week 14 was 2.33 (95% CI: 0.68 to 3.98; *P*=0.007) and 5.75 (95% CI: 4.48 to 7.01; *P*<0.0001) for patients in the moderately severe and moderate categories, respectively.

### Table 3. Observed FGA Total Scores Over Time and Change From Baseline

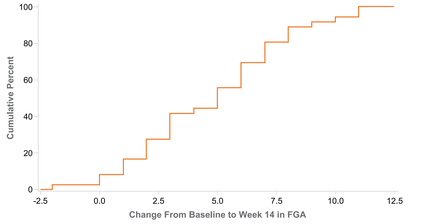
**Observed FGA Total Scores Over Time**

| Visit | N | Mean (SD) | Median | Minimum | Maximum | 95% CI |
|---|---|---|---|---|---|---|
| Week 0 (Baseline) | 42 | 10.19 (6.26) | 9.50 | 0.00 | 28.00 | 8.24–12.14 |
| Week 2 (Progress) | 39 | 13.10 (6.50) | 11.00 | 3.00 | 3.000 | 10.99–15.21 |
| Week 8 (BenchMark) | 34 | 13.79 (6.42) | 13.00 | 3.00 | 30.00 | 11.55–16.03 |
| Week 14 (Discharge) | 36 | 15.69 (6.28) | 15.50 | 7.00 | 29.00 | 13.57–17.82 |

**Observed Changes From Baseline in FGA Total Scores**

| Visit | N | Mean (SD) | Median | 95% CI | P-value |
|---|---|---|---|---|---|
| Week 2 (Progress) | 39 | 2.79 (3.69) | 3.00 | 1.60–3.99 | <0.0001 |
| Week 8 (BenchMark) | 34 | 3.24 (3.10) | 3.00 | 2.16–4.32 | <0.0001 |
| Week 14 (Discharge) | 36 | 4.75 (3.22) | 5.00 | 3.66–5.84 | <0.0001 |

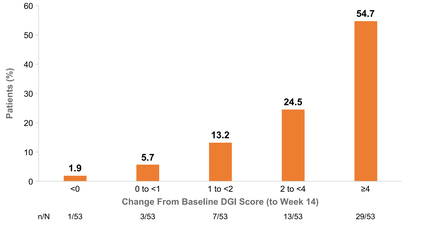
### Figure 3. Cumulative Distribution of Observed Changes From Baseline to Week 14 in FGA




*Pooled Analysis of RWE Sample and RCT Active Cohorts*

- MMRM adjusted mean improvement in DGI from baseline to Week 14 was 4.58 (95% CI: 3.62 to 5.54) for the pooled RWE and RCT analysis including all possible data at all weeks.
- Among 53 patients with Week 14 data, 29 (55%) experienced ≥4 point improvement from baseline in DGI. (**Figure 4**)

### Figure 4. Pooled RWE/RCT Data: Summary of Categorical Response—DGI Improvements (to Week 14)




*Safety*

- In the real-world data collected with use of PoNS therapy in patients with MS, minimal adverse events were reported, with all determined to be typical for this patient population with or without use of the device.
- No serious adverse events related to the PoNS device were reported in the MS RCTs or have occurred during its use in clinical rehabilitation settings to treat balance and gait disorders (>45, 128 patient-use sessions since March 4, 2019).

## Conclusions

- In this evaluation of a real-world dataset of patients with MS with generally long duration of disease, translingual neurostimulation (PoNS) combined with a therapeutic exercise program significantly improved gait deficit at Week 2, the earliest evaluated time point, and at every subsequent time point.
- At Week 14, 58.3% of patients had an FGA improvement of ≥4 points, surpassing the MDC for older adults, stroke patients, and persons with other neurological disease.
- Analysis of real-world data pooled with the 2 randomized clinical trials demonstrated, consistent with the RCT data, that translingual neurostimulation (PoNS) combined with a therapeutic exercise program is safe and effective for improving gait deficit in individuals with mild and moderate symptoms from MS.

**References:** **1.** Wiles CM, et al. *Neurol Neurosurg Psychiatry.* 2001;70:174-9. **2.** Devasahayam AJ, et al. *Mult Scler Int.* 2017;2017:4815958. **3.** Pearson M, et al. *Arch Phys Med Rehabil.* 2015;96:1339-48. **4.** Danilov Y et al. In: Kobessey FH, ed. *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects.* Boca-Raton, FL: CRC Press; 2015:605-28. **5.** Tyler ME, et al. *J Neurobeng Rehabil.* 2014;11:79. **6.** Chisholm AE, et al. *J Neurobeng Rehabil.* 2014;11:96. **7.** Galea MP, et al. *Brain Stimul.* 2017;10:1133-15. **8.** Ignatova TS, et al. In: *Proceedings of the 11th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2018).* 2018;4:332-7. **9.** Tyler M, et al. Translingual neurostimulation for the treatment of chronic symptoms due to mild-to-moderate traumatic brain injury. *Arch Rehabil Res Clin Transl.* 2019;1(3-4):100026. **10.** Leonard G, et al. *Mult Scler J Exp Transl Clin.* 2017;3(1):2055217317690561; **11.** Wrisley DM, et al. *Phys Ther.* 2004;84:906-18. **12.** Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data.* New York: Springer 2000. **13.** Shumway-Cook A, Woollacott MH. *Motor Control: Theory and Practical Applications.* Baltimore, MD: Williams & Wilkins; 1995. **14.** Lin JH, et al. *Stroke.* 2010;41:2021-5. **15.** Petersen C, et al. *J Geriatr Phys Ther.* 2017;40:223-6. **16.** Beninato M, et al. *Phys Ther.* 2014;94:1594-603.

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