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Supplemental material

Durable responses at 24 months with high-frequency spinal cord stimulation for nonsurgical refractory back pain

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Eligibility criteria

Supplementary Table 1: Full inclusion and exclusion criteria for the crossover randomized controlled trial[1,2]

INCLUSION CRITERIA
1. Have been diagnosed with chronic, refractory[a] axial low back pain and not a candidate for surgery based on a spine surgeons' assessment. 2. Pain should have a predominant neuropathic component as per the investigator's clinical assessment 3. Have not had any surgery for back or leg pain, or any surgery resulting in back or leg pain 4. Considering daily activity and rest, have average back pain intensity of ≥ 5 out of 10 cm on the Visual Analog Scale (VAS) at enrollment 5. Be on no or stable pain medications, as determined by the Investigator, for at least 28 days prior to enrolling in this study 6. Be 18 years of age or older at the time of enrollment 7. Be willing and capable of giving informed consent 8. Be willing and able to comply with study-related requirements, procedures, and visits 9. Be capable of subjective evaluation, able to read and understand written questionnaires in the local language and are able to read, understand and sign the written inform consent

EXCLUSION CRITERIA

1. Have a diagnosed back condition with inflammatory causes of back pain (e.g., ankylosing spondylitis or diseases of the viscera)
2. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator
3. Have evidence of an active disruptive psychological or psychiatric disorder identified as the primary condition or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcome, as determined by the investigator in consultation with a psychologist
4. Have a current diagnosis of a progressive neurological disease, spinal cord tumor, or severe/critical spinal stenosis
5. Have a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus that would add unacceptable risk to the procedure
6. Be benefitting within 30 days prior to enrollment from an interventional procedure to treat back and/or leg pain[†]
7. Have an opioid addiction or drug seeking behavior as determined by the Investigator
8. Have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker
9. Have prior experience with neuromodulation devices (SCS, PNS, DRG, multifidus muscle stimulation)

10. Have a condition currently requiring or likely to require the use of diathermy or MRI that is inconsistent with Senza system guideline in the Physician's Manual
11. Have metastatic malignant disease or active local malignant disease
12. Have a life expectancy of less than 1 year
13. Have an active systemic or local infection
14. Be pregnant (participants of child-bearing potential that are sexually active must use a reliable form of birth control)
15. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications or have been a substance abuser (including alcohol and illicit drugs)
16. Be concomitantly participating in another clinical study
17. Be involved in an injury claim under current litigation
18. Have a pending or approved worker's compensation claim

CMM, conventional medical management; DRG, dorsal root ganglion; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

[a]Pain is defined as refractory, regardless of etiology, when conventional medical management has failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects.

[†]Interventions should not be performed less than 30 days prior to enrollment or a follow-up visit to ensure that pain level is stable and representative of their long-term response to CMM.

Responder rate missing data imputation method comparison

Supplementary Table 2: Analysis of responder rates[a] by visit using different imputation methods for missing time points

VISIT	PIS[b] (MI)[c]	PIS[b] (LOCF)[d]	CC[e]
3 months			
N	125	125	123
RR	78.8%	79.2%	78.9%
95% CI	(71.6%, 86.0%)	(71.3%, 85.4%)	(70.8%, 85.2%)
6 months			
N	125	125	120
RR	78.8%	78.4%	79.2%
95% CI	(71.4%, 86.2%)	(70.4%, 84.7%)	(71.1%, 85.5%)
9 months			
N	125	125	64
RR	76.2%	77.6%	78.1%
95% CI	(66.0%, 86.3%)	(69.5%, 84.0%)	(66.6%, 86.5%)
12 months			
N	125	125	104
RR	78.5%	76.8%	79.8%
95% CI	(71.0%, 86.0%)	(68.7%, 83.3%)	(71.1%, 86.4%)
18 months			
N	125	125	91
RR	83.5%	81.6%	86.8%
95% CI	(76.5%, 90.5%)	(73.9%, 87.4%)	(78.4%, 92.3%)

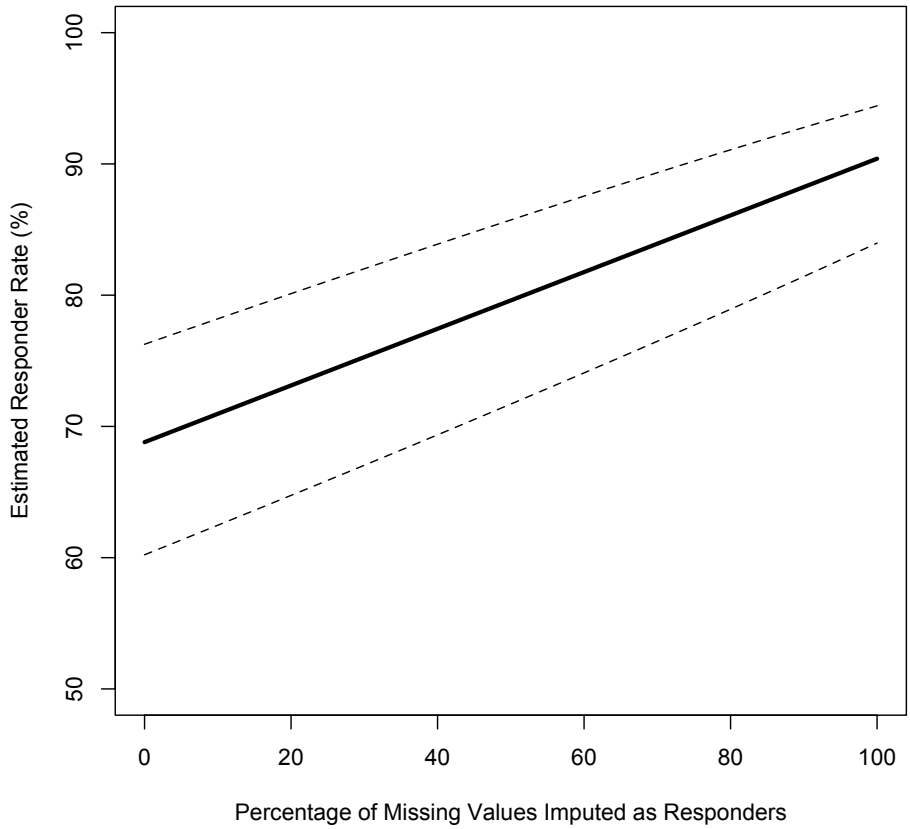
24 months			
N	125	125	98
RR	82.8%	81.6%	87.8%
95% CI	(75.9%, 89.7%)	(73.9%, 87.4%)	(79.8%, 92.9%)

CC, complete-case; CI, confidence interval; LOCF, last observation carried forward; MI, multiple imputation; N, number of patients; PIS, permanent implant subgroup; RR, responder rate; SCS, spinal cord stimulation.

[a]Responders were defined as patients who reported ≥50% back pain relief as measured using a 10-cm visual analog scale (VAS) score. [b]The PIS population included all patients who received permanent implantation with the 10 kHz SCS device. [c]In the MI analysis, non-missing VAS scores from other time points were imputed for the missing VAS scores using a summary of ten imputations. [d]In the LOCF analysis, the last observed VAS score was used to impute missing 24-month VAS scores. [e]For the CC population, only subjects with a 24-month VAS score were included in the analysis.

24-month responder rate tipping point analysis

We performed a tipping point analysis to estimate the 24-month responder rates using all possible imputations for each of the 27 missing values in the modified intent-to-treat population. We started with the worst-case scenario, in which all missing values were imputed as non-responders (yielding a responder rate of 86/125 [68.8%]), and ending with the best-case scenario, in which all missing values were imputed as responders (yielding a responder rate of 113/125 [90.4%]).



Supplementary Figure 1: Tipping point analysis for 24-month responder rates presenting all possible imputations and the corresponding responder rates and 95% Wilson-score confidence intervals

Supplementary Table 3 Comparison between CMM group who crossed over vs did not crossover.

Crossover **n**	**No** 16	**Yes** 60	**p**	**SMD**
Sex = Male (%)	9 (56.2)	27 (45.0)	0.604	0.226
Age (mean (SD))	55.94 (10.95)	56.27 (11.91)	0.921	0.029
BMI (mean (SD))	30.33 (6.60)	30.86 (6.51)	0.771	0.082
Pain_Detect (mean (SD))	17.62 (8.44)	17.07 (7.23)	0.792	0.071
Leg_Pain (%)	10 (62.5)	39 (65.0)	1	0.052
Pain Etiologies				
DDD(%)	10 (62.5)	42 (70.0)	0.787	0.159
Spondylosis (%)	9 (56.2)	40 (66.7)	0.632	0.215
Radicular (%)	7 (43.8)	28 (46.7)	1	0.059
Mild/Moderate Spinal Stenosis (%)	5 (31.2)	19 (31.7)	1	0.009
Spondylolisthesis (%)	2 (12.5)	7 (11.7)	1	0.026
Sacroiliac dysfunction (%)	2 (12.5)	3 (5.0)	0.612	0.268
Baseline VAS (SD)	7.28 (1.24)	7.22 (0.96)	0.84	0.053
Nonsurgical Candidate due to:				
Underlying Pathology	13 (81.2)	48 (80.0)	1	0.032
Surgical Risk	1 (6.2)	4 (6.7)	1	0.017
Declined Surgery	2 (12.5)	8 (13.3)	1	0.025
Reported Pain at 6 months (mean (SD))	7.18 (2.33)	7.75 (1.31)	0.205	0.299

CMM, conventional medical management; n, number of patients; SCS, spinal cord stimulation; SD, standard deviation; [d]CMM therapies reported by >20% of patients.

Study-related serious adverse events reported during the 12-month follow-up

Supplementary Table 4: Summary of study-related SAEs[1]

SAE	N	Patients, n (%) (n=145)	Action taken/ Comments
Implant site infection	2	2 (1.4%)	IPGs were explanted & reimplanted when infection resolved
Poor wound healing	1	1 (0.7%)	Treated with device explant & primary closure
Lethargy	1	1 (0.7%)	Severe lethargy due to narcotic use, resulting in extended hospital stay; symptoms resolved without further sequelae
Osteomyelitis	1	1 (0.7%)	Developed osteomyelitis as a complication of the trial & did not go on to receive a permanent implant
Total	**5**	**5 (3.4%)**	

IPG, implantable pulse generator; N, number of SAEs; n, number of patients; SAE, serious adverse event.

Supplementary Table 5: Study-related adverse events with ≥3 occurrences during the 24-month follow-up

AE	N	Patients n (%) (n=145)	Treatment	Resolution
Implant site pain	13	12 (8.3%)	IPG revision surgery (n=8) Medication (n=2)	All resolved, except 1 patient who continued to experience mild tolerable discomfort
Lead dislodgement	7	7 (4.8%)	Lead revision (n=6) Reprogramming (n=1)	All resolved
Implant site infection	6	6 (4.1%)	Explant (n=3) Medication (n=3)	All resolved
Device stimulation issue	3	3 (2.1%)	Reprogramming (n=2) Resolved with no treatment (n=1)	All resolved
Cerebrospinal fluid leakage	3	3 (2.1%)	Slow leaks that resolved with rest (n=3)	All resolved

AE, adverse event; IPG, implantable pulse generator; N, number of AEs; n, number of patients.

Supplementary Table 6 Summary of CMM treatments patients received prior to study enrollment.

	CMM	10 kHz SCS
Previous CMM reported, n (%)[d]	**(n=71)**	**(n=78)**
Epidural injections	56 (78.9%)	66 (84.6%)
Radiofrequency ablation	23 (32.4%)	22 (28.2%)
Facet injections	25 (35.2%)	27 (34.6%)
Nerve root blocks	21 (29.6%)	28 (35.9%)
Physical therapy	19 (26.8%)	27 (34.6%)
Chiropractic	10 (14.1%)	19 (24.4%)

Supplementary References

1. Kapural L, Jameson J, Johnson C, et al. Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial. *J Neurosurg Spine*. Feb 11 2022:1-12. doi:10.3171/2021.12.SPINE211301
2. Patel N, Calodney A, Kapural L, et al. High-Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Nonsurgical Refractory Back Pain: Design of a Pragmatic, Multicenter, Randomized Controlled Trial. *Pain Pract*. Feb 2021;21(2):171-183. doi:10.1111/papr.12945