Supplemental Online Content

eMETHODS

Procedures

Leads were implanted between T5 and T12 with the majority being placed between T7 and T11. Intraoperative testing was performed to confirm stimulation sensation in the dermatomes associated with pain before fixing the leads and connecting them to the stimulator.

Device programming was performed by sponsor field clinical engineers using the same standardized workflow for both treatment groups, which utilized the individuals' unique ECAP measurements and their feedback to optimize therapy. The only difference between groups was enabling closed-loop mode in the investigational group. Oversight by the investigators was documented in accordance with FDA guidelines.[1 2]

ECAP-guided programming included ECAP acquisition, collection of dose-response data, and determination of individual sensitivity. The dose-response data show the relationship between the charge delivered (current amplitude x pulse duration [μC per pulse]) and the corresponding neural response (ECAP amplitude [μV]). This data was collected at the patient perception threshold, the level of greatest patient comfort (prescribed level), and the highest level of stimulation the patient could tolerate (maximum). The neural response at the patient perception threshold to maximum defined the therapeutic window in this study. The slope of the dose-response (μV/μC per pulse) describes an individual's sensitivity to stimulation and can vary significantly between patients due to individual differences in anatomy (e.g., morphometrics of the epidural space). To provide personalized therapy in ECAP-controlled, closed-loop SCS, the sensitivity is used by the stimulator to control the rate at which the stimulation is automatically adjusted. This adjustment allows an optimized response time for patients with different physiological characteristics.

Randomization and masking

Patients were randomized 1:1 to ECAP-controlled, closed-loop SCS (CL; investigational group) or fixed-output, open-loop SCS (OL; control group). The randomization scheme was generated by an independent statistician using permuted blocks, stratified by study site to ensure within-site balance, and uploaded to a secure database. The randomization assignments were generated by the database when the patient was approved for enrolment, following trial lead placement, and sent to the Field Clinical Engineer (FCE).

Treatment allocation was concealed from the patients, the investigator and site staff. The study is double-blind in that study subjects and the Investigators and their staff were not

made aware of the subjects' randomization assignments in order to reduce the potential of data being systematically distorted by knowledge of the treatment received. The method of blinding known as 'blind to the study hypothesis' was used for the subjects by not informing them that one treatment was presumed to be of greater efficacy than the other. As required per protocol, the subjects had not been exposed to SCS prior to their involvement in the study, and therefore had no prior experience with how the system would or should operate. Careful description of the treatments and expectations in the informed consent, study training, and other communications and interactions was utilized by FCE. In the informed consent, this included informing the subjects that the same investigational device, same procedure, same remote control and remote control functionality would be implemented in both treatment arms. The only difference indicated was the stimulation mode (automatic vs. manual), but no definition or indication how the stimulation modes would change the subject's perception of the therapy was given. FCEs were also trained to use the same words for both groups throughout the course of the study, which is consistent with how they programmed patients. A blinding assessment was completed by the patients and investigators at 3 and 12 months to determine if they were unblinded to the treatment assignment. A blinding assessment was also completed by all patients at the 24 month visit and during the crossover phase for participating patients.

The consent language describing the two stimulation modes was as follows:

"You will be randomized (assigned by chance, by a computer) to one of two stimulation modes. You have an equal chance of being in either group, like the flip of a coin (1:1). Both groups will receive the same device with active stimulation that continuously measures your body's response to the stimulation and the same remote control functions, but you will experience one of two different stimulation modes (automatic or manual) based on which group you are assigned to. In the automatic stimulation mode, the system changes settings automatically based on your body's response and your remote control, whereas in the manual stimulation mode, the system makes changes based on your remote control only. You, the study doctor and clinic staff will not know which group you are assigned until after the study is completed."

Programming

Programming was performed by sponsor FCEs with documented oversight from the investigators in accordance with FDA guidelines[2] in the same manner for both treatment groups utilizing ECAP measurement and patient feedback. Adjustments were permitted for both groups as many times as needed to optimize the therapy. For each patient,

programming involved first identifying the optimal stimulating electrodes and settings via patient reported dermatome coverage. Then, the recording (and reference) electrodes and settings were configured in order to optimize the ECAP signal and measurement. Next, the ECAP signal was used to measure the therapeutic window before finally testing the measurement and (if applicable) loop performance. Stimulation therapy settings were within the range of conventional parameters for both groups. The only difference between treatment groups was enabling the feedback mechanism in the closed-loop group.

Outcomes

Percent whole provides an estimate of patient proximity to a holistic treatment response. It is calculated based on the individuals' number of baseline dysfunctional domains in which at least one MCID was achieved at follow-up divided by the total number of dysfunctional domains at baseline (e.g., response of at least 1 MCID for three out of four impaired domains equals 75% whole).

Real-time measurement of the ECAP amplitude (in microvolts [μV]) was representative of the number of fibers activated with every stimulation pulse. How close the evoked neural response is to the prescribed neural response is comprised of both patient adherence (i.e., patient compliance to the prescription) and device performance (i.e., the ability of the device to adhere to the prescribed neural response). Patient adherence was measured by device utilization, the percentage total time the patient's stimulator was turned on, and by patient adjustment of their set point. Device performance was calculated using Root Mean Square Error (RMSE) to determine the deviation (error) of the observed ECAP response from the target ECAP response (programmed in a sitting position) during various posture changes in clinic. Outside the clinic, actual neural activation was measured and compared to the therapeutic window from the dose-response curves collected in the clinic. Additional neurophysiological measures were also collected to gain insights into the properties of the activated fibers.

eTable 1. Minimal clinically important differences and population normative values

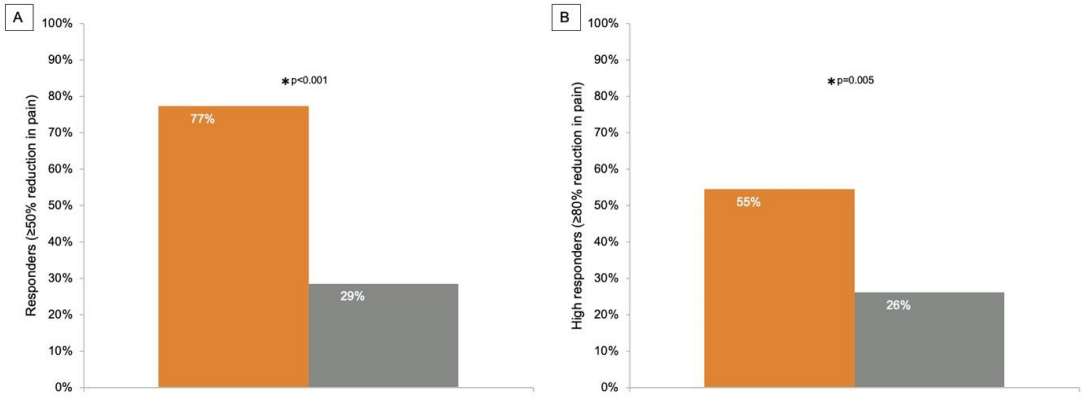
Domain	Normative Value	MCID Responder Thresholds	Cumulative MCIDs (examples)
VAS	<60 mm (Evoke RCT eligibility criterion)[1]	≥30% decrease = 1 MCID[3]	50% decrease = 1.67 MCID 80% decrease = 2.67 MCID
ODI	<10.19 (normative value)[4,1]	≥10-point decrease = 1 MCID[5]	15-point decrease = 1.5 MCID 20-point decrease = 2 MCID
EQ-5D	0.830 (US normative value for 55 to 64 years)[6]	≥0.074-point increase = 1 MCID[7]	0.148-point increase = 2 MCID 0.1665-point increase = 2.25 MCID
PSQI	6.3 (US community sample)[8]	≥3-point decrease = 1 MCID[9]	4-point decrease = 1.33 MCID 6-point decrease = 2 MCID
POMS	17.7	≥10-point decrease = 1 MCID[3]	15-point decrease = 1.5 MCID

	(US adult normative value)[10]		20-point decrease = 2 MCID

MCID=minimal clinically important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; RCT=randomized controlled trial; VAS=visual analogue scale

Secondary analysis

In accord with our primary analysis, secondary analyses treating crossovers as treatment failures showed the reduction in overall back and leg pain intensity was significantly greater for closed-loop (mean [SD] score, 24.7 [27.0]; point decrease, 57.2 [27.2]; percent decrease, 70.2% [32.3%]) than open-loop patients (mean [SD] score, 54.0 [34.3]; point decrease, 27.5 [33.6]; percent decrease, 34.0% [41.6%]) (between groups: mean score difference, -29.4 [95% CI: -42.6 to -16.2], p<0.001; point decrease difference, 29.7 [95% CI: 16.6-42.8], p<0.001; percent decrease difference, 36.2% [95% CI: 20.3%-52.2%], p<0.001). Additionally, a significantly greater proportion of closed-loop patients had ≥50% reduction (CL-SCS=77.3%, OL-SCS=28.6%; risk difference: 48.7%, 95% CI: 30.3%-67.1%, p<0.001) and ≥80% reduction (CL-SCS=54.5%, OL-SCS=26.2%; risk difference: 28.4, 95% CI: 8.5%-48.2%, p=0.005) in overall back and leg pain intensity when compared to open-loop patients (eFigure 1).



eFigure 1. A. Proportion of Patients with ≥50% Reduction in Overall Back and Leg Pain Intensity at 36-month follow-up; B. Proportion of Patients with ≥80% Reduction in Overall Back and Leg Pain Intensity at 36-month follow-up

Supplementary results tables

eTable 2. Patient-Reported Outcome Measures at 36-Months

	Closed-Loop	Open-Loop
Patient-Reported Outcomes (PRO)	N=67	N=67
Oswestry Disability Index (ODI)		
Change from Baseline	23.2 (17.0)*	16.4 (17.5)
Percent Change from Baseline	42.9 (31.2)*	29.6 (32.0)
Minimal Clinically Important Difference (≥10)	47/67 (70.1%)	42/67 (62.7%)
Minimal or Moderate Disability (score 0-40)†	44/67 (65.7%)	33/67 (49.3%)
Profile of Mood States (POMS) Total Mood Disturbance (TMD)		
Change from Baseline	16.8 (18.3)*	6.1 (14.2)
Minimal Clinically Important Difference (≥10)	40/67 (59.7%)*	23/67 (34.3%)
EQ-5D-5L Index Score		
Change from Baseline	0.207 (0.177)	0.162 (0.164)
Minimal Clinically Important Difference (≥0.074)	46/67 (68.7%)	41/67 (61.2%)
EQ-Visual Analog Scale (VAS)		
Change from Baseline	25.4 (23.1)*	13.9 (22.7)
Pittsburgh Sleep Quality Index (PSQI)		
Change from Baseline	4.7 (4.8)*	2.9 (4.3)
Minimal Clinically Important Difference (≥3)	40/67 (59.7%)*	27/67 (40.3%)
Patient Global Impression of Change (PGIC)		
Very Much Improved or Much Improved	47/58 (81.0%)	35/53 (66.0%)
Opioid Usage (Morphine Milligram Equivalents [MMEs])		
Percent Reduction	21.5 (60.2)	18.5 (68.7)
Minimal Clinically Important Difference (≥20%)	20/41 (48.8%)	19/40 (47.5%)

Data are mean (SD) or n (%).
Positive change indicates improvement. All were significant within-group improvements from baseline.
*Statistically significant difference between groups (p<0.05).
†No patients had 'minimal' or 'moderate' severity on the ODI (score 0-40) at baseline. For study inclusion, patients were required to be classified as 'severe disability' or 'crippled' on the ODI (score 41-80).
Patient-reported outcomes (PROs) collected included health-related quality of life (HRQoL) measured by the European Quality of Life Five-Dimensional Five-Level (EQ-5D-5L),[11] which has an MCID of 0.074[7] for the index score; functional disability measured by the Oswestry Disability Index (ODI),[4] which has an MCID of 10 points;[5] emotional functioning measured by the Profile of Mood States (POMS Brief),[10] which has an MCID of 10 points for Total Mood Disturbance (TMD);[3] sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI),[12] which has an MCID of 3 points;[9] and Patient Global Impression of Change (PGIC), which measures the impact of therapy on health status and tends to reflect other aspects such as treatment convenience, cost, and side effect burden. Opioid usage was also collected,[13] which has an MCID of ≥20% reduction in morphine milligram equivalents (MME).[14]

eTable 3. Percent whole at 36-months

	Closed-loop SCS	Open-loop SCS
Percent whole, mean (SD)	69.9 (34.3)	59.3 (36.6)
Mean difference and 95% CI	10.5 (-1.6, 22.6), p=0.088	

SD=standard deviation; SCS=spinal cord stimulation

eTable 4. Neural activation in CL-SCS and OL-SCS

	Closed-loop SCS	Open-loop SCS
Most Frequent Neural Activation / Neural Response Level (μv)	19.8	9.8
IQR	7.0-46.5	1.0-23.0
P-value †	0.049	
Device Performance / Deviation from target neural activation (μv)	4.1	12.4
IQR	2.7-6.2	3.6-25.8
P-value †	<0.001	
System Utilization (% time on)	77.6	75.5
IQR	0.6-96.1	7.7-97.4
P-value †	0.263	

SCS=spinal cord stimulation
† difference between medians

eTable 5. Reasons for device explant out of patients that received a SCS implant

Reason	Closed-loop (n=59)	Open-loop (n=54)
SCS device related - need for MRI	3 (5.1%)	2 (3.7%)
SCS device related - need for paddle lead	1 (1.7%)	0 (0.0%)
SCS procedure related - infection	2 (3.4%)	1 (1.9%)
SCS stimulation therapy related - LOE	0 (0.0%)	3 (5.6%)
Subsequent unrelated comorbid condition/treatment	2 (3.4%)	1 (1.9%)
Pain free	1 (1.7%)	1 (1.9%)
Study burden	1 (1.7%)	0 (0.0%)

LOE=loss of efficacy; MRI=magnetic resonance imaging; SCS=spinal cord stimulation

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