Supplemental Online Content

Mekhail N, Levy RM, Deer TR, et al; and the Evoke Study Group. Durability of clinical and quality-of-life outcomes of closed-loop spinal cord stimulation for chronic back and leg pain: a secondary analysis of the Evoke Randomized Clinical Trial. *JAMA Neurol*. Published online January 8, 2022. doi:10.1001/jamaneurol.2021.4998

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1 RESEARCH IN CONTEXT – 24-MONTH RCT EVIDENCE

Evidence before this study Spinal cord stimulation (SCS) for the treatment of chronic back and leg pain was developed a half century ago. Since that time there have been advances in the technology underpinning SCS, including new stimulation paradigms which have been the focus of recent trials. However, there are few randomized controlled trials (RCTs) with long-term data and even fewer RCTs with blinded designs. Moreover, until recently, there was no way to objectively measure the neural response produced by SCS or to thereby determine therapy delivery and adherence, in conjunction with clinical outcomes. How close the evoked neural response is to the prescribed neural response is defined by both device performance (i.e., ability of the device to adhere to the prescribed neural response) and patient adherence (i.e., patient compliance to the prescription). This data provides important information about the therapy received and is necessary for interpreting clinical outcomes.

In 2019, Mekhail and colleagues published the primary outcomes (measured at 3- and 12-months post-implant) of the first double-blind RCT (Evoke) of an SCS system capable of measuring the dose-response relationship, merging mechanism with clinical evidence. This study compared two stimulation modes of the system: fixed-output, open-loop with the additional ability to measure the neural response (ECAPs) and inform programming (i.e., ECAP-guided programming); and ECAP-controlled, closed-loop with the further ability to automatically adjust the dose on each stimulation pulse to maintain a consistent neural response at the prescribed level. This study not only demonstrated the superiority of closed-loop compared to open-loop SCS, but also demonstrated the benefit of ECAP measurement for open-loop therapy in its ability to confirm activation of the intended target when determining the patient stimulation parameters.

We performed a literature review to identify RCTs evaluating SCS of any stimulation paradigm for the treatment of chronic pain of the back and legs reporting long-term outcomes through 24 months. The search was performed in PubMed and Google Scholar for publications through October 2020. Three RCTs reporting 24-month outcomes were identified, none of which had a blinded study design. These included the PROCESS[1] and PROMISE[2] RCTs comparing open-loop SCS to medical management, and the SENZA RCT[3] comparing two types of open-loop SCS.

Herein we report the 24-month outcomes of the Evoke RCT comparing ECAP-controlled, closed-loop SCS to open-loop SCS, adding to this limited body of evidence.

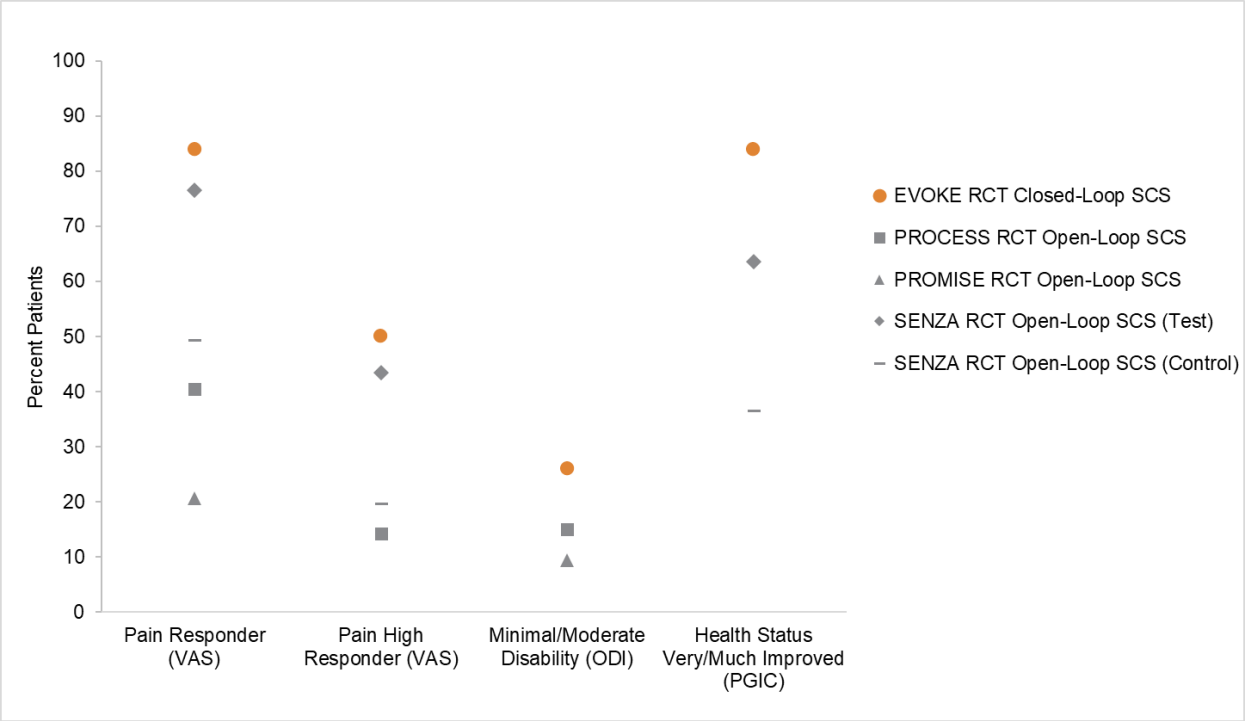
Added value of this study Refer to eFigure 1, eFigure 2, and eTable 1 for Evoke closed-loop outcomes compared to the literature open-loop outcomes at 24 months. Compared to the literature on other open-loop SCS systems at 24 months, ECAP-controlled, closed-loop SCS, which maintains the neural response within the patients' therapeutic window at the prescribed level, performed as well as or better on all measures including pain relief, disability, emotional functioning, health-related quality of life (HRQoL), and overall health status. The mean percent change from baseline in pain (for overall back and leg) was 72.6% in Evoke, compared to 28.0-66.9% (either leg or back) in open-loop studies. Similarly, a larger percentage of patients in the Evoke trial experienced a ≥50% (responder) or ≥80% (high responder) reduction of pain from baseline than did those in open-loop SCS trials. Oswestry Disability Index (ODI) scores were reduced at 24 months in Evoke patients to a greater degree than in patients in open-loop RCTs that also reported ODI values at 24 months, with more than twice the mean percent improvement from baseline. The percent of subjects with minimal to moderate disability was also greater for Evoke compared to these other open-loop trials. The mean change in quality of life, measured by the EQ-5D, was greater than or similar to the changes reported at 24 months in open-loop trials, as were improvements on both the physical and mental components of the short-form health survey (SF-12 PCS and MCS). More patients in the Evoke trial reported very much or much improvement in Global Impression of Change (PGIC) at 24 months (84.0% of patients) compared to the open-loop RCTS (36.6% and 63.5% of patients in those reporting 24-month PGIC data).

Additionally, the Evoke study reports several outcomes, subjective and objective, for which there is no comparative RCT evidence at 24 months. While most open-loop RCTs did not report opioid usage data, patients in the Evoke

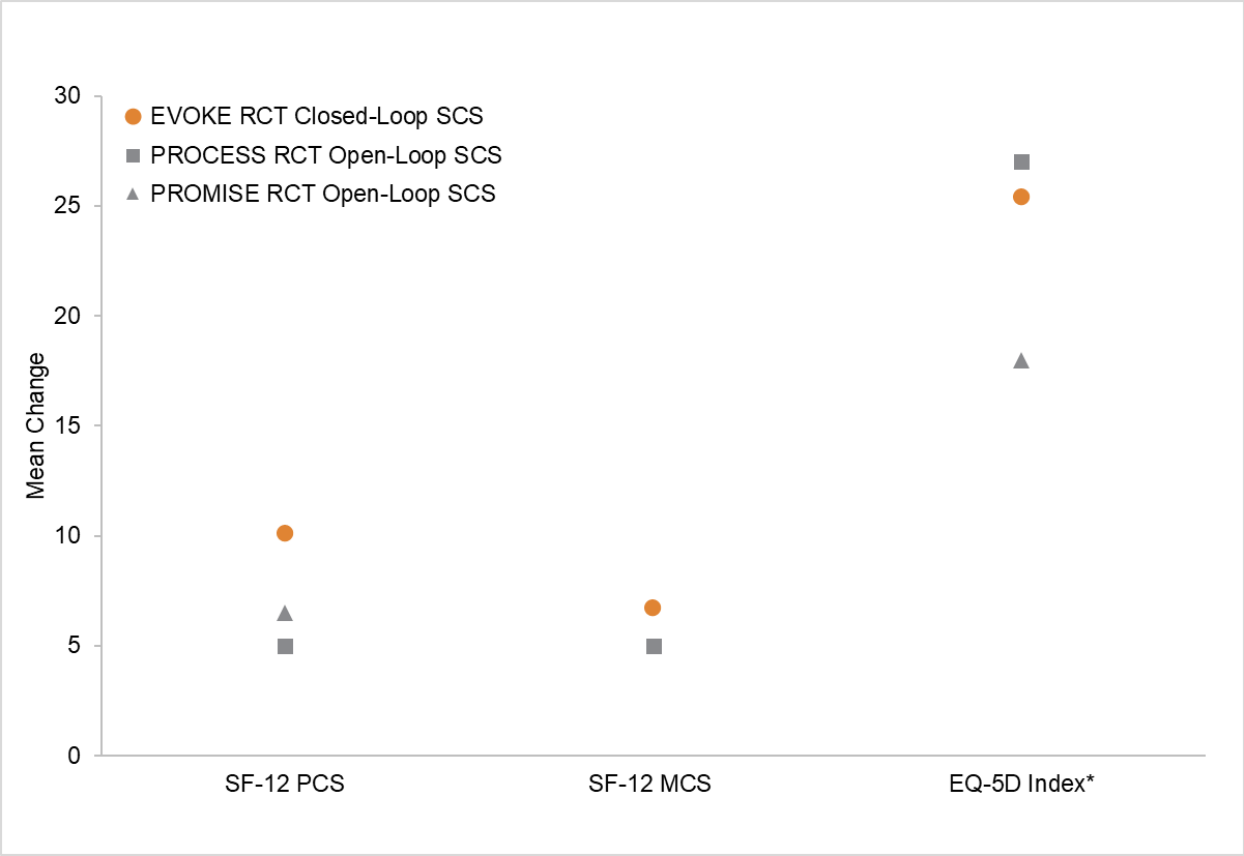
trial demonstrated a greater reduction in morphine milligram equivalent (MME) use than those in open-loop trials that reported this outcome at 24 months (42.3% reduction in Evoke versus slight increases in the open-loop trial). No 24-month comparison of outcomes on the Profile of Mood States – Total Mood Disturbance scale (POMS TMD) or the Pittsburgh Sleep Quality Index (PSQI) were possible because the identified open-loop RCTs did not collect or report these scales. Given the lack of published comparisons at 24 months, when compared to the 12-month outcomes from these studies, Evoke closed-loop demonstrated greater improvement even at a year longer follow-up.

Furthermore, Evoke is the first to report objective measures on device utilization in conjunction with spinal cord activation and other neurophysiological properties, providing evidence of therapy delivery and adherence in parallel with clinical outcomes. Thus, no comparison to these measures is available from these other open-loop RCTs.

Implications of all the available evidence This study provides evidence that ECAP-controlled, closed-loop SCS is an effective, long-term therapy to alleviate chronic pain and improve quality of life with the potential to reduce or eliminate opioid use. This therapy, which delivered higher, more consistent neural response within patients' therapeutic window and at the prescribed level, demonstrated long-term improvements in pain relief, disability, emotional functioning, sleep, and HRQoL with a substantial number of patients approaching population norms in parallel with meaningful opioid reduction. The outcomes of this study are substantiated by objective evidence of patient compliance from device utilization and activation of the pain inhibitory mechanisms from ECAP recordings. The long-term results of this study demonstrate the effective, reliable delivery of SCS therapy through ECAP-controlled closed-loop stimulation and the stability and longevity of ECAPs for measurement and physiological closed-loop control over time.



eFigure 1. 24-Month RCT Evidence for SCS



*EQ-5D Index multiplied by a factor of 100 to represent visually.

eFigure 2. 24-Month RCT Evidence for SCS – Health-Related Quality of Life Outcomes

eTable 1. 24-Month RCT Evidence for SCS

	EVOKE RCT Closed-Loop SCS	PROCESS RCT Open-loop SCS (MDT)	SENZA RCT Open-loop SCS (Test [NVR])	SENZA RCT Open-loop SCS (Control [BSC])	PROMISE RCT Open-loop SCS (MDT)
Pain (Primary Outcome)	Overall Back and Leg, VAS	Leg, VAS	Back, VAS	Back, VAS	Back, NRS
Percent Change from Baseline (mean)	72.6%	43.5%[1]	66.9%	41.1%	29.3%[1]
≥50% Reduction from Baseline	84.0%	40.5%	76.5%	49.3%	20.6%
≥80% Reduction from Baseline	50.0%	14.3%	43.5%[1]	19.7%[1]	NR
ODI					
Change from Baseline (mean)	26.0	15[1]	NR[2]	NR[3]	9.4
Percent Change from Baseline (mean)	47.8%	20.3%[1]	NR[4]	NR[5]	NR
Percent Minimal to Moderate	78.0%	NR	64.7%	49.3%	NR
EQ-5D Index					
Change from Baseline (mean)	0.254	0.27[1]	NC	NC	0.18
SF-12 PCS					
Change from Baseline (mean)	10.1	NR in Kumar 2008; 5[1,6] in Eldabe 2009	NR[7]	NR[8]	6.5[6]
SF-12 MCS					
Change from Baseline (mean)	6.7	NR in Kumar 2008; 5[1,6] in Eldabe 2009	NR[9]	NR[10]	NR
POMS					
Change from Baseline (mean)	18.6	NC	NC	NC	NC
PSQI					
Change from Baseline (mean)	4.1	NC	NR[11]	NR[12]	NR
PGIC					
Percent Very Much or Much Improved	84.0%	NC	63.5%[13]	36.6%	NR
Opioid Usage					

	EVOKE RCT Closed-Loop SCS	PROCESS RCT Open-loop SCS (MDT)	SENZA RCT Open-loop SCS (Test [NVR])	SENZA RCT Open-loop SCS (Control [BSC])	PROMISE RCT Open-loop SCS (MDT)
Percent Decrease MME (mean)	42.3%	-2.2% / -6.1%[1] (increases in MME for low-use and high-use patients)	NR	NR	NR
Percent Reduced or Eliminated	66.7%	NR	NR[14]	NR[15]	NR
Patient Adherence					
Percent Device Utilization Outside the Clinic (median)	88.0%	NC	NC	NC	NC
Device Performance					
Deviation in Elicited Neural Response from Target Neural Response Inside the Clinic (RMSE, median)	3.2 µV	NC	NC	NC	NC
Neural Activation					
Most Frequent Neural Response Outside the Clinic (µV, median)	22.5	NC	NC	NC	NC
Percent Time Within Therapeutic Window Outside the Clinic (median)	93.9%	NC	NC	NC	NC

BSC = Boston Scientific Corporation, EQ-5D = European Quality of Life Five-Dimensional (multiplied by a factor of 100 to represent visually), HR-QoL = Health-Related Quality of Life, MDT = Medtronic, NC = Not Collected, NR = Not Reported, NVR = Nevro, ODI = Oswestry Disability Index, PGIC = Patient Global Impression of Change, POMS = Profile of Mood States (TMD = Total Mood Disturbance), PSQI = Pittsburgh Sleep Quality Index, SF-12 = Short-Form Health Survey (MCS = Mental Component Score, PCS = Physical Component Score), VAS = Visual Analog Scale

[1]Estimated from data provided in the publication.

[2]Senza RCT Open-Loop SCS Test: 16.5 mean change from baseline in ODI at 12 months [Kapural 2015[4]]

[3]Senza RCT Open-Loop SCS Control: 13.0 mean change from baseline in ODI at 12 months [Kapural 2015[4]]

[4]Senza RCT Open-Loop SCS Test: 29.2% mean percent change from baseline in ODI at 12 months [SSED P130022[5]]

[5]Senza RCT Open-Loop SCS Control: 21.6% mean percent change from baseline in ODI at 12 months [SSED P130022[5]]

[6]SF-36
[7]Senza RCT Open-Loop SCS Test: 8.1 mean change from baseline in SF-12 PCS at 12 months [SSED P130022[5]]
[8]Senza RCT Open-Loop SCS Control: 6.0 mean change from baseline in SF-12 PCS at 12 months [SSED P130022[5]]
[9]Senza RCT Open-Loop SCS Test: 2.7 mean change from baseline in SF-12 MCS at 12 months [SSED P130022[5]]
[10]Senza RCT Open-Loop SCS Control: 1.2 mean change from baseline in SF-12 MCS at 12 months [SSED P130022[5]]
[11]Senza RCT Open-Loop SCS Test: 2.6 mean change from baseline in PSQI at 12 months [SSED P130022[5]]
[12]Senza RCT Open-Loop SCS Control: 1.8 mean change from baseline in PSQI at 12 months [SSED P130022[5]]
[13]Percent a great deal better or better
[14]Senza RCT Open-Loop SCS Test: 35.5% patients reduced or eliminated opioids at 12 months [SSED P130022[5]]
[15]Senza RCT Open-Loop SCS Control: 26.4% patients reduced or eliminated opioids at 12 months [SSED P130022[5]]

2 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 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 in the investigational group. Oversight by the investigators was documented in accordance with FDA guidelines[6,7].

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 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 and electrophysiology (e.g., morphometrics of the epidural space). To provide personalised 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 very different physiological characteristics.

Outcomes 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., 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.

3 STATISTICAL ANALYSIS

Since an analysis based on all randomized patients is important for preserving the intent to treat principle, a last value carried forward (LVCF) analysis was performed for the primary outcome of pain assessed by the Visual Analog Scale (VAS) to make full use of the information on all randomized patients with careful attention to the assumptions about the nature of the missing data. This was performed as a conservative measure to minimize potential bias of an enriched population (i.e., only patients benefiting from treatment remained in the study and those not benefiting withdrew early)[8]. An independent blinded review of missing data at 24-months for all randomized patients was performed by an independent medical monitor to confirm the use of last value carried forward (LVCF) was appropriate. The review evaluated the patient's reason for study exit and their last VAS pain score prior to exit to confirm the reason for exit and pain score were not conflicting. For all but one patient, LVCF was determined to be appropriate. For one patient, in which the patient had ≥50% reduction in VAS pain but the reason for exit was the patient "felt no significant difference in pain," baseline value carried forward (BVCF) was utilized. The normal approximation to the binomial was used for binary outcomes and a two-sample t-test was used for continuous outcomes.

The additional secondary patient-reported outcomes (PROs) and pain medication usage were compared between treatment groups using Fisher exact tests for categorical measures and two-sample t-tests for continuous measures summarized as means. Non-parametric testing using Kruskal-Wallis tests for medians were used for the device data measurements due to the observed distributions of the data. The analyses were based on patients with complete data, with no imputation for missing data.

An additional sensitivity analysis using likelihood based repeated measures linear regression models was also performed to confirm the robustness of the analysis methods. These approaches are valid under a missing at random assumption for missing data and so are preferred over approaches that ignore missing data. Visit was treated as a categorical variable, and the treatment effect was allowed to vary over time by inclusion of an interaction term for treatment group and visit. A compound symmetric covariance structure was used to account for within-patient correlation. Estimates from these models are based on least-square means.

4 BASELINE DEMOGRAPHICS AND CHARACTERISTICS

No differences were observed between the baseline characteristics of all randomized patients and the cohort of patients who completed the 24-month follow-up (eTable 2).

eTable 2. Baseline Characteristics for all Randomized Patients and for the Cohort of Patients who Completed 24-month Follow-up

	All Randomized		24-Month Completers	
	Closed-Loop (N=67)	**Open-Loop (N=67)**	**Closed-Loop (N=50)**	**Open-Loop (N=42)**
Age (years)	54.6 (9.7)	55.9 (11.6)	56.3 (8.1)	56.6 (11.6)
Sex				
Male	34 (50.7%)	35 (52.2%)	25 (50.0%)	22 (52.4%)
Female	33 (49.3%)	32 (47.8%)	25 (50.0%)	20 (47.6%)
BMI (kg/m^2)	31.3 (5.7)	32.4 (6.8)	32.4 (5.7)	33.7 (7.0)
Duration of Pain (years)	13.6 (9.6)	11.2 (9.9)	13.4 (9.9)	10.4 (9.8)
Pain Etiology (not mutually exclusive)				
Arachnoiditis	0 (0.0%)	2 (3.0%)	0 (0.0%)	2 (4.8%)
Complex Regional Pain Syndrome (CRPS) I	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (2.4%)
Degenerative Disc Disease	33 (49.3%)	42 (62.7%)	21 (42.0%)	22 (52.4%)
Failed Back Surgery Syndrome (FBSS)	38 (56.7%)	41 (61.2%)	27 (54.0%)	30 (71.4%)
Internal Disc Disruption or Tear / Discogenic Pain	7 (10.4%)	10 (14.9%)	2 (4.0%)	4 (9.5%)
Lumbar Facet-Mediated Pain	8 (11.9%)	8 (11.9%)	4 (8.0%)	5 (11.9%)
Mild-Moderate Spinal Stenosis	26 (38.8%)	27 (40.3%)	20 (40.0%)	17 (40.5%)
Radiculopathy	61 (91.0%)	59 (88.1%)	44 (88.0%)	35 (83.3%)
Sacroiliac Joint-Mediated Pain	9 (13.4%)	5 (7.5%)	7 (14.0%)	2 (4.8%)
Spondylolisthesis	6 (9.0%)	5 (7.5%)	5 (10.0%)	4 (9.5%)
Spondylosis with Myelopathy	2 (3.0%)	3 (4.5%)	1 (2.0%)	1 (2.4%)
Spondylosis without Myelopathy	26 (38.8%)	24 (35.8%)	21 (42.0%)	12 (28.6%)
Other Chronic Pain	5 (7.5%)	3 (4.5%)	5 (10.0%)	3 (7.1%)
Baseline Pain Medication Usage	62 (92.5%)	59 (88.1%)	46 (92.0%)	35 (83.3%)
Opioids	41 (61.2%)	40 (59.7%)	27 (54.0%)	23 (54.8%)
Non-opioids[1]	50 (74.6%)	52 (77.6%)	37 (74.0%)	31 (73.8%)
Previous Non-Invasive Therapies[2]	65 (97.0%)	64 (95.5%)	49 (98.0%)	40 (95.2%)
Previous Interventional Procedure[3]	63 (94.0%)	62 (92.5%)	47 (94.0%)	39 (92.9%)

	All Randomized		24-Month Completers	
	Closed-Loop (N=67)	**Open-Loop (N=67)**	**Closed-Loop (N=50)**	**Open-Loop (N=42)**
Previous Back Surgery[4]	39 (58.2%)	41 (61.2%)	27 (54.0%)	30 (71.4%)
Overall Back and Leg Pain VAS Score (mm)	82.0	82.2	81.1	82.5

Abbreviations: CRPS = Complex Regional Pain Syndrome, BMI = Body Mass Index, FBSS = Failed Back Surgery Syndrome, MME = Morphine Milligram Equivalent, VAS = Visual Analog Scale

Data are mean (SD) or n (%).

[1]Non-opioid pain medication classes include: anticonvulsant, antidepressant, local anaesthetic, muscle relaxant, NSAIDs, and other pain medications.

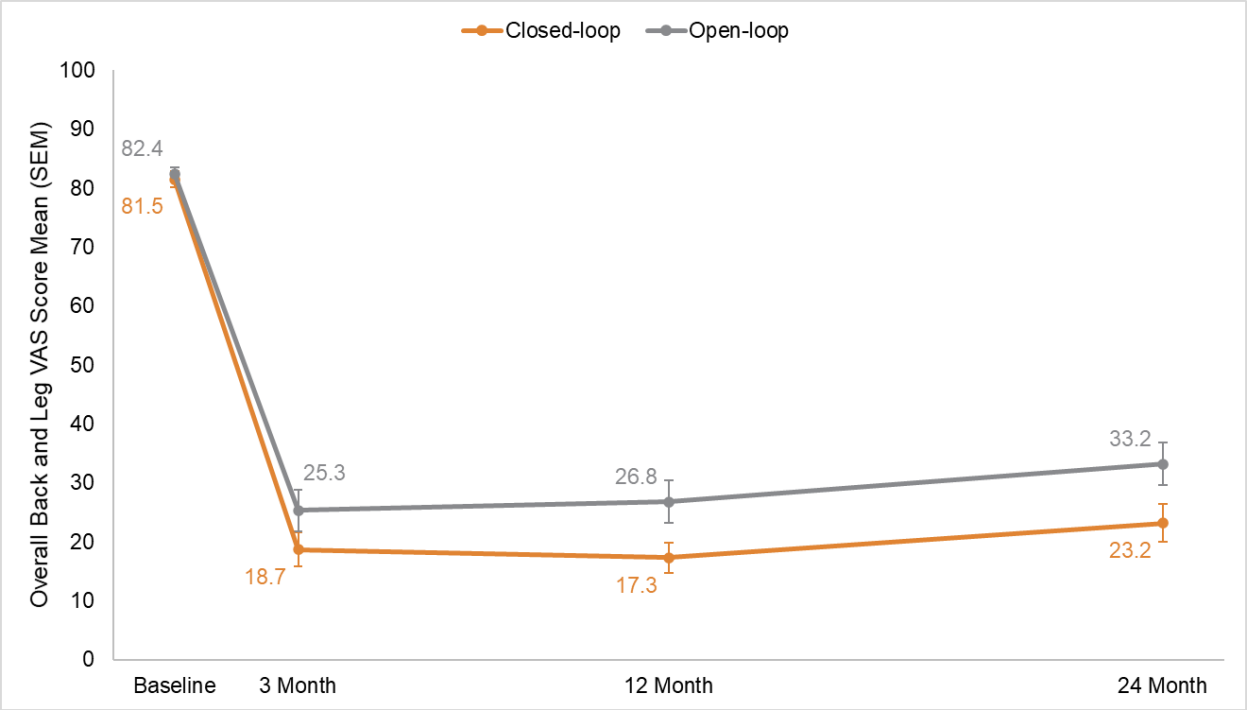
[2]Non-invasive therapies include: acupuncture, aquatherapy, assistive device, biofeedback, chiropractic care, exercise therapy, massage therapy, psychotherapy, physical therapy, transcutaneous electro-nerve stimulator (TENS).

[3]Interventional procedures include: ankle surgery, benign cyst removal, block/injection – other, epidural steroid injection, facet joint injection, intradiscal bilateral lumbar biacuplasty, intradiscal procedure (e.g., Intradiscal Electrothermal Therapy (IDET)), lumbar rhizotomy, lumbar surgical ablation, lumbar sympathetic block, medial branch block, radiofrequency denervation, sacroiliac joint injection, trigger point injection.

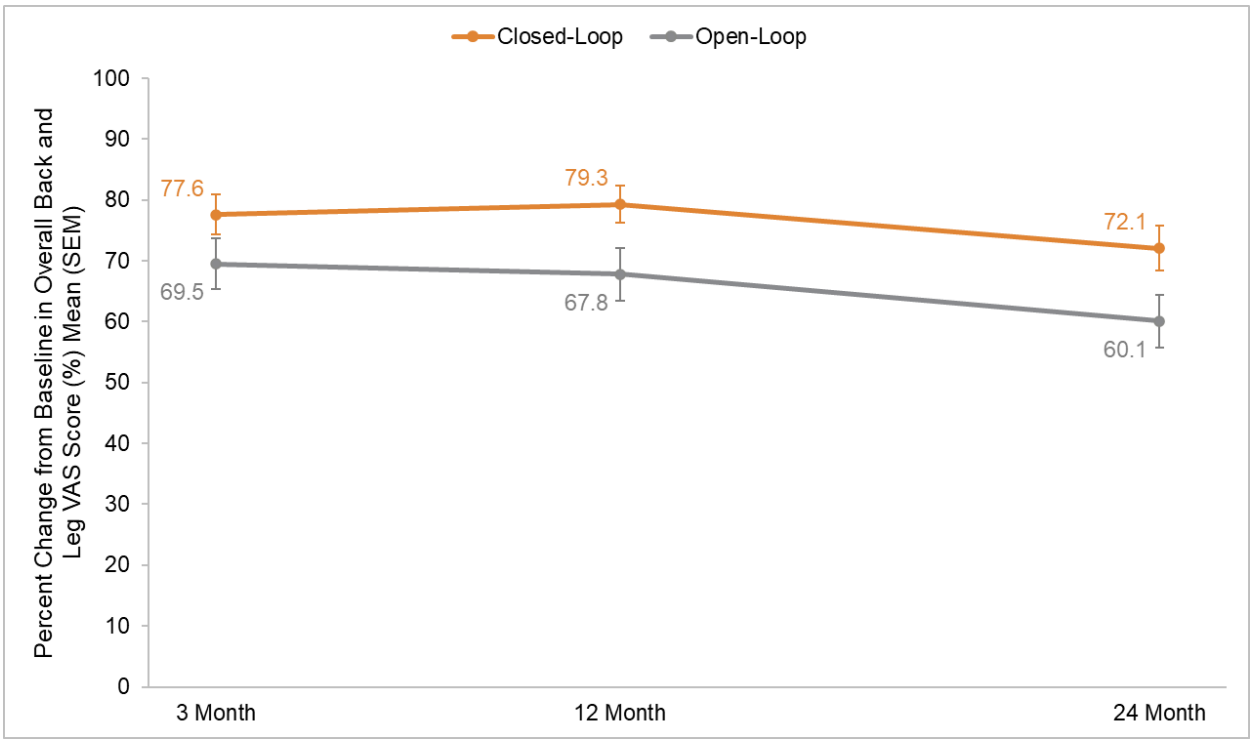
[4]Back surgeries include: artificial disc replacement, discectomy or microdiscectomy, foraminotomy, kyphoplasty or vertebroplasty, laminectomy, nucleoplasty (e.g., disc decompression, laser surgery), spinal fusion, back surgery – not otherwise specified, back surgery – other.

5 VAS OUTCOMES – IMPLANTED POPULATION

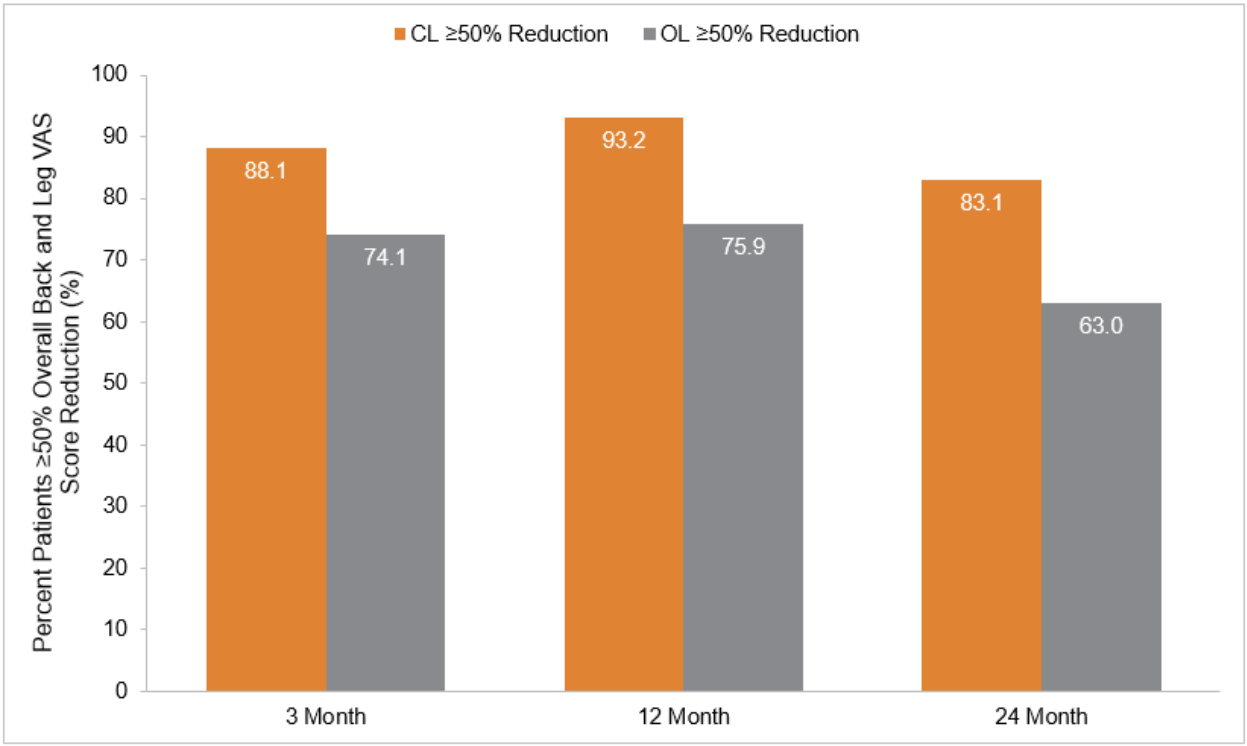
Fifty-nine closed-loop patients and 54 open-loop patients were implanted in this study. In this population at 24 months, the reduction in overall back and leg pain was significantly greater for closed-loop (mean [SD] score: 23.2 [24.0]; point decrease: 58.3 [23.4]; percent decrease: 72.1% [28.2]) than open-loop (mean [SD] score: 33.2 [28.1%]; point decrease: 49.3 [27.8]; percent decrease: 60.1% [33.3%]) (p-value between groups =0.040) (eFigure 3, eFigure 4). There was also a significantly greater proportion of closed-loop patients who were responders with ≥50% reduction in overall back and leg pain compared to open-loop patients (49/59 [83.1%] CL, 34/54 [63.0%] OL, difference=20.1%, 95% CI=4.0%-36.1%, p=0.014) at 24 months (eFigure 5).



eFigure 3. Overall Back and Leg VAS Scores through 24 Months



eFigure 4. Percent Reduction in Overall Back and Leg Pain through 24 Months



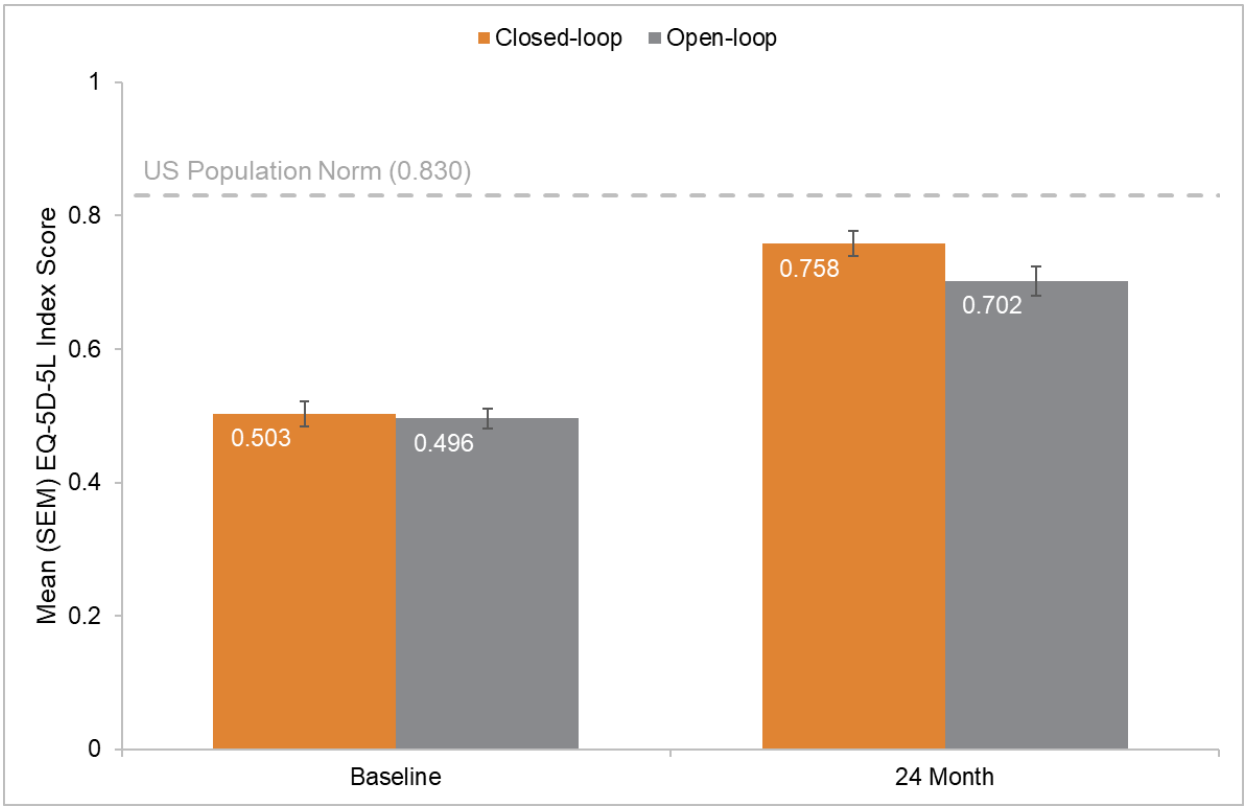
eFigure 5. ≥50% Reduction (Responder) in Overall Back and Leg Pain through 24 Months

6 SLEEP

Mean change in the Pittsburgh Sleep Quality Index (PSQI)[9] from baseline to 24 months was 4.1 in both treatment groups (mean [SD] 4.1 [4.3] CL, 4.1 [4.7] OL). Greater than 60% of patients had a minimum clinically important difference in PSQI of ≥3 (31/49 [63.3%] CL, 26/42 [61.9%])[10]. On average, falling asleep time was reduced by more than 15 minutes (mean [SD] 17.6 [42.4] CL, 16.8 [36.2] OL) and sleep time per night increased by approximately one hour (mean [SD] 1.0 [1.6] CL, 0.8 [1.3] OL) at 24 months compared to baseline. Furthermore, almost one quarter of the patients reported no trouble sleeping due to pain in the past month (12/50 [24.0%] CL, 10/42 [23.8%] OL) compared to only one patient who reported this at baseline.

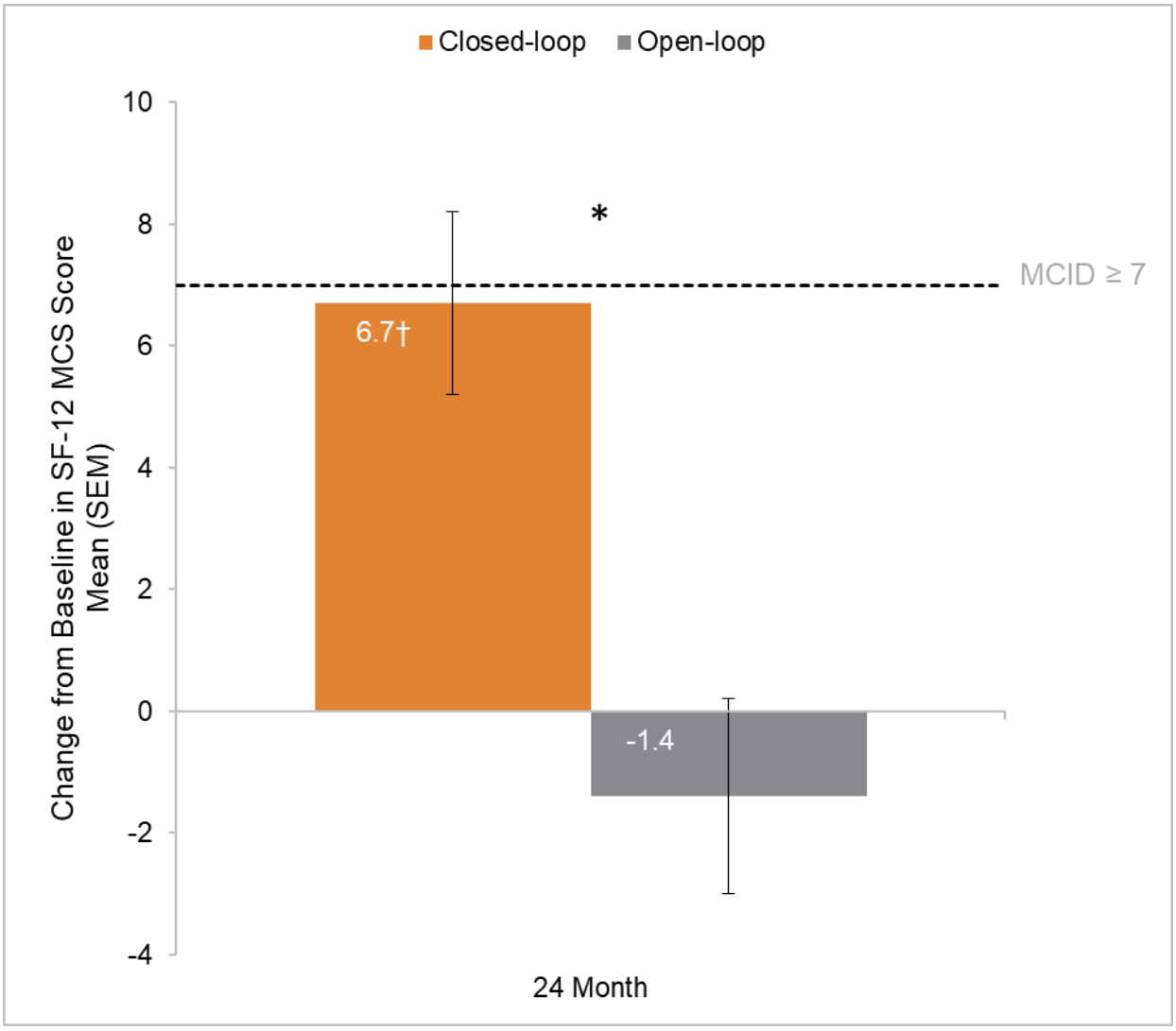
7 QUALITY OF LIFE

Improvement in Health-Related Quality of Life (HR-QoL) from baseline (mean [SD] 0.503 [0.153] CL, 0.496 [0.120] OL) was demonstrated by the European Quality of Life Five-Dimensional Five-Level (EQ-5D-5L) at 24-months (mean [SD] 0.758 [0.135] CL, 0.702 [0.145] OL), with subjects approaching the population norm (0.830 for the US value set ages 55-64, age range for the mean age of Evoke study subjects[11]) (eFigure 6)[12].



eFigure 6. Mean EQ-5D Index Score at Baseline and 24 Months

Improvement in HR-QoL was also demonstrated by the Short Form Health Survey (SF-12)[13]. Mean change from baseline to 24 months in the SF-12 Mental Component Summary (MCS) was almost five-fold in the closed-loop compared to the open-loop group (mean [SD] 6.7 [11.6] CL, -1.4 [10.0] OL, $p<0.001$; repeated measures model: estimate of the difference = 9.1, 95% CI = [4.9, 13.4], $p<0.001$) (eFigure 7). In addition, the proportion of patients with a minimum clinically important difference in SF-12 MCS of ≥7 was 46.0% (23/50) for closed-loop versus 22.0% (9/41) for open-loop SCS (difference=24.0, 95% CI=5.3-42.8, $p=0.027$)[13].



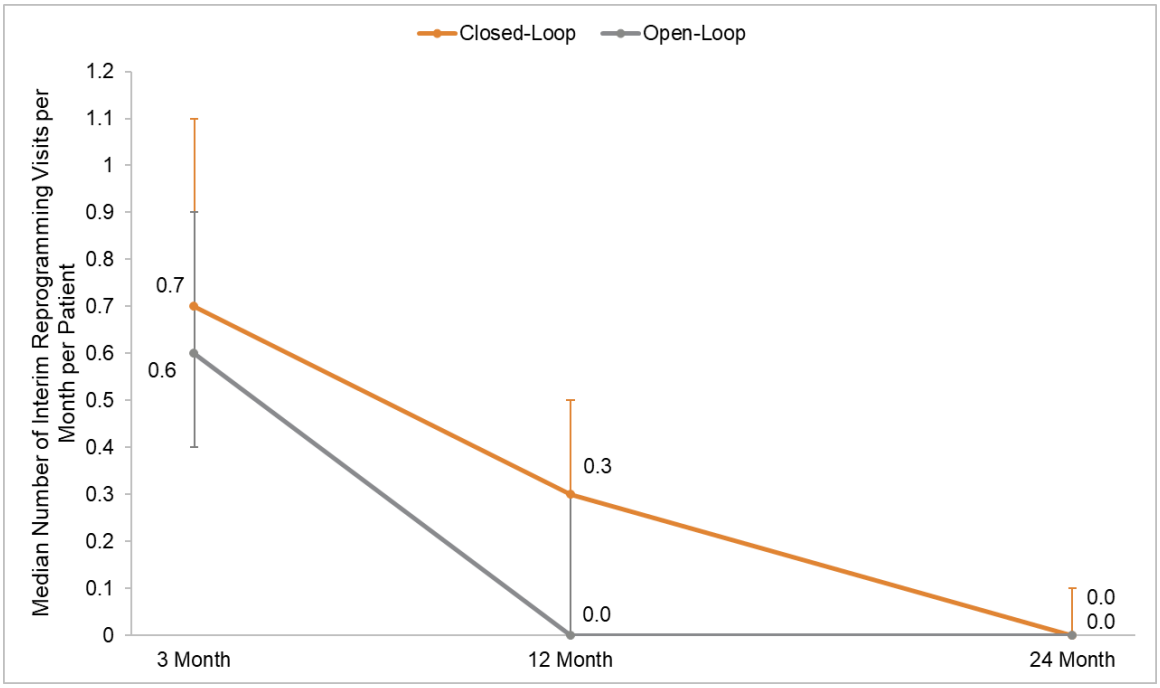
*Significant difference between treatment groups (p<0.05).

eFigure 7. Mean Change from Baseline in SF-12 MCS Score at 24 Months

8 PROGRAMMING

There was no differences between treatment groups in prescribed stimulation parameters with average frequency approximately 40 Hz (mean [range] 37.9 [10.0-70.0] CL, 40.3 [10.0-60.0] OL, p=0.29), pulse duration approximately 290 µs (294.3 [150.0-400.0] CL, 290.9 [120.0-500.0] OL, p=0.84); and stimulation amplitude approximately 7 mA (7.0 [0.5-22.3] CL, 6.5 [1.6-17.7] OL, p=0.75) in both groups. The neural responses (ECAP amplitude [µV]) measured from the dose-response curves were comparable between groups for perception threshold (median [IQR] 6.0 [1.0-15.0] CL, 4.0 [2.0-13.5] OL, p=0.99), comfort (28.0 [12.0-57.0] CL, 16.0 [6-61.5] OL, p=0.35), and maximum (115.0 [53.0-171.0] CL, 65.5 [30.0-157.5] OL, p=0.091). Measured sensitivity (slope of the dose-response; µV/µC per pulse) was also similar between groups (median [IQR]):109.5 [67.5-235.6] CL, 204.7 [83.7-333.6] OL; p=0.13).

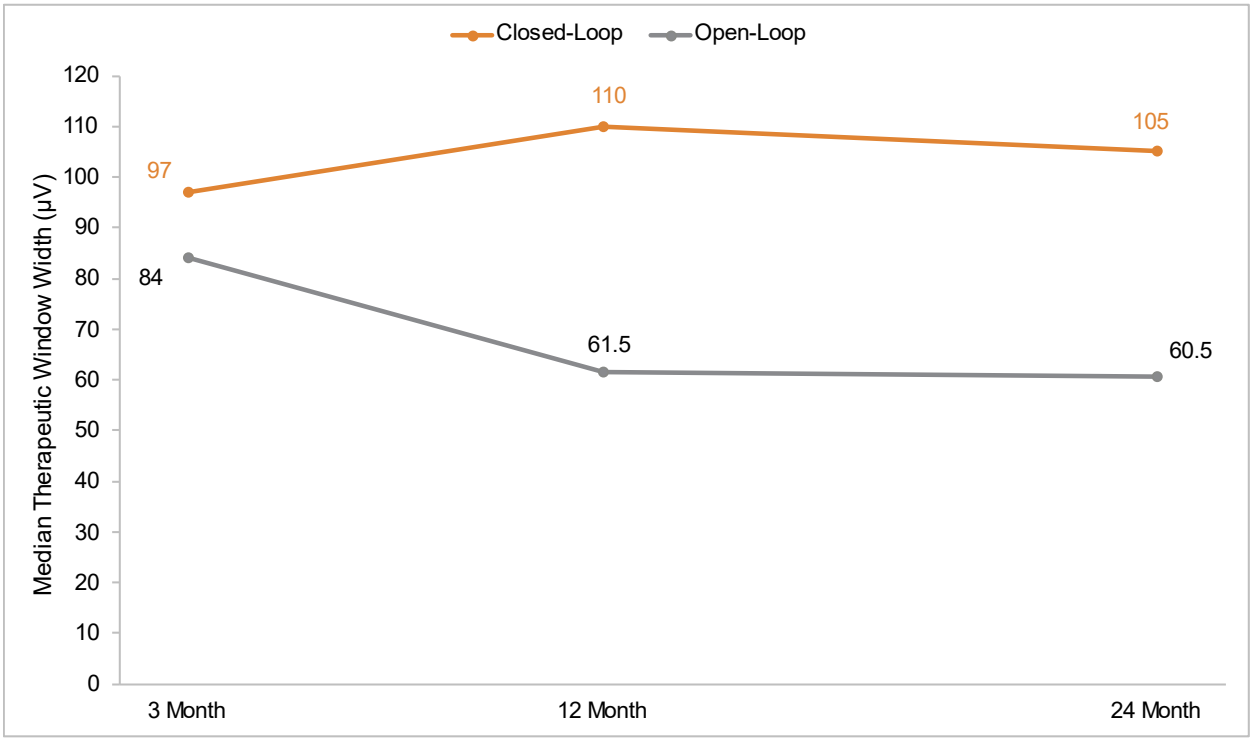
Patients were able to return to the clinic for reprogramming as needed in between scheduled visits. In the first three months following the implant, patients were reprogrammed on average (median [IQR]) 0.7 (0.4-1.1) and 0.6 (0.4-0.9) times per month in the closed-loop and open-loop groups, respectively (p=0.29). The need for reprogramming decreased over time in both treatment groups (eFigure 8). Between the 12-month and the 24-month visit, the average number of interim reprogramming visits per month was approximately zero in both treatment groups (0.0 [0.0-0.1] CL, 0.0 [0.0-0.0] OL, p=0.066).



eFigure 8. Interim Reprogramming Visits per Month per Patient through 24 Months

9 THERAPEUTIC WINDOW

The therapeutic window in this study was measured from the ECAP amplitude at patient perception threshold, when the patient reported initially feeling stimulation, to the ECAP amplitude at the maximum level the patient could tolerate. Compared to 3 months, at 12 and 24 months the upper boundary of the therapeutic window increased for closed-loop and decreased for open-loop, expanding and contracting the usable neural activation range in these groups, respectively (eFigure 9). Open-loop patients adjusted their stimulation to lower levels sacrificing pain relief to likely avoid over stimulations. At 24 months, on average (median) 0.1% of stimuli produced neural responses above the therapeutic window in the open-loop group (compared to 0.0% in the closed-loop group). Such an event occurs once for every 1000 presented stimuli (e.g., at a stimulation rate of 50 Hz, over 4000 potentially painful overstimulation events occur each day). Closed-loop control, which adjusts on every stimulation pulse, is highly effective at reducing these 1 in 1000 overstimulation events, while allowing patients to maintain a higher degree of therapeutic stimulation than open-loop SCS.



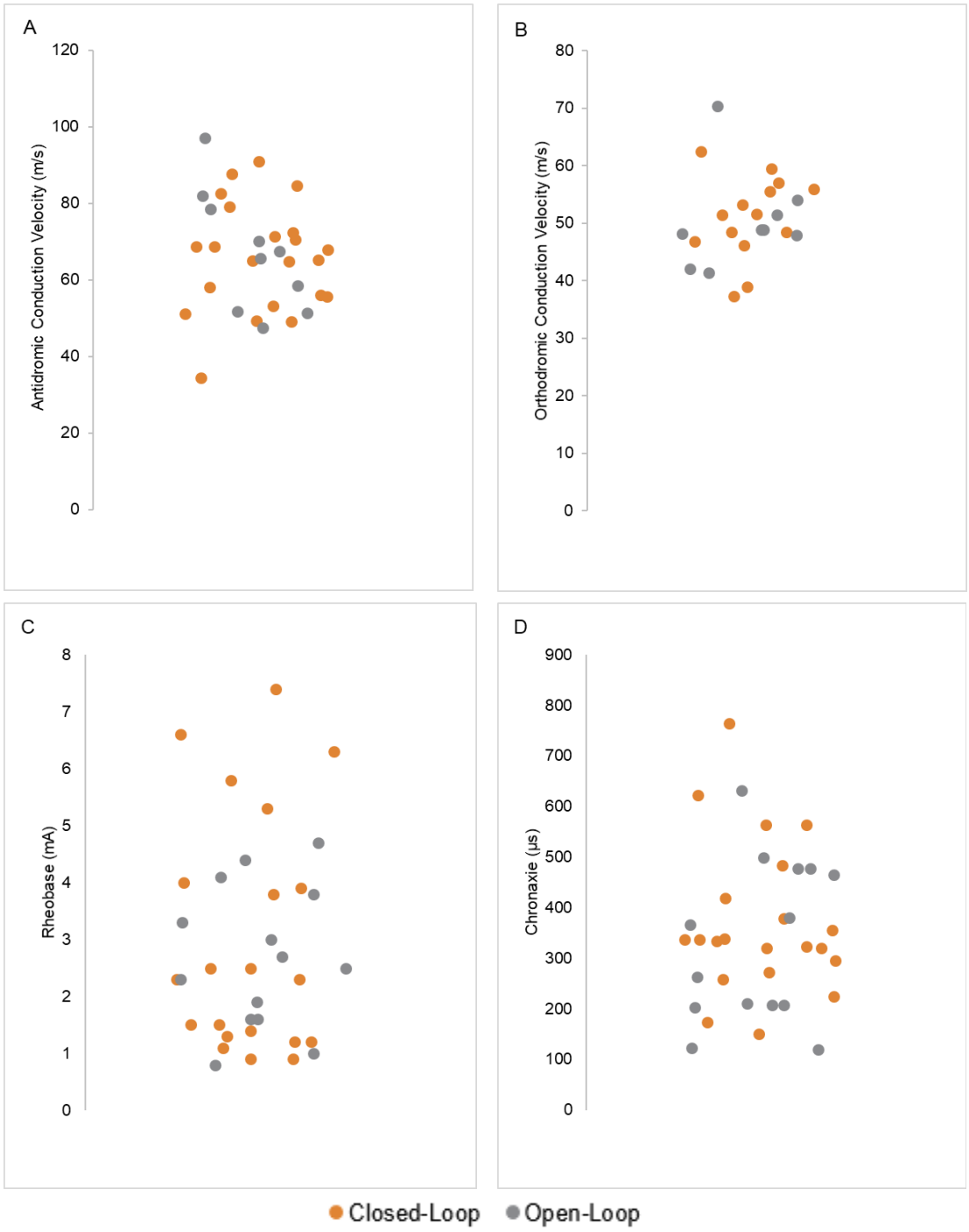
eFigure 9. Therapeutic Window Width through 24 Months

10 NEUROPHYSIOLOGICAL PROPERTIES

Neurophysiological measures were collected in this study to gain knowledge on the properties of the activated fibers. Both antidromic and orthodromic conduction velocity of the stimulated nerve fibers, the speed at which an action potential propagates along the neural pathway, was measured to determine the type of nerve fibers being activated. The rheobase and chronaxie were measured to determine the excitability of the stimulated nerve fibers. The rheobase, or axonal excitability, is the minimum stimulus current needed for a neural response (i.e., that will produce an action potential) at infinitely long pulse duration. The chronaxie, or membrane time constant, is the minimum pulse duration needed for a neural response at twice the rheobase current.

Neurophysiological properties were highly variable among patients in the Evoke study due to expected, intrinsic patient differences in activation; however, there was not a significant difference between treatment groups in any parameter (eFigure 10). In the closed-loop and open-loop groups, respectively, antidromic conduction velocity (m/s; median [IQR]) was 66.6 [55.6-72.3] compared to 66.5 [51.7-78.4] (p=1.00), and the orthodromic conduction velocity was 51.5 [46.8-55.9] compared to 48.8 [47.9-51.4] (p=0.53). Rheobase (mA; median [IQR]) was 2.3 [1.3-4.0] versus 2.6 [1.6-3.8] (p=0.84), and chronaxie (μs; median [IQR]) was 336.9 [295.6-419.3] versus 314.8 [207.8-477.4] (p=0.48).

Monitoring fiber properties (e.g., activated fiber types and excitability) may provide insight into neural health (disease, injury, mechanical changes), effects of medications, and neural selectivity for SCS programming.



eFigure 10. Patient Neurophysiological Property Measures at 24 Months. A) Antidromic Conduction Velocity (m/s); B) Orthodromic Conduction Velocity (m/s); C) Rheobase (mA); D) Chronaxie (µs)

11 ADDITIONAL SAFETY DATA

Investigators in the Evoke study were required to report all adverse events (AEs) that occurred during the course of the study in accordance with the protocol. All adverse events were subsequently adjudicated by an independent Clinical Events Committee and are reported herein per the CEC's adjudication. Adverse events adjudicated by the independent Clinical Events Committee as definitely or possibly related to the device, procedure, and/or stimulation therapy were considered "study-related." All subjects in the Evoke study received the same investigational device, underwent the same trial and permanent implant procedures per the Evoke Surgical Manual, and received active stimulation. The only difference between treatment groups was the stimulation mode (open-loop or closed-loop). Thus, the true indicator of the safety differences between treatment groups were stimulation therapy-related adverse events.

There were no differences in the safety profiles between treatment groups; and the type, frequency, and severity of adverse events were similar to those reported in other SCS studies (eTable 3 and eTable 4). There were 42 study-related AEs in 28 patients (20.9%) (CL: 28 AEs, 23.9% patients. OL: 14 AEs, 17.9% patients. Difference [95% CI]: 6.0 [-7.8, 19.7]). The most frequently reported study-related AEs in both groups were IPG pocket pain (10 AEs, 6.7% patients) and lead migration (10 AEs, 6.7% patients). Importantly, there were no differences between groups in stimulation therapy-related adverse events with 10 stimulation therapy-related AEs in 8 patients (CL: 7 AEs, 7.5% patients. OL: 3 AEs, 4.5% patients. Difference [95% CI]: 3.0 [-5.0, 11.0]). Four serious AEs in four patients (3.0%) (CL: 2 AEs, 3.0% patients. OL: 2 AEs, 3.0% patients. Difference [95% CI]: 0.0 [-5.8, 5.8]) were study-related, but not stimulation related, including wound infection (2 [1.5%]), epidural abscess (1 [0.7%]), and lead breakage/fracture (1 [0.7%]). There were two explants due to loss of efficacy (CL: 0 [0.0%], OL: 2 [3.0%]) and three explants due to procedure-related infections (CL: 2 [3.0%], OL: 1 [1.5%]). There has been one death due to cardiac arrest secondary to uncontrolled hypertension and unrelated to the study.

eTable 3. Summary of Study-Related Adverse Events for all Randomized Patients

	Total N=134		Difference Between Groups
Adverse Events (AEs)	**Events n**	**Patients n (%)**	**Rate Difference (%) and 95% CI**
Study-Related AEs[1]	42	28 (20.9%)	6.0 (-7.8, 19.7)
Procedure-Related AEs	28	21 (15.7%)	4.5 (-7.8, 16.8)
Device-Related AEs	18	17 (12.7%)	4.5 (-6.8, 15.7)
Stimulation Therapy- Related AEs	10	8 (6.0%)	3.0 (-5.0, 11.0)

[1]Adverse events adjudicated as definitely or possibly related to the device, procedure, or stimulation therapy were considered study-related.

eTable 4. Rates of Study-Related Adverse Events for All Randomized Patients

	Total N=134 Patients	
Preferred Term	**Events n**	**Patients n (%)**
Total Adverse Events	**42**	**28 (20.9%)**
IPG Pocket Pain	10	9 (6.7%)
Lead Migration	10	9 (6.7%)
Muscle Spasm or Muscle Cramp	3	3 (2.2%)

	Total N=134 Patients	
Preferred Term	**Events n**	**Patients n (%)**
Wound Infection	3	3 (2.2%)
Dural Puncture or Tear	2	2 (1.5%)
IPG Malfunction due to Electrocautery	2	2 (1.5%)
Unwanted Stimulation Location	2	2 (1.5%)
Back Pain and Bilateral Radiation into Legs	1	1 (0.7%)
Dysesthesia - Lower Extremity	1	1 (0.7%)
Epidural Abscess	1	1 (0.7%)
Inadequate Lead Placement	1	1 (0.7%)
Lead Breakage/Fracture	1	1 (0.7%)
Low Back Pain	1	1 (0.7%)
Nausea and/or vomiting	1	1 (0.7%)
Pain - Implant/Incision site	1	1 (0.7%)
Skin Irritation or Redness	1	1 (0.7%)
Wound Dehiscence	1	1 (0.7%)

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