

Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform

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Objective: The purpose of the multicenter, randomized, unblinded, crossover Success Using Neuromodulation with BURST (SUNBURST) study was to determine the safety and efficacy of a device delivering both traditional tonic stimulation and burst stimulation to patients with chronic pain of the trunk and/or limbs.

Methods: Following a successful tonic trial, 100 subjects were randomized to receive one stimulation mode for the first 12 weeks, and then the other stimulation mode for the next 12 weeks. The primary endpoint assessed the noninferiority of the within-subject difference between tonic and burst for the mean daily overall VAS score. An intention-to-treat analysis was conducted using data at the 12- and 24-week visits. Subjects then used the stimulation mode of their choice and were followed for one year. Descriptive statistics were used to analyze additional endpoints and to characterize the safety profile of the device.

Results: The SUNBURST study demonstrated that burst stimulation is noninferior to tonic stimulation ($p < 0.001$). Superiority of burst was also achieved ($p < 0.017$). Significantly more subjects (70.8%) preferred burst stimulation over tonic stimulation ($p < 0.001$). Preference was sustained through one year: 68.2% of subjects preferred burst stimulation, 23.9% of subjects preferred tonic, and 8.0% of subjects had no preference. No unanticipated adverse events were reported and the safety profile was similar to other spinal cord stimulation studies.

Conclusions: The SUNBURST study demonstrated that burst spinal cord stimulation is safe and effective. Burst stimulation was not only noninferior but also superior to tonic stimulation for the treatment of chronic pain. A multimodal stimulation device has advantages.

Keywords: Burst stimulation, chronic pain, spinal cord stimulation, tonic stimulation, waveform

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INTRODUCTION

Spinal cord stimulation (SCS), an established therapy for treatment of chronic, intractable pain of the back and limbs, was first introduced in 1967 by Shealy et al. (1). Conventional SCS provides tonic stimulation, consisting of continuous individual pulses delivered at the same amplitude, duration (pulse width), and frequency (or interpulse interval). Traditional tonic stimulation at clinically relevant settings typically produces paresthesia. Recently developed alternatives to tonic stimulation have shown some promise: new waveforms, frequencies, and stimulation modes (2,3). One such stimulation mode, burst stimulation, consists of groups of higher-frequency pulsed stimulatory (charge) phases, separated by pulse-free interphase delays, ultimately followed by a passive recharge (discharge) phase, allowing full recovery of any briefly accumulated charge during the stimulatory or charge phase. The burst waveform potentially emulates naturally occurring neuronal firing modes in the central nervous system (4).

Though certain types of burst stimulation had been used previously in transcutaneous electrical nerve stimulation (5,6), its use in an SCS device for treatment of chronic pain was first reported in 2010 by De Ridder et al. (2). This pilot study presented 12 patients who underwent a one-month trial period with an externalized pulse generator. During the trial period, burst stimulation resulted in an 84% and 96% reduction from baseline in mean overall visual analog scale (VAS) scores for both axial and limb pain, respectively. Further, only 17% of the study patients experienced paresthesia with burst stimulation, while 92% of patients experienced paresthesia during traditional tonic stimulation. Following the trial evaluation period, patients with more than 50% pain reduction using either stimulation mode received permanent implants and were followed for an average 20.5 months. After one year, the investigators reported that pain reduction and improvements in the sensory and affective components of pain were sustained with burst stimulation (2). Other clinical studies have continued to show effective pain control with burst stimulation, with the suggestion that burst stimulation

provides greater pain relief than tonic stimulation (7–11). Specifically, De Ridder et al. showed a decrease of approximately 1.7 points on the Numeric Rating Scale from burst stimulation compared to tonic stimulation (8). Another study which evaluated patients with failed back surgery syndrome (FBSS) and painful diabetic neuropathy showed that burst stimulation provided an additional 12 mm absolute decrease in VAS scores when compared to tonic stimulation (9). Studies also reported a marked reduction in paresthesia during burst stimulation, with only 17–25% of patients feeling paresthesia (2,7). However, these early studies evaluating burst stimulation enrolled small cohorts of patients in Europe and Australia over a short period of time, and only one was a randomized, controlled trial (11). A larger controlled study was necessary to demonstrate the safety and efficacy burst stimulation (2) which includes the very specific patterns with passive recharge and to gain United States Food and Drug Administration (FDA) approval of this stimulation paradigm. The primary objective of the success using neuromodulation with BURST (SUNBURST) study was to establish the non-inferiority of pain intensity after three months of burst stimulation compared to three months of tonic stimulation.

METHODS

The SUNBURST study is a randomized, controlled, unblinded trial with two distinct phases: 1) a 24-week cross-over phase during which subjects used one stimulation mode for 12 weeks and then crossed over to the other for the remaining 12 weeks, followed by 2) an open-label phase during which study participants could use either waveform (Fig. 1). These methods were described in further detail in a previous publication (12). In brief, subjects at least 22 years of age with chronic intractable pain of the trunk and/or limbs with the ability to provide informed consent were included in this study. Subjects with a baseline average daily overall pain score of ≥ 60 on the VAS collected with a seven-day Pain Diary were also included. Subjects with a history of a neurostimulation trial or implant system, an overall Beck Depression Inventory II score > 24 ,

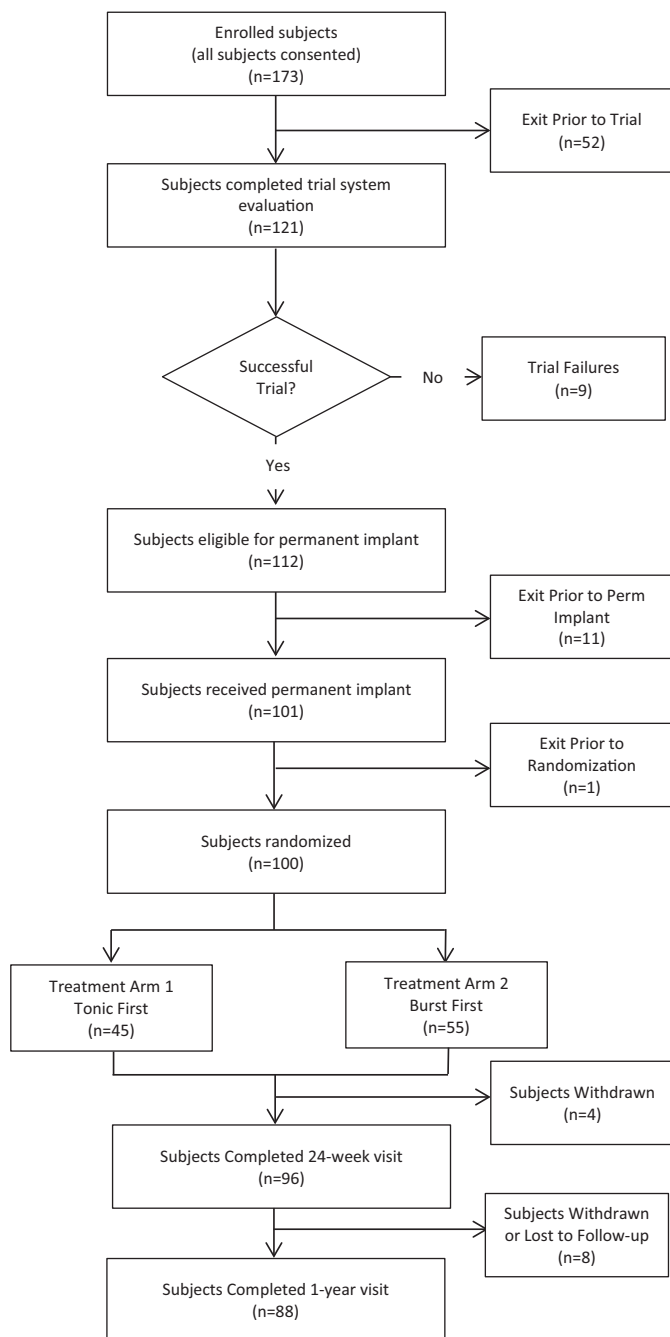


Figure 1. CONSORT [Correction added on 08 January 2018, after first online publication: Figure 1 has been updated to complete the Consort study].

or who were already participated in a clinical trial with an active treatment arm were excluded from the study. Full inclusion and exclusion criteria for the study are found in a previous manuscript detailing the study design of the clinical trial (12). In collaboration with the FDA, the study was designed with an enrichment strategy aimed at minimizing variability and assessing the efficacy of burst compared to an already approved SCS stimulation mode: Following a within-subject cross-over design, participants were limited to those who achieved adequate pain relief during a traditional tonic trial evaluation. Those with a successful tonic trial (at least 50% improvement in patient-reported pain) were implanted with a rechargeable neurostimulation system (Prodigy™, Abbott, Plano, TX, USA) that

can deliver both tonic and burst (BurstDR™, Abbott, Plano, TX, USA) stimulation modes. Leads were placed to maximize paresthesia coverage of the primary areas of pain using tonic stimulation. Subjects were randomly assigned (1:1) to one of two groups. Subjects in group 1 received 12 weeks of tonic stimulation followed by 12 weeks of burst stimulation. Subjects in group 2 received 12 weeks of burst stimulation followed by 12 weeks of tonic stimulation. Assessments were performed at 6, 12, 18, and 24 weeks following randomization. During the open-label phase of the study after 24 weeks, participants were assessed every six months for up to two years following randomization. Assessments included seven-day Pain Diaries prior to each study visit, SF-36v2™ Health Survey (13) for quality of life assessment, the pain catastrophizing scale (PCS) to assess the quality of thoughts and feelings during pain, the Oswestry Disability Index 2.1a (ODI) to assess a person's functional level, and paresthesia mapping. The principal investigator, sub-investigator, or research coordinator at each study site collected study data from the subjects at each visit. Complete details are described in the study design manuscript (12). Neither patients nor investigators were blinded to the treatment sequence since detectable differences in paresthesia between the two waveforms were expected [Correction added on 08 January 2018, after first online publication: the preceding sentence has been updated to clarify the statement.]. To recruit patients into the study, a study website, study poster, study brochure, and other materials were developed which provided information evaluating the safety and effectiveness of the investigative device with two stimulation modes, including a new stimulation mode called burst. General information on neurostimulation therapy, surgical procedures, study time commitment, and eligibility criteria were provided. The information contained in recruitment materials made patients aware than an investigational stimulation mode was part of the study without imparting any biases or expectations about the new mode. All study-eligible subjects underwent a consent process prior to initiation of study-related activities.

Initial device programming occurred at the activation visit, which took place approximately 2–3 weeks after system implantation. For tonic stimulation, pulse width was programmed in the range of 100–500 μ sec with frequencies typically between 30 and 100 Hz, and at amplitudes producing comfortable paresthesia according to each individual patient's perception. For burst programming, 500 Hz stimulation was delivered in groups of five pulses with a 1 msec pulse width, with the five pulses repeated at a frequency of 40 Hz. After each burst, a passive repolarization (discharge) period occurs with a duration time defined by the resistance and capacitance of each patient's tissue. Target amplitude during burst stimulation programming was tailored to each individual patient's perceived comfort level. Programming occurred on as needed basis, during follow-up visits or during any unscheduled visits. Under the guidance of the investigative team, study sponsor personnel may have assisted with device programming but did not collect study data. All subjects received a Patient Programmer that enabled him or her to activate the ON and OFF positions and adjust amplitude within the prescribed range. Each subject also received a charging system to charge the device.

Unless specified, all statistical analyses were performed with a significance level of $p = 0.05$, and 95% confidence intervals were computed. The primary analysis for the primary endpoint was a noninferiority test of the difference in VAS score between tonic and burst stimulation. Assuming noninferiority of the VAS score during burst compared to tonic to be within 7.5 mm on the 100 mm VAS, with a type I error rate of 0.05, a minimum of 76 participants was

required to achieve 80% power to show noninferiority between tonic and burst stimulation.

Prior to analyzing the primary endpoint, a pretest was performed to check the assumption of equality of carryover effects. The primary analysis for the efficacy endpoint was a noninferiority test of the difference in the average overall VAS score between tonic and burst stimulation. An intention-to-treat analysis was conducted using data recorded at the 12- and 24-week visits for all randomized participants. Missing data were imputed using the hot-deck or last-observation-carried-forward (LOCF) method, as appropriate. Details of this analysis are explained elsewhere (12). If noninferiority of burst stimulation was established in the primary endpoint analysis, secondary endpoints were formally analyzed in a step-down process, where testing only continued if significant results were achieved. At the first nonsignificant result, all testing would stop. The first secondary endpoint was a VAS pain diary responder analysis determining the proportion of participants achieving a 30% or greater change from baseline in overall VAS score. Secondary endpoint #2 was an analysis of the presence of paresthesia to demonstrate the differences between the two stimulation modes. Finally, the secondary analysis of the VAS pain diary scores for average overall pain was the superiority test to demonstrate that the change in VAS score with burst stimulation is superior to that using tonic stimulation. The superiority test was accomplished using a two-sample *t*-test which was compared to a standard normal distribution with appropriate degrees of freedom to assess significance. The null hypothesis was rejected if the 95% upper confidence bound for the difference was less than 0 mm. Further details can be found in the study design manuscript (12). Additional analysis included within-subject difference for trunk and limb VAS score. Finally, appropriate descriptive statistics were used to characterize the safety profile of both stimulation modes.

RESULTS

Subjects were enrolled between January 2014 and May 2015. A total of 173 subjects gave consent and were enrolled across 20 investigational sites. Thirty-two subjects were excluded prior to the baseline visit, thus 141 subjects received baseline evaluations. An additional 20 subjects were excluded following the baseline visit [Correction added on 08 January 2018, after first online publication: the preceding sentence has been added to indicate the number of subjects excluded from the study.]. Of 52 patients who did not meet inclusion/exclusion criteria, 28 were screening failures, 17 subjects chose to withdraw from the study, and the investigator withdrew six subjects. One patient could not continue due to financial reasons. Thus, a total of 121 subjects underwent an evaluation using an SCS trial system with tonic stimulation. Nine subjects failed the trial evaluation while 12 subjects exited the trial for other reasons (four subjects were withdrawn by the investigator, 1 subject was a screening failure, 1 subject withdrew for financial reasons, 2 subjects exited because of an unrelated adverse event, and 4 for other reasons). A total of 100 subjects received a permanent implant and were randomized to either Treatment Arm 1 (tonic first/burst second, $n = 45$) or Treatment Arm 2 (burst first/tonic second, $n = 55$). Of the 100 randomized subjects, 96 subjects completed the 24-week follow-up for the primary endpoint (see CONSORT flowchart, Fig. 1). A total of 88 subjects completed the study visit one year after implant. Two of the subjects were lost to follow-up, three subjects chose to withdraw, the investigator withdrew one subject, and there were two deaths unrelated to the study or device.

Statistical methods were used to impute VAS scores for various reasons. Of the 100 randomized subjects, four subjects withdrew from the study before week 24, and their overall VAS score was imputed using the hot deck method, which replaces missing values of a visit for one subject with observed values during the same visit from another subject who shares similar characteristics observed by both cases. Three subjects underwent an invasive procedure for a clinically significant or disabling pain problem that was not present at baseline, and their overall VAS score was imputed using the LOCF method, if a previous observation was available, or using the hot deck method if a previous observation was not available during that stimulation period. Imputations were also made due to medication increases. An independent, blinded pharmacist reviewed all randomized subjects' medication usage. During the first 12 weeks of the study, six subjects had medication increases and thus, trial baseline overall VAS score was used to impute these subjects' 12-week overall VAS score (i.e., no benefit of SCS was imputed). Similarly, during the next 12 weeks of the study, 15 subjects had medication increases and their trial baseline overall VAS score was imputed as the 24-week overall VAS score [Correction added on 08 January 2018, after first online publication: the preceding paragraph has been revised to clarify the results of the study.].

Subject Demographics and Baseline Characteristics

Table 1 shows basic subject demographics, primary diagnosis, and pain duration for all baseline and randomized subjects. The average age of the subjects was 59.1 ± 13.5 years, and 60% of the subjects were female. Most subjects were diagnosed with either FBSS (59/141, 41.8%) or radiculopathy (52/141, 36.9%). Subjects had experienced chronic pain for an average of 12.8 ± 10.9 years prior to entering the study. Demographics and baseline characteristics were comparable between the two randomized arms.

SUNBURST Study Effectiveness Results

Primary Effectiveness

By intention-to-treat (ITT) analysis the estimated difference in the overall VAS score between burst and tonic stimulation was -5.1 mm, and the 95% upper confidence bound for the mean difference between burst and tonic stimulation was -1.14 , which is less than the noninferiority margin of 7.5 mm. Therefore, the primary endpoint was met, demonstrating that burst stimulation is noninferior to tonic stimulation ($p < 0.001$). In addition to demonstrating noninferiority, superiority of burst stimulation over tonic stimulation was also achieved ($p < 0.017$) (Fig. 2).

Analysis of carry-over effects examined differences in VAS scores for burst and tonic from baseline. The within-subject sums of burst-baseline and tonic-baseline in arm 1 and arm 2 were not significantly different at the 0.15 significance level $p = 0.883$, suggesting that any carryover effect did not impact these results [Correction added on 08 January 2018, after first online publication: the preceding sentence has been updated to correct the significance values.].

Secondary Effectiveness

Clinically significant reductions, or responder rates, were defined in the study protocol as a decrease in the overall daily VAS score from baseline by at least 30%. A total of 69/100 subjects (69.0%) responded to tonic stimulation, burst stimulation, or both. For the individual stimulation modes, 60.0% (60/100) of subjects were responders to burst stimulation and 51.0% (51/100) of subjects were responders to tonic stimulation (Fig. 3).

Table 1. Demographics, Primary Diagnosis, and Pain Duration.				
Variable	Subjects with baseline visit (N = 141)	Randomization (N = 100)		p-value
		Arm 1: (tonic/burst) (N = 45)	Arm 2: (burst/tonic) (N = 55)	
Age				
Mean ± SD (N)	59.1 ± 13.5 (141)	58.8 ± 13.6 (45)	60.4 ± 13.4 (55)	0.562*
Gender, n/N (%)				
Female	85/141 (60.3%)	26/45 (57.8%)	31/55 (56.4%)	0.887 [†]
Male	56/141 (39.7%)	19/45 (42.2%)	24/55 (43.6%)	
Weight (lb)				
Mean ± SD (N)	191.7 ± 48.0 (141)	189.0 ± 42.8 (45)	195.0 ± 47.1 (55)	0.509*
Height (in)				
Mean ± SD (N)	66.7 ± 4.4 (141)	66.2 ± 4.4 (45)	66.8 ± 4.4 (55)	0.502*
Marital status, n/N (%)				
Married	107/141 (75.9%)	39/45 (86.7%)	41/55 (74.5%)	0.479 [‡]
Separated/divorced	13/141 (9.2%)	2/45 (4.4%)	4/55 (7.3%)	
Single	8/141 (5.7%)	2/45 (4.4%)	3/55 (5.5%)	
Widowed	13/141 (9.2%)	2/45 (4.4%)	7/55 (12.7%)	
Diagnosis, n/N (%)				
Arachnoiditis	1/141 (0.7%)	1/45 (2.2%)	0/55 (0.0%)	0.189 [‡]
CRPS I/CRPS II	2/141 (1.4%)	0/45 (0.0%)	2/55 (3.6%)	
Degenerative spine disease	7/141 (5.0%)	1/45 (2.2%)	2/55 (3.6%)	
Failed back surgery syndrome	59/141 (41.8%)	15/45 (33.3%)	27/55 (49.1%)	
Neuritis/neuropathy/neuralgia	3/141 (2.1%)	0/45 (0.0%)	2/55 (3.6%)	
Postoperative chronic pain	5/141 (3.5%)	1/45 (2.2%)	2/55 (3.6%)	
Radiculopathies	52/141 (36.9%)	21/45 (46.7%)	17/55 (30.9%)	
Chronic pain (Non-Postop)	12/141 (8.5%)	6/45 (13.3%)	3/55 (5.5%)	
Pain duration (years)				
Mean ± SD (N)	12.8 ± 10.9 (141)	11.1 ± 9.5 (45)	15.1 ± 12.1 (55)	0.075 [§]
*Two sample <i>t</i> -test.				
†Chi-square test.				
‡Fisher's exact test.				
§Wilcoxon rank sum test.				

Information on programming amplitudes was available for 92 subjects. Average amplitudes for burst stimulation was 1.73 ± 1.05 mA (range 0.2–4.4) while average amplitude for tonic stimulation was 6.42 ± 4.00 (range 0.8–18.5). Data for paresthesia mapping at both 12 and 24 weeks were available for 73 subjects (Fig. 4). More than half of the subjects (45 out of 73 [61.6%]) were paresthesia-free using burst stimulation while only two subjects (2.7%) were paresthesia-free using tonic stimulation. In addition, 89.0% of

subjects (65/73) experienced a reduction in paresthesia or no paresthesia with burst stimulation compared to tonic stimulation. The mean area of paresthesia sensations on the body map for burst was significantly lower than that for tonic; only 4.5% of the mapped body segments had paresthesia with burst stimulation compared to 22.7% with tonic stimulation ($p < 0.001$; Table 2), which represents an 80.2% relative reduction in paresthesia area with burst stimulation vs. tonic stimulation.

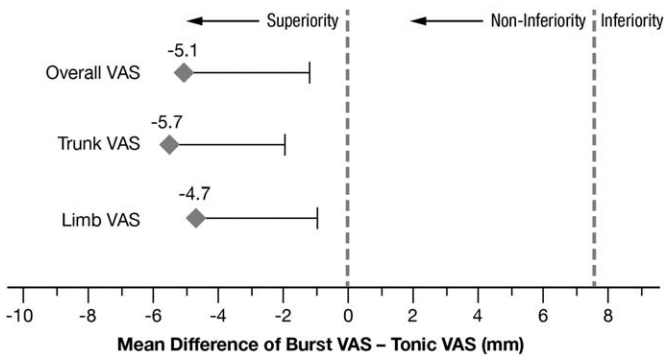


Figure 2. SUNBURST Study Effectiveness Results: An ITT analysis demonstrated that burst stimulation was noninferior to tonic stimulation and the primary endpoint of the study was met. In addition to noninferiority, statistical superiority of burst stimulation over tonic stimulation in overall VAS ($p < 0.017$), trunk VAS ($p < 0.013$), and limb VAS ($p < 0.045$) were also achieved. Trunk VAS and Limb VAS superiority analyses were done *post-hoc*.

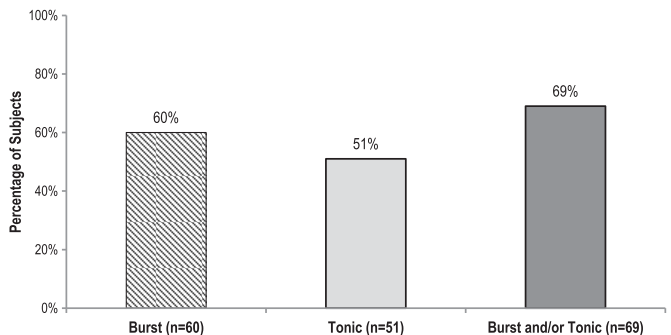


Figure 3. Clinically significant reductions ($\geq 30\%$), or responder rate, in overall VAS from baseline show that a total of 69/100 (69%) of all randomized subjects achieved clinically significant pain reductions using the investigational device with two different stimulation modalities. Sixty percent (60/100) of subjects responded to burst stimulation while 51% (51/100) of subjects responded to tonic stimulation.

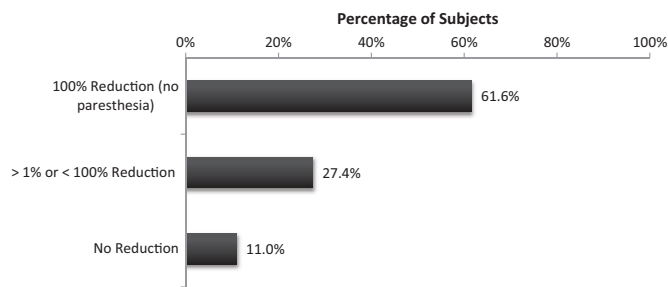


Figure 4. Paresthesia reduction during burst stimulation. Data on paresthesia mapping were available for 73 subjects. During burst stimulation, 61.6% (45/73) of subjects reported no paresthesia sensations while 27.4% (20/73) of subjects reported some reduction in paresthesia sensations on the body map during burst stimulation as compared to tonic stimulation.

Additional Endpoints

Trunk and Limb Pain, Worst Overall VAS, and 50% Overall VAS Reduction

As was the case for the primary overall VAS score analysis, equality of carryover effect was verified for both trunk and limb VAS scores (data not shown). VAS scores for trunk and limb pain were assessed after 12 weeks of each stimulation mode. Trunk VAS scores following burst stimulation were 5.7 mm lower than scores following tonic stimulation (90% CI: -9.5 , -2.0) (Fig. 2). Similar results were seen with limb pain, with lower VAS scores following burst stimulation than VAS scores following tonic stimulation (90% CI: -8.5 , -0.9) (Fig. 2). *Post hoc* analysis revealed that burst stimulation provided superior pain relief compared to tonic stimulation for both trunk pain ($p < 0.013$) and limb pain ($p < 0.045$).

Descriptive endpoints included worst daily overall VAS score and 50% decrease in VAS pain diary scores for average daily overall pain. The worst VAS score for burst was lower than that for tonic stimulation by 4.1 points (90% CI: -8.2 , -0.1). The difference in within-subject sums of burst-baseline and tonic-baseline between arm 1 and arm 2 was $p = 0.734$, which was not statistically significant at the 0.15 significance level, suggesting that any carryover effect did not impact these results [Correction added on 08 January 2018, after first online publication: the preceding sentence has been updated to clarify the statement.]. More subjects experienced $\geq 50\%$ overall reduction in VAS score with burst stimulation than tonic stimulation (39 vs. 32) with fewer subjects experiencing $< 30\%$ reduction in overall VAS score with burst stimulation than tonic stimulation (40 vs. 49).

Subject Satisfaction and Stimulation Preference

Subjects were asked to rate overall level of satisfaction with the device at each follow-up visit, and to report stimulation mode preference at the 24-week visit. After 24 weeks, 78.1% (75/96) of subjects were satisfied with the device during both stimulation modes while 4.2% (4/96) of subjects were dissatisfied (Table 3). Significantly more subjects preferred burst stimulation over tonic stimulation (70.8% vs. 18.8%, $p < 0.001$), while 18 subjects (18.8%) preferred tonic stimulation over burst stimulation, and 10 subjects (10.4%) had no preference between the two stimulation modes (Fig. 5). Of the subjects that chose burst stimulation as his/her preferred stimulation mode, 47.1% (32/68) cited a "lack of paresthesia" as the primary reason for preferring burst stimulation while 45.6% (31/68) cited "better pain relief." One subject in this cohort (1/68) cited "prefer paresthesia" as the reason for preferring burst stimulation, while four subjects (4/68) cited "other" as the reason for preferring burst stimulation (Fig. 6a). In the cohort of subjects who preferred tonic stimulation over burst stimulation, 44.4% (8/18) cited "better pain relief" as the reason for preferring tonic stimulation while an additional 44.4% (8/18) preferred the paresthesia sensation associated with tonic stimulation. Only one subject in the cohort (1/18) reported a lack of paresthesia sensation as the reason for preferring tonic stimulation, while another subject (1/18) cited "other" reasons for preferring tonic stimulation over burst stimulation. In this study, 10.4% of subjects (10/96) had no preference for one stimulation mode over the other.

Psychosocial Health and Physical Function Measures

In addition to VAS pain scores, several psychosocial and physical function assessments were examined over the course of the study. The Short Form McGill Pain Questionnaire (SF MPQ-2) was used to assess both the sensory and affective components of pain. Pooled results showed improvement from baseline scores with both burst and tonic stimulation, but no clinically significant differences between the two stimulation paradigms (difference of 0.4 ± 3.6 for the physical component score, and 0.7 ± 4.1 for the mental component score). Pooled results from the Patient Global Impression of Change questionnaire revealed that overall, the proportion of subjects whose global impression was moderately better, better, or a great deal better was comparable between the two stimulation modes (72/97 for burst stimulation vs. 71/96 for tonic stimulation). Higher scores on the PCS indicate that the experience of pain greatly affects thoughts and feelings of the subject (14). Neither stimulation modes produced clinically meaningful changes on the PCS, likely due to the relatively low baseline scores observed in the study population. Each subject's depression was evaluated using the Beck Depression Inventory®-II (BDI-II). Subjects with moderate to severe

Table 2. Paresthesia Distribution (Percentage of Body Map Exhibiting Paresthesia Sensations).

Randomization	Arm1: tonic/burst	Arm 2: burst/tonic	Pooled
Burst			
Mean $\pm$ SD (N)	3.9 $\pm$ 6.6 (37)	5.0 $\pm$ 10.5 (36)	4.5 $\pm$ 8.7 (73)
Tonic			
Mean $\pm$ SD (N)	20.1 $\pm$ 14.3 (37)	25.3 $\pm$ 18.1 (36)	22.7 $\pm$ 16.3 (73)
Burst-Tonic			
Mean $\pm$ SD (N)	-16.2 ± 14.5 (37)	-20.3 ± 19.5 (36)	–
Burst-Tonic Average $\pm$ Pooled SD Across Arms	-18.2 ± 8.6		
p-Value	$< 0.001^*$		

*Based on a *t*-distribution with $n_1 + n_2 - 2$ degrees of freedom, where n_1 and n_2 are the number of subjects in each arm.

Table 3. Satisfaction Level by Stimulation Mode at Week 24.

Stimulation mode		Tonic	
Satisfaction level		Dissatisfied*	Satisfied**
Burst	Dissatisfied*	4/96 (4.2%)	7/96 (7.3%)
	Satisfied**	10/96 (10.4%)	75/96 (78.1%)

*Dissatisfied is a combination of "Very Dissatisfied," "Dissatisfied," and "Neither Satisfied Nor Dissatisfied."
 **Satisfied is a combination of "Satisfied" and "Very Satisfied."

depression (a score of 24 or more on the BDI-II) at baseline were not eligible to continue in the study. Thus, it is not surprising that no significant differences were seen between the burst and tonic arms ($p = 0.230$). Baseline pooled mean scores were 10.1 ± 6.0 , indicating minimal depression (defined as 0–13) and there was little change in scores from baseline to follow-up in either treatment arm. Specifically, pooled mean scores for burst stimulation was 8.9 ± 7.6 while pooled mean scores for tonic stimulation was 9.6 ± 7.0 . Each subject's disability was assessed using the validated ODI (15), with higher percentages indicating a greater disability. Results from this study showed that subjects experienced a reduction in ODI from baseline following both stimulation modes, however there was no significant difference between burst and tonic stimulation ($p = 0.991$).

Device, Medication, and Recharging Data

The number of programming sessions was higher during tonic stimulation as compared to burst stimulation, with a total of 141 programming sessions during both scheduled and unscheduled visits occurred for tonic stimulation and 117 programming sessions for burst stimulation. Both treatment arms showed similar device information with 53% of subjects receiving 2 leads and 38% of subjects receiving 1 lead. IPG placement was primarily on the left side (83%) and the upper buttock (73%). An external pharmacist reviewed and categorized the use of pain medication during the study. Results showed that from the time of device activation, 9.4% of subjects (9/96) increased medication usage during burst stimulation while 12.5% of subjects (12/96) increased medication usage during tonic stimulation. Recharging data of all available subjects was collected and analyzed at follow-up visits including unscheduled programming; missing data was not imputed. Recharging data were similar between groups. Overall, the majority of subjects in both groups recharged their IPG as part of their normal routine (66.7% [10/15] for burst stimulation, 68.2% [15/22] for tonic stimulation) while other

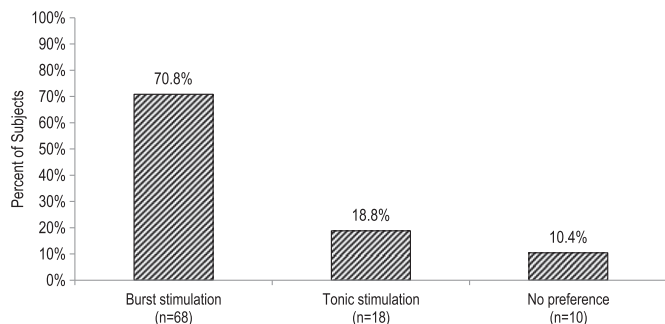


Figure 5. Patient-reported stimulation preference. At the 24-week follow-up, subjects were asked to choose their preferred mode of stimulation (burst stimulation, tonic stimulation, or no preference). The majority of subjects (70.8%) preferred burst stimulation over tonic stimulation (68 vs. 18, $p < 0.001$), while 10.4% of subjects had no stimulation preference.

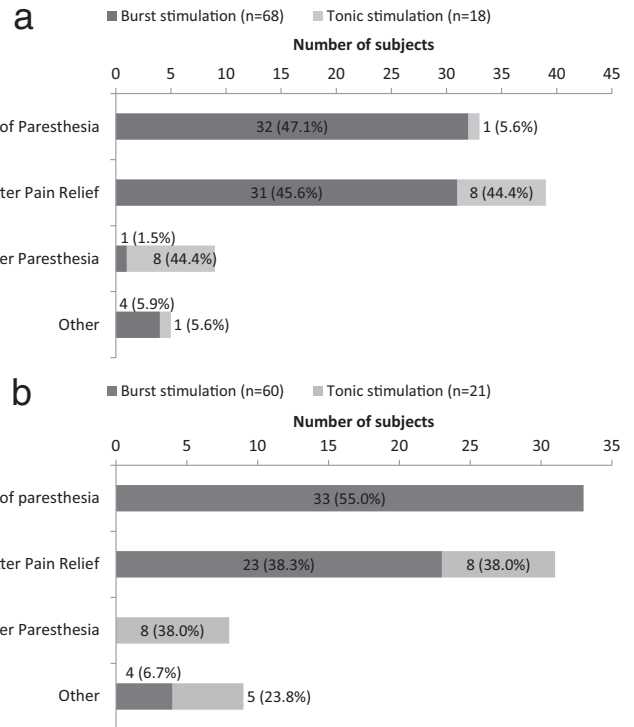


Figure 6. Reasons for stimulation preference. Subjects who preferred one stimulation mode over the other were asked to indicate the main reason for their preference. (a) At 24 weeks, of the 68 subjects who preferred burst stimulation, the majority cited "lack of paresthesia" (32/68 subjects, or 47.1% of the cohort) or "better pain relief" (31/68 subjects or 45.6%) as the reasons for preferring burst stimulation. Of the 18 subjects who preferred tonic stimulation, the majority cited "better pain relief" (8/18 subjects or 44.4%) or "prefer paresthesia" (8/18 subjects or 44.4%) as the main reasons for preferring tonic stimulation. (b) At 1 year follow-up, 88 subjects reported reasons for stimulation preference, 7 of whom had no preference for either burst or tonic stimulation. Of the 60 subjects who preferred burst stimulation over tonic stimulation, the majority (33/60 or 55.0%) of the cohort cited "lack of paresthesia" as the reason, while an additional 23/60 (38.3%) of the cohort cited "better pain relief" as the reason for preferring burst over tonic stimulation. Only 4/60 (6.7%) of the cohort had other reasons for choosing burst stimulation. There were 21 subjects who preferred tonic stimulation at 1 year follow-up, with 8/21 (38.0%) citing "preference for paresthesia" and another 8/21 (38.0%) citing "better pain relief" as the reasons for preferring tonic stimulation. An additional 5/21 (23.8%) of the cohort had other reasons for preferring tonic stimulation.

subjects recharged when the battery is less than 50% depleted or during the recommended timeframe. At the 18-week follow-up, 63.6% (28/44) of burst subjects and 56.9% (29/51) of tonic subjects recharged their IPGs on a weekly basis with 100% (44/44) of burst subjects and 88.2% (45/51) of tonic subjects recharging as part of the normal routine. At 24 weeks, 55.6% (25/45) of burst subjects and 64.0% (32/50) of tonic subjects recharged their IPGs on a weekly basis with 93.3% (42/45) of burst subjects and 92.0% (46/50) of tonic subjects recharging as part of the normal routine.

One-Year Outcomes

A total of 88 subjects completed the one-year visit; data were not imputed if missing. Stimulation preference was sustained through one year, with 68.2% (60/88) of subjects preferring burst stimulation, 23.9% (21/88) of subjects preferring tonic stimulation, and 8.0% (7/88) of subjects having no preference of one stimulation mode over the other. Reasons for stimulation preference at one year are

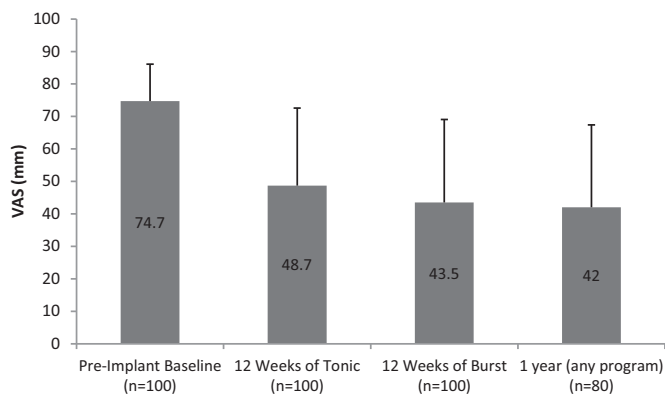


Figure 7. Sustained pain relief after 1 year of therapy. A total of 88 subjects completed the 1 year visit, but data were not imputed if missing. A total of 80 subjects reported pain diary scores at the 1 year visit. Following 12 weeks of tonic stimulation and 12 weeks of burst stimulation, average VAS score was 48.7 mm and 43.5 mm, respectively. After 1 year of therapy, pain relief was sustained across the entire subject cohort with an average 42 mm VAS score.

shown in Figure 6b. Specifically, of the 60 subjects who preferred burst stimulation at one year, 55.0% (33/60) cited “lack of paresthesia” as the reason for preference, while 38.3% (23/60) of subjects cited “better pain relief” and 6.7% (4/60) of subjects cited “other” as the reasons for preferring burst stimulation. Of the 21 subjects who preferred tonic stimulation at one year, 38.0% (8/21) of the subjects cited a “preference for paresthesia” as the reason for choosing tonic stimulation while an additional 38.0% (8/21) of subjects cited “better pain relief” and 23.8% (5/21) of subjects cited “other” as the reasons for preferring tonic stimulation. As shown in Figure 7 significant reductions in mean VAS scores also persisted through one year of therapy. Additionally, at the one-year visit, 49% (43/88) of subjects reported being very satisfied with the therapy, and 40% (35/88) reported being satisfied with the therapy. The remaining subjects were neither satisfied nor dissatisfied (7%; 6/88), dissatisfied (2%; 2/88), or very dissatisfied (2%; 2/88). Examination of subjects most used programs revealed that 68% (60/88) indicated burst as their most used program type.

SUNBURST Study Safety Results

There were no unanticipated adverse events (AEs) reported in the study. As expected, the AE profile of the device was similar to other

SCS studies. A total of 158 AEs were reported during the study, 94 (59.5%) of which were considered to be non-study related. Twenty-one (21) events were considered serious adverse events (SAEs) and were reported in a total of 16 subjects (9.2%). Of all SAEs reported, only two events occurring in two subjects (1.2%) were considered study-related. Both study-related SAEs occurred between the enrollment phase and activation phase of the study and included one event of persistent pain and/or numbness and one unsuccessful lead placement. Two deaths occurred during the study, both of which were un-related to the study or device [Correction added on 08 January 2018, after first online publication: the preceding sentence has been updated to correct the number of deaths.]. Non-study related SAEs occurring between enrollment and activation of the study included events such as abdominal pain, femur fracture, hip pain/hip replacement, and low potassium levels. Following activation, non-study related SAEs included 1 infection, 1 subject with a scheduled right total knee arthroplasty, 1 subject with shortness of breath, 1 infection, among others. Table 4 summarizes all the reported adverse events.

DISCUSSION

The pivotal SUNBURST study—the first large, prospective, multi-center, randomized cross-over study of burst stimulation—was designed to provide evidence to support U.S. FDA approval of the burst spinal cord stimulation mode as a treatment for chronic intractable pain, using a single device which allows patients to use both tonic and burst stimulation (U.S. FDA approval October 4, 2016). The primary effectiveness endpoint of the study was met, and burst stimulation was established to be not only noninferior but also superior to traditional tonic stimulation in overall VAS improvement. Although all subjects responded to tonic stimulation during the trial evaluation, burst stimulation was preferred by over two-thirds of subjects (70.8%). At the time of this manuscript, the authors are unaware of previous randomized controlled trials in neuromodulation in which subjects experienced two modes of stimulation for treatment of chronic, intractable pain. The preference for burst stimulation over tonic stimulation—irrespective of the absolute differences in VAS scores—may have significant clinical implications, particularly in patient-perceived conditions such as chronic pain. In addition, clinical situations in which burst stimulation may be used in place of tonic stimulation (i.e., in patients who experience waning pain relief with tonic stimulation or in nonresponders to tonic stimulation) were not evaluated in the SUNBURST study, but future studies are warranted and may help guide clinical practice in chronic pain.

The main criticisms of crossover trials include the potential carryover and order effects inherent in this type of study design, both of which can bias the results. Specifically, carry-over effects may result in the residual influence of treatments on subsequent treatment periods; order effects may occur when the order in which treatments are administered affect the outcome. Washout periods are typically used to minimize any carry-over effects. However, previous stimulation studies suggest that 25–80% of patients fail to comply with the study protocol when asked to undergo periods without stimulation (16,17), making washout periods difficult to implement. In the current study, pain relief assessments occurred at 12 weeks after changing stimulation modes, which was adequate time to ensure that any residual of the previous therapy would not influence the assessment of the current therapy (18,19). To further support

Table 4. Summary of Adverse Events (AE) for All Enrolled Patients (N = 173).

AE description	Number of events	Number of subjects	% of subjects (n/N*)
SAEs			
Study-related	2	2	2% (2/100)
Non-study related	19	15	15% (15/100)
SAE subtotal	21	16**	16% (16/100)
Non-SAEs			
Study-related	62	31	31% (31/100)
Non-study related	75	44	44% (44/100)
Non-SAE subtotal	137	58**	58% (58/100)
All AEs total	158	67**	67% (67/100)

*Subjects at risk = all subjects enrolled in study.

**Some subjects experienced more than one event.

this, the equality of carryover effects for overall VAS score was assessed in this current study by summing the differences in VAS scores for burst and tonic from baseline. As mentioned previously, results suggest that any potential confounding effects of carryover were minimized [Correction added on 08 January 2018, after first online publication: this sentence has been updated to clarify the statement.].

Enrichment design strategies in this study aimed to decrease variability and effectively evaluate burst stimulation as compared to tonic stimulation. The within-subject comparison, or cross-over study design, helps to control variability by ensuring that lead location, programming, and other subject-specific variables are held constant (20). In studies randomizing subjects to separate experimental and control groups, it is possible that patient bias toward the new technology vs. the standard or traditional treatment may confound study results. At the time of this study, only a tonic trial stimulator was available. Thus, only subjects who responded to tonic stimulation during the trial evaluation period were randomized, which minimized subject attrition and allowed investigators to compare two therapies in subjects who are accepted as candidates for SCS. This however favors the tonic group by inclusion of tonic responders. At the timing of the preparation of this manuscript, a trial evaluation system with burst stimulation has become available and future studies should utilize burst stimulation during the trial evaluation. Furthermore, subjects with marked depression symptoms (overall BDITM-II score greater than 24 or a score of 3 at the screening visit on question 9, which relates to having suicidal thoughts or wishes) were excluded from this study, providing an intrasubject comparative analysis of pain relief that was less exposed to affective components which might indirectly influence a subject's assessment of therapy. By limiting the study to subjects with low to neutral affective scores, we limited the ability to quantify a change in the affective dimension of pain in both arms.

It is well known that pain response is complex and multidimensional, encompassing both sensory and emotional responses. In fact, the Initiative on Methods, Measurement, and Pain Assessment on Clinical Trials (IMMPACT) (21) recommendations suggest core outcome measures for clinical trials of chronic pain include assessments not only for pain but also for physical and emotional functioning, patient-reported improvement and satisfaction (22). In accordance with these recommendations, assessments beyond VAS were included in this study. As mentioned previously, pooled SF-36 scores for burst stimulation were higher than for tonic stimulation, however, the difference between the two stimulation modes was not statistically significantly different. It is worth noting that the baseline score for the mental component of the SF-36 (48.7) is near the normative mean of 50.0 for this subscale (13), suggesting that the subjects in this study were nearly representative of the general chronic pain population (23). However, the average baseline PCS score of all randomized subjects was 20.4, well below that which is considered a clinically relevant level of pain catastrophizing (to be considered clinically catastrophizing, a score of greater than 30 is required on the PCS scale (24)). The exclusion of subjects with a BDI-II score of >24 may have contributed to the low baseline scores for the PCS, as depression has been shown to be directly correlated with catastrophizing (25,26). Therefore, a significant improvement in PCS following either burst or tonic stimulation is not to be expected. In addition, neither burst nor tonic stimulation produced clinically meaningful changes on the ODI. One reason for this observation may be due to the

relatively low baseline scores observed in this population. The baseline score for the ODI was 49.1, which is below what is typically seen for chronic pain patients (typical scores in the 61–80 point range (27)). The exclusion of subjects with a BDI-II score of >24 may have contributed to this low baseline ODI score, as depression has been shown to be directly correlated with disability (28). Thus, in light of the low baseline ODI scores, a significant improvement would not necessarily be expected. Studies in more typical chronic pain patient populations might result in significant improvements in these other components of pain, as suggested by previous studies (7,10), and further investigations in such populations are warranted. More importantly, these data suggest that management of chronic pain requires individualized and personalized therapy with the recognition of pain medicine specialists that improvement in one aspect of chronic pain may not be associated with improvement in other aspects. In other words, pain is perceived differently in varying contexts, resulting in very distinct experiences (29).

Limitations

As with all studies, this pivotal study is not without its limitations. Due to the cross-over design, assessments of changes in pain across time cannot be made without losing the benefits of the within-subjects design. Much of the literature for chronic pain treatments focuses on a calculated change in pain from baseline to follow-up—typically defined as a minimal clinically important difference of 30% from baseline. However, this study was not intended for such an analysis and any inspection of the similar results in our study will lead to limited conclusions, at best. Furthermore, although there were small differences in VAS scores between burst and tonic stimulation and the study was conducted in tonic responders, there was a preference for burst stimulation, with 70.8% of subjects in this study preferring burst stimulation over tonic stimulation (68 vs. 18, $p < 0.001$). As mentioned previously, this preference for burst stimulation may have significant clinical implications, but future studies are warranted. Moreover, the study protocol included testing all patients with tonic stimulation during the initial screening process as the trialing process with burst stimulation was not available at that time. Therefore, it is conceivable that in the future patients will have an option of using burst stimulation as the screening for permanent implantation. A separate study is needed to establish whether such an approach is more relevant for patients with specific pain features and types. In addition, this analysis did not evaluate the concordance of paresthesia to pain locations. Rather, the focus of this analysis was to compare the amount of paresthesia each subject experienced during burst vs. tonic stimulation. Concordance of paresthesia with pain locations was outside the scope of this study's primary aim and may be assessed in a future analysis. Furthermore, as all subjects in this study needed to respond to traditional tonic SCS as a requirement for randomization, this study was unable to assess the effectiveness of burst stimulation in subjects who had failed traditional tonic SCS. Other studies, however, have suggested that burst stimulation may be used to salvage chronic pain patients who fail to respond, or who have over time become poor responders to traditional tonic stimulation (8,9). Future studies are needed to confirm these preliminary findings.

Since burst stimulation is a relatively new technology in the United States, there was limited experience in optimizing burst programming during the execution of this study. This may have resulted in less-than-optimal pain relief with burst stimulation in

some subjects. In fact, programming parameters in the beginning of the study were not standardized, but over the course of the study, a more standardized approach with lower amplitudes was implemented. To more formally evaluate this, an exploratory programming optimization sub-study (SUNBURST Programming Sub-Study) was done with a small cohort of SUNBURST study subjects ($n = 32$) across 8 of the 18 centers participating in the study. Only subjects who had completed the 24-week primary endpoint were enrolled in the sub-study. Burst programming was optimized and subjects were evaluated after experiencing the new programming for two weeks. Details of the rationale, methods, and results of the study will be explained in a future publication. In brief, the majority of subjects optimized with burst programming experienced additional symptom improvement and/or reductions in pain intensity and stimulation-related sensations. The sub-study as well as guidance from our European colleagues has led to further understanding of burst programming.

Future Directions

Now that a trial evaluation system with burst stimulation is available, future studies should compare the efficacy of burst stimulation with traditional tonic stimulation utilizing both stimulation modes during the evaluation period. Confirmation of sustainable pain relief using a device with both stimulation modes should also be assessed. Studies should also evaluate the role that passive and active recharge may play in the clinical effects associated with burst stimulation. Preliminary studies have suggested that mechanistic differences exist between burst stimulation and traditional tonic stimulation (30–32). Future studies should also focus on further elucidating the potential mechanism of action behind burst stimulation. To that end, a small cohort of subjects in the current study underwent 18-fluorodeoxyglucose-Positron Emission Tomography scans to evaluate neural activity differences during tonic and burst stimulation. Details of this sub-study, along with an analysis of the results, will be described in a future publication.

CONCLUSION

This pivotal, prospective, multicenter, randomized, crossover study assessed the safety and effectiveness of a neurostimulation system, which enables the use of both tonic and burst stimulation in a single device. The SUNBURST study demonstrated that burst spinal cord stimulation is safe and effective. Burst stimulation efficacy was not only noninferior but also superior to tonic stimulation for the treatment of chronic pain. Burst stimulation provided several additional advantages and is preferred by over two thirds of subjects exposed to both modalities. However, it is important to note that a significant minority of patients preferred tonic stimulation. Thus, having the ability to provide both tonic and burst stimulation in a single device has advantages.

Authorship Statements

Timothy Deer, MD, Konstantin V. Slavin, MD, Kasra Amirdelfan, MD, substantively contributed to the conception and design of the clinical trial and with the acquisition of data, and assisted with data analysis and interpretation, and manuscript preparation. Richard B. North, MD, substantively contributed to the conception and design of the clinical trial and assisted with the analysis and interpretation of the data and document preparation. Allen W. Burton, MD,

substantively contributed to the conception and design of the clinical trial and assisted with the acquisition of data and document preparation. Thomas L. Yearwood, MD, PhD, contributed to the acquisition of the data and assisted with the analysis and interpretation of data and document preparation. Ed Tavel, MD, substantively contributed to the acquisition of data and assisted with document preparation. Peter Staats, MD, assisted with the conception and design of the clinical trial, analysis and interpretation of data, and document preparation. Steven Falowski, MD and Jason Pope, MD, contributed to the acquisition of data and assisted with analysis and interpretation of data, and document preparation. Rafael Justiz, MD, Alain Y. Fabi, MD, Alexander Taghva, MD, Richard Paicius, MD, Timothy Houden, MD, and Derron Wilson, MD substantively contributed to the acquisition of data and assisted with document preparation. All authors reviewed and approved the final manuscript for submission.

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COMMENTS

This unblinded randomized prospective trial has been well written, such that the reader can make sense of the data quality and strength of conclusions reached.

It is not a strong study methodologically but it does address some of the commercial needs of the sponsor. It is more comforting to see such comparator studies “within device” rather than comparing between devices as there should be more equipoise.

As a clinical scientist you cannot draw too many firm conclusions about the outcomes between “tonic” versus “burst”.

Simon Thomson, MBBS
Basildon, Essex, United Kingdom

It is without any doubt a serious and well-constructed study proving that Burst stimulation is an effective method that adds to our armament in neurostimulation for chronic pain.

Y. Eugene Mironer, MD
Spartanburg, SC, USA

This is an excellent piece of work which I am sure has taken a huge effort on the part of the sponsor as well as the investigators. Having said that the work is typical of an industry sponsored study that is set for success. Given the tiny non-inferiority margin assumed of 7.5 mm it would have been unusual for a new technology not to demonstrate that difference versus an old technology.

While the study achieves the sponsor's stated aim it fails, in my view, to clarify/establish the role of burst stimulation in a neuromodulation algorithm. Given that the mean differences between the intervention and comparator have no clinical impact, I believe that the statistical differences are secondary and not of great clinical significance. It may well be that the investigators view burst as useful for reasons other than direct impact on pain scores. If so this should be clarified.

Sam Eldabe, MD
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Comments not included in the Early View version of this paper.