

CLINICAL HIGHLIGHTS

A publication delivering concise clinical data

DORSAL ROOT GANGLION (DRG) STIMULATION

ACCURATE Study: A Prospective, Randomized, Multi-Center, Controlled Clinical Trial to Assess the Safety and Efficacy of the Axium™ Neurostimulator System in the Treatment of Chronic Intractable Pain¹

As presented at the Ground Breaking Clinical Trials session at the 2015 Annual Meeting of the North American Neuromodulation Society (NANS) Meeting, Las Vegas, Nevada, USA

OVERVIEW

The dorsal root ganglion (DRG) is a subdural, intraspinal nerve structure that houses primary sensory neurons.² These cells process and filter non-painful and painful information from the periphery to the central nervous system. Why is DRG a good neuromodulatory target? Research has shown that during chronic pain, neurons associated with the injured anatomy exhibit measurable differences in membrane function, which allows for selective stimulation or activation without recruiting the non-painful neurons.³ This unique pathophysiology also makes stimulation highly selective and steerable to difficult to treat anatomies like the groin and foot. Finally, the minimal surrounding cerebrospinal fluid (CSF) may allow for a closer and more stable neuronal-electrode interface.

KEY TAKEAWAYS:

- The ACCURATE study is the largest randomized, controlled neuromodulation trial conducted in CRPS and peripheral causalgia[†] patients to provide evidence of safety and efficacy for market approval in the United States.
- The ACCURATE study **met its primary endpoint, demonstrating non-inferiority and superiority** over traditional SCS at three months.
- **Results were sustained at 12 months**, with DRG stimulation providing effective pain relief in 74.2% of patients, versus 53.0% in traditional SCS patients.
- In subjects who experienced paresthesia, **DRG stimulation confined the sensation to the primary area of pain in 94.5% of subjects versus 61.2% in the control.**
- DRG stimulation provided mean improvements over baseline in quality of life measures, psychological disposition, and physical/activity levels.
- The data from the ACCURATE study suggests that DRG stimulation may offer a meaningful option for patients suffering from chronic intractable pain conditions that are currently underserved by traditional SCS.

STUDY SUMMARY

- Objective: To assess the safety and efficacy of DRG stimulation compared to a commercially available SCS device.
- 152 subjects with chronic, intractable pain of the lower limbs were randomized to a DRG stimulation group or a control group (commercially available SCS device) across 22 investigational sites.
- A composite of safety and efficacy was used to define primary endpoint success provided the subjects met the following three criteria:
 - ≥ 50% pain relief in their primary area of pain at the end of the trial phase, *and*
 - ≥ 50% pain relief in their primary area of pain at three months post implant, *and*
 - Freedom from stimulation-induced neurological deficit through three months.
- Secondary and tertiary endpoints included:
 - Stimulation specificity
 - HR-QoL (SF-36)
 - Psychological disposition
 - Functional status (Brief Pain Inventory, BPI)
 - Patient satisfaction
- Three different populations were analyzed:
 - Intention-to-treat (ITT): All randomized subjects (n = 152)
 - Modified intent-to-treat (MITT): All subjects that received a trial stimulator (n = 139)
 - Implant only (IO): All subjects that received a fully implantable system (n = 114)

[†] Please note that in 1994, a consensus group of pain medicine experts gathered by the International Association for the Study of Pain (IASP) reviewed diagnostic criteria and agreed to rename reflex sympathetic dystrophy (RSD) and causalgia, as complex regional pain syndrome (CRPS) types I and II, respectively.



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SAFETY AND EFFICACY RESULTS THROUGH 12 MONTHS

- At three months, in the MITT population, **81.2% of the patients receiving DRG stimulation achieved the primary endpoint versus 55.7% of patients receiving traditional SCS stimulation** (Non-inferiority $p < 0.0001$; superiority $p = 0.0004$) (Figure 1).
- The durability of DRG stimulation was confirmed at 12 months, with 74.2% of the patients receiving DRG stimulation** ($n = 66$) having persistent reduction in pain as compared to only 53% of subjects receiving traditional SCS ($n = 66$). (Figure 1).
- At three months, in the IO population, 93.3% of patients receiving DRG stimulation achieved the primary endpoint versus 72.2% of patients receiving traditional SCS (Non-inferiority $p < 0.0001$; Superiority $p = 0.0011$) (Figure 2).
- At 12 months, in the IO population, 86.0% of patients receiving DRG stimulation ($n = 57$) had a $\geq 50\%$ improvement in VAS scores and freedom from a stimulation related neurological deficit versus 70.0% ($n = 50$) of patients receiving traditional SCS (Figure 2).
- There were no stimulation-induced neurologic deficits in either group and no unanticipated device-related adverse events in either group.

FIGURE 1. ANALYSIS OF MITT POPULATION AT 3 MONTHS AND 12 MONTHS

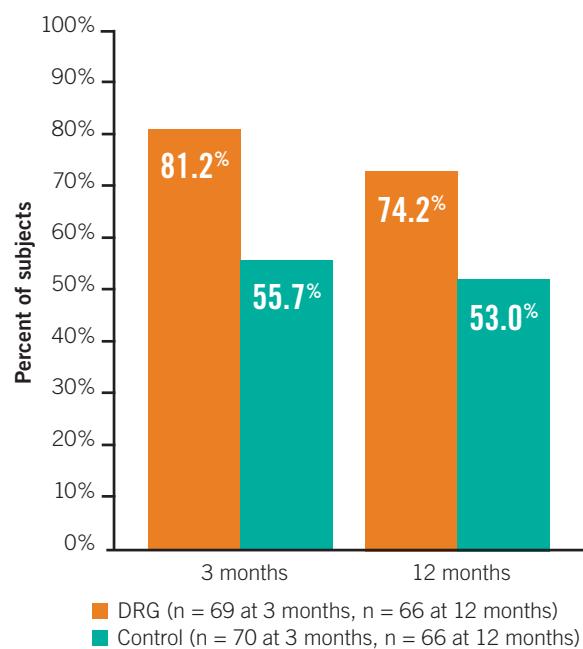
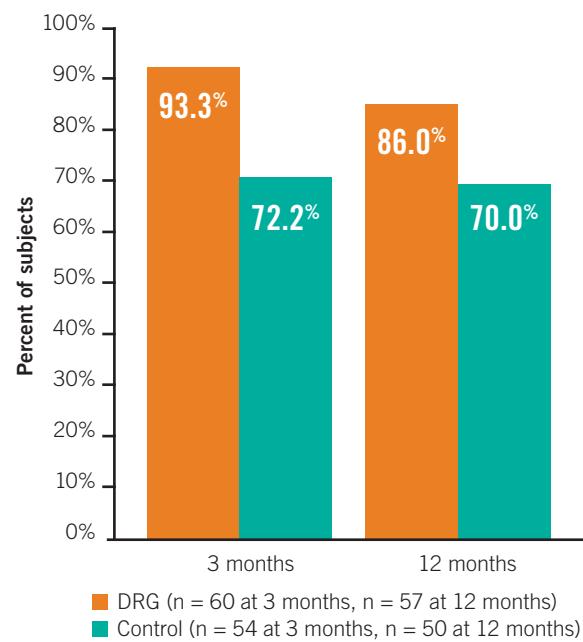


FIGURE 2. ANALYSIS OF IMPLANT ONLY POPULATION AT 3 MONTHS AND 12 MONTHS



SECONDARY AND TERTIARY ENDPOINT RESULTS

THROUGH 12 MONTHS:

- In this study cohort, twelve-month data suggests that more than a third of DRG stimulation subjects experienced greater than 80% pain relief in the absence of paresthesia. Future studies are needed to confirm this finding* (Table 1).
- In patients that experienced paresthesia, DRG stimulation confined paresthesia to the primary area of pain in 94.5% of subjects versus 61.2% of subjects in the control. In other words, at 12 months post implant, **subjects receiving traditional tonic stimulation were 7.1 times more likely to report feeling paresthesia in non-painful regions** as compared to subjects receiving DRG stimulation.

- At three months, DRG stimulation resulted in a mean improvement of 11.8 (95% CI [9.8,13.8]) over baseline in the physical component of the SF-36 QoL questionnaire compared to a mean improvement of 9.4 (95% CI [6.8, 12.0]) in the control group. Mean improvements were also seen in physical functioning, general health, social functioning, and all other components of the SF-36 QoL questionnaire.

- Results from the SF-36 QoL questionnaire were sustained at 12 months.
- Data from the Profile of Mood States (POMS) showed that subjects receiving DRG stimulation experienced greater improvements than the control group in Total Mood Disturbance at 3 months (19.9 vs. 13.1 respectively, 95% CI 0.1, 13.7) and 12 months post-implant (18.1 vs. 8.1, 95% CI 2.4, 17.4)
- Mean improvements were also seen in the Brief Pain Inventory (BPI) questionnaire following DRG stimulation at 3, 6, and 12 months post-implant.

TABLE 1. PAIN RELIEF FOR SUBJECTS WITH AND WITHOUT PARESTHESIA AT 12 MONTHS*

	DRG		CONTROL	
	Subjects with Paresthesia	Subjects without Paresthesia	Subjects with Paresthesia	Subjects without Paresthesia
N	35	19	43	6
% Mean VAS Decrease (SD)	81.4 (22.8)	86.0 (25.3)	70.2 (34.9)	48.1 (50.8)
% Median VAS Decrease	89.1	100.0	83.0	51.2
Difference between means 95% CI	-4.6 (-18.2, 8.9)		22.1 (-10.2, 54.5)	

* The instructions for use for the Control device requires the device be programmed for subjects to receive paresthesia. In addition, this endpoint was not adequately powered to detect significant differences in pain relief for subjects without and without paresthesia in this cohort.

1. Levy, R. and Deer, T., (2015). *A Prospective, Randomized, Multi-Center, Controlled Clinical Trial to Assess the Safety and Efficacy of the Spinal Modulation Axium™ Neurostimulator System in the Treatment of Chronic Pain*. Presented at NANS 2015.
2. Hasegawa, T., Mkiawa, Y., & Watanabe, R. (1996). Morphometric analysis of the lumbosacral nerve roots and dorsal root ganglia by magnetic resonance imaging. *Spine*. 21, 1005-1009.
3. Chung, J.M., & Chung, K. (2002) Importance of hyperexcitability of DRG neurons in neuropathic pain. *Pain Practice*, 2(2), 87-97.

Rx Only

Brief Summary: Prior to using these devices, please review the Instructions for Use for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use.

Indications for Use

The Axium™ Neurostimulator System is indicated for spinal column stimulation via epidural and intra-spinal lead access to the dorsal root ganglion as an aid in the management of moderate to severe chronic intractable* pain of the lower limbs in adult patients with Complex Regional Pain Syndrome (CRPS) types I and II.**

*Study subjects from the ACCURATE clinical study had failed to achieve adequate pain relief from at least 2 prior pharmacologic treatments from at least 2 different drug classes and continued their pharmacologic therapy during the clinical study.

**Please note that in 1994, a consensus group of pain medicine experts gathered by the International Association for the Study of Pain (IASP) reviewed diagnostic criteria and agreed to rename reflex sympathetic dystrophy (RSD) and causalgia, as complex regional pain syndrome (CRPS) types I and II, respectively.

Contraindications

Patients contraindicated for the Axium Neurostimulator System are those who are unable to operate the system and are poor surgical risks.

Patients who failed to receive effective pain relief during trial stimulation are contraindicated to proceed to the INS procedure.

Potential Adverse Events

The implantation of a neurostimulation system involves risk. Implant Manual must be reviewed for detailed disclosure.

Refer to the User's Manual for detailed indications, contraindications, warnings, precautions and potential adverse events.

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