CLINICAL HIGHLIGHTS
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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 Pain

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. 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. 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
• 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.

† 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 1 and 2, respectively.
• 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 the end of the trial phase, 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)

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

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 ≥ 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.
SECONDARY AND TERTIARY ENDPOINT RESULTS THROUGH 12 MONTHS:

- Using an 11-point scale to assess paresthesia intensity, results showed that DRG stimulation produced less changes in intensity between upright and supine positions when compared to the control group (Figure 3).

- In this study cohort, more than a third of DRG stimulation patients experienced no paresthesia at 12 months, while having on average an 86% reduction in pain. Further 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.

- DRG stimulation provided improvements in quality of life measures, as measured by SF-36, over baseline at 12 months (Figure 4).

- 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 three 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) (Figure 5).

- At 12 months, DRG stimulation provided significant improvements in total mood disturbance (p = 0.004 vs. control) and three out of the four components of the brief pain inventory (interference, activity, and affective components) (Figure 6).

| 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 with paresthesia in this cohort.
Figure 5. DRG Stimulation Subjects Experienced Greater Improvements in POMS Scores over Baseline at 12 Months

Figure 6. At 12 months, DRG Stimulation Provided Significant Improvements Three out of the Four Components of the Brief Pain Inventory (Interference, Activity, and Affective Components)