SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Noninvasive Bone Growth Stimulator
Device Trade Name:	ActaStim-S Spine Fusion Stimulator
Device Procode:	LOF
Applicant's Name and Address:	Theragen, Inc. 11220 Assett Loop Suite 101 Manassas, Virginia 20109
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P190030
Date of FDA Notice of Approval:	December 9, 2020

II. INDICATIONS FOR USE

The ActaStim-S Spine Fusion Stimulator is a noninvasive bone growth stimulator indicated as an adjunct electrical treatment to primary lumbar spinal fusion surgery for one or two levels.

The device is Rx only, and intended for single patient use in adult patients only.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ActaStim-S Spine Fusion Stimulator labeling.

V. DEVICE DESCRIPTION

The ActaStim-S Spine Fusion Stimulator (ActaStim-S) is a small, portable, wearable noninvasive, capacitively coupled (CC), bone growth stimulator (BGS) device that delivers a 60 kHz symmetric sine wave signal to the patient electrodes. The ActaStim-S consists of the CC BGS unit, its rechargeable battery pack and charging unit, and electrodes attached to the CC BGS unit with lead wires, and shower covers for use to allow the electrodes, but not the CC BGS unit itself, to remain attached to the patient

when showering. The ActaStim-S promotes healing by passing a specific current between the patient electrodes, which generates a low energy electrical field at the fusion site.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

For patients undergoing lumbar spinal fusion, there are several other alternatives to the ActaStim-S for providing adjunct treatment to primary lumbar spinal fusion surgery. These include physical therapy, external bracing, invasive bone growth stimulators, and other commercially available noninvasive bone growth stimulators. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The ActaStim-S has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse events that may occur with treatment with ActaStim-S are among those that may occur in association with lumbar spinal fusion and adjunctive treatment with noninvasive bone growth simulators, and include failure or delay of osteogenesis, burns, electric shock, electromagnetic interference, adverse tissue reaction such as skin irritation, pain at the fusion site, or pain at the treatment site.

For the specific adverse events that occurred in the clinical studies of a non-invasive bone growth simulator with similar design characteristics (SpinalPak, approved under P850022/S009), please see Section X below. Based on the clinical study, the most common, and only clearly device-related, adverse event was skin irritation, occurring in 9 patients (2.6% of the patient population) – four (4) patients treated with the active device and five (5) patients treated with the placebo device.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

A summary of laboratory testing conducted is presented in the following table (Table 1).

Table 1: Non-Clinical Study Summary

Test	Purpose	Acceptance Criteria	Results
Electrical Safety Testing	To demonstrate that the hazards related to electrical safety are mitigated.	Compliance with: • American National Standards Institute (ANSI)/ Association for the Advancement of Medical Instrumentation (AAMI) ES 60601-1:2005/(R)2012 and	Passed The device met all requirements for electrical safety testing.

		A1:2012 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance • ANSI/AAMI HA 60601-1-11:2015 Medical electrical equipment – Part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment • International Electrotechnical Commission (IEC) 60529 Ed. 2.2 b:2013 Degrees of Protection Electrical Enclosures Package	
Electromagnetic Compatibility Testing	To demonstrate that the device is protected from electrical interference (immunity) and meets appropriate standards for electrical emissions.	Compliance with: • International Electrotechnical Commision (IEC) 60601-1-2, Ed. 4.0 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests • International Special Committee on Radio Interference (CISPR)) 11:2009 Industrial, scientific and medical equipment - Radio-frequency disturbance characteristics - Limits	Passed All requirements to demonstrate electromagnetic compatibility for home use were met.

		and methods of measurement	
Other Electrical Testing	To assess if the device met supplemental requirements of additional applicable electrical standards.	Compliance with: • IEC 60601-1-6 Edition 3.1 Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability • AAMI ANSI IEC 60601-1-8:2006 & A1:2012 Medical electrical equipment – Part 1-8: General requirements for basic safety and essential performance – Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems • IEC 60601-2-10 Edition 2.1 Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators	Passed All requirements in the supplemental electrical standards were met.
Software	To demonstrate that the software meets the design specifications, and that risks related to the software have been mitigated.	Software documentation was provided in accordance with the CDRH Guidance Document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," for a moderate level of concern. The software is embedded within the generator and consists of the Treatment and Communication software items. The Treatment software item controls all software functionality associated with generation and delivery of the therapeutic signal. All software	Passed Software passed all appropriate verification and validation activities.

		system requirements should be verified and/or validated.	
Generator Verification	To verify the implementation of the signal generator system requirements.	Testing included evaluation of: • Generator leads reliability- components survive 270 days of simulated use • Physical characteristics verification – manufactured device meets all design specifications • User interface verification – device visually or audibly display all required information to the user • Board level verification- device board meets design specifications • Bluetooth and Universal Serial Bus (USB) verification – communication systems can output device usage logs • Electrical verification – electrical system design specifications are met • Overcurrent fault verification- system deactivates if sustained overcurrent fault is detected	Passed All requirements were met.
Electrode and Electrode Lead Verification	To show there is no functional or performance difference between the electrodes used in the ActaStim-S and those used for the SpinalPak. ActaStim-S will be provided with two types of electrodes to allow for choice based on patient preference.	The electrodes were evaluated to assess the following: • Insertion and removal force is less than 35 N • Demonstration the electrode leads can survive 60 insertion/removal cycles without damage	Passed Testing successfully verified implementation of the electrodes and electrode leads' associated system requirements. • Upper tolerance interval of insertion and removal force was 31.2 N

			• Electrode lead survived 60 insertion cycles
Shelf Life	To show the ActaStim-S system and electrodes maintain their performance characteristics for the labeled shelf life (1-year).	Real-time aging of the system components was performed, followed by revalidation of electrode and electrode lead verification testing. Electrodes must meet all specifications following aging.	Passed Following real-time aging, the system met the acceptance criteria for performance characteristics.
Cleanability	To assess if the control unit could withstand repeated cleaning as expected for the use-life of the device.	Repeated cleaning simulating the expected use-life of the device was performed on the control unit, followed by revalidation of system performance. Device must meet all system requirements following repeated cleaning.	Passed Following cleaning testing, the control unit met all specifications.
Battery Safety and Functional Verification	To demonstrate the suitability of the battery's performance for use with the ActaStim-S.	ActaStim-S relies on a Lithium-ion battery. A series of functional verification tests were performed to evaluate Lithium-ion battery's performance and conformity to IEC 62133, Edition 2.0, United Nations (UN)/ Department of Transportation (DOT) 38.3, Edition 5, and Underwriters Laboratories (UL) 2054, Edition 2.	Passed All requirements of IEC 62133 were met.
Shipping and Transportation	To ensure the packaging was appropriately designed to allow for shipment of the device.	The ActaStim-S packaging configuration was tested according to the applicable requirements of International Safe Transit Association (ISTA) 3A:2008.	Passed All requirements of ISTA 3A:2008 were met.
Additional System Requirements Verification	Additional verification testing was performed to demonstrate that the ActaStim-S device in its final finished form fulfills all the defined system requirements.	Testing included verification of the belt clip, button longevity on the generator, verification of labeling, operating environment parameters, and confirmation of compliance to applicable consensus standards.	Passed All components met requirements demonstrating they can function for their expected use-life.
User Needs Validation Study	An empirical and analytical human factors engineering process was applied throughout	A simulated-use user need validation study was conducted with fifteen representative users to demonstrate that the	Passed All user needs were met.

	product development including analysis of the intended use, user interface specification development, analysis of use-related hazards and tasks, formative and formal evaluations.	ActaStim-S fulfills the defined designed specifications to suit the intended user.	

B. Animal Studies

No animal studies were provided in this submission.

C. Additional Studies

Biocompatibility

Biocompatibility of the patient contacting surfaces was evaluated according to International Organization for Standardization (ISO) 10993-1:2018 and FDA Guidance Document "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process". The Generator, Battery Pack, Belt Clip, Charger, Charging Dock, Electrode spun lace top layer and carbon conductive film are intended to have transitory contact. The electrode hydrogel, electrode shower cover, and generator lead wires are intended to have long-term exposure on intact skin. The biocompatibility tests conducted included Cytotoxicity (ISO 10993-5), Irritation (ISO 10993-10), and Sensitization (ISO 10993-10). Results of testing in combination with a biologic risk evaluation and labeling demonstrated biocompatibility in line with the requirements of ISO 10993-1.

Technological Comparison

In lieu of providing a clinical dataset for ActaStim-S, the applicant provided various nonclinical comparison studies of ActaStim-S and SpinalPak, another BGS previously approved under P850022/S009 with the same indications for use as ActaStim-S. The purpose of these nonclinical signal characterization tests was to establish sufficient similarity of the two BGS devices such that FDA could apply Section 216 of the Food and Drug Modernization Act (FDAMA), i.e., the "six-year rule", to assess the safety and effectiveness profiles of ActaStim-S.

According to FDA's "Guidance on Section 216 of the Food and Drug Modernization Act of 1997", available at https://www.fda.gov/media/71743/download, FDA may choose to utilize the publicly available detailed SSED of a previously approved device to support approval of a PMA for a new device if the applicant provides "a detailed justification of how the information in the earlier SSED applies to the applicant's device" and if the applicant is able "to describe how the devices are similar enough to allow for the data from the earlier device to apply to the new device."

For the purpose of establishing sufficient similarity of ActaStim-S and SpinalPak, the applicant provided the following comparisons of the two devices: Table 2A provides an overall comparison of device components and functionality, while Table 2B provides a comparison of key specifications to establish sufficient similarity of the two devices.

Table 2A: Technological Comparison

Device Component	Function	ActaStim-S	SpinalPak® (P850022/S009)
Stimulator/Generator	Promotes healing by inducing low electrical current between electrodes at the fusion site.	Promotes healing by inducing low electrical current between electrodes at the fusion site.	Includes audible and visible self-checking alarm mechanism and operational indicators. Stores patient daily usage and therapeutic treatment data which may be downloaded to a personal computer for viewing, storage and/or printout using data software
Battery Pack and Battery Charger	Rechargeable battery (12V) allowing for ambulatory use.	2 battery packs provided	2 battery packs provided
Electrodes	Hydrogel electrode options having different characteristics for different skin types and preferences. Various range of stickiness for different skin types.	2 options: both measuring 35mm (+/-2mm) in diameter	3 options (with one being one of the exact electrodes provided with the ActaStim-S device): both measuring 35mm (+/-2mm) in diameter
Electrode Covers	Water resistant covers to enhance electrode security to the skin, may be used in the shower	Pack of 20 provided	Pack of 20 provided
Device Holster/ Belt Clip	Securely holds simulator in place allowing wear on a waistband or belt.	Belt clip provided	Holster with belt clip provided
Lead Wires/ Cables	2 different lengths	48" and 12" lengths	48" and 20" lengths

While there are, as shown in Table 2A, modest differences in the components and user interface, none of these differences would lead to appreciable differences in the safety or effectiveness profiles of the two devices. This is supported by the results of the testing described above, as well as the comparative signal and system characterization, as follows.

To establish sufficient operational similarity of the devices, the following parameters were considered:

- Therapeutic waveform: Frequency and the controlled current profile across the range of operating impedances, along with voltage which generates that current and which varies as expected with Ohm's Law. These are described in the SpinalPak SSED for PMA850022/S009 and were confirmed by testing.

- Waveform generation: The time taken to detect and adjust to the (changing) impedance (impedance discovery time), and measures of purity or consistency of the signal, being duty cycle bias, jitter and harmonic content. These parameters were identified as the important ones from a comprehensive analysis of the SpinalPak device and that testing was the basis of the specification.

- Current delivery: Electrode impedance determines the degree to which the input waveform is attenuated and is part of the impedance detected by the generator for calculations of current levels and operation limits. Dispersivity is a measure of the consistency of the delivery of the current across the surface of the electrode with greater dispersivity and more consistency resulting in lower current intensity spikes.

- Electrode adhesion: The ability of the electrodes to adhere is driven predominantly by the hydrogel choice and all three (3) SpinalPak hydrogel types, as well as the two (2) ActaStim-S hydrogels (of which one is the same as that provided with the SpinalPak device) are typical skin contact hydrogels designed for secure application and easy removal.

Table 2B: Signal and System Characterization

	SpinalPak Test Parameters		ActaStim-S Test Parameters	
	Min	Max	Min	Max
Frequency (kHz)	54	66	60.13	60.33
Treatment Current (Arms, mA) in 100 to 450 Ohm range	5	10	5.53	9.22
Treatment Current (Arms, mA) in 100 to 700 Ohm range	3.3	10	3.61	9.22
Impedance Operating Limit (Ohms)	100	750	100	765
Treatment Vrms (mV)	-	2.91	-	2.59
Impedance Discovery Time (s)	-	24.0	-	14.8
Duty Cycle Bias (%)	48.9	51.1	50.1	50.5
Jitter (ns)	-	600	-	410
Harmonic Content (%)	-	3.1	-	1.3
Electrode Impedance (Ohm)	32	102	46	80

Electrode Current Dispersivity (cm^2)	0.27		1.80	
Electrode Adhesion (g/cm)	80.4 ± 21.9	92.5 ± 11.4	145.1 ± 48.3	221.5 ± 50.0

As shown in Table 2B, testing of the ActaStim-S device signal and system characteristics described above demonstrated similarity between ActaStim-S and SpinalPak. Where a specification was defined by a range or operating windows, the ActaStim-S results were shown to be within the window/range, often showing a tighter distribution than what was observed for the SpinalPak device. Where a specification was solely defined by a maximum or minim value, the ActaStim-S device did not exceed those values. For electrode adhesion, two sets of electrodes were tested for each system, with the results showing the mean and standard deviation of the low and high adhesion electrodes. Based upon these results, the ActaStim-S is sufficiently similar to the SpinalPak device with no significant deviation in any area of characterization, such that the clinical dataset from the SpinalPak device can be leveraged for an assessment of the safety and effectiveness profiles of the ActaStim-S device.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant cited a clinical dataset, summarized in the SSED of the approval documentation of P850022/S009 for the SpinalPak device, for the purpose of establishing a reasonable assurance of safety and effectiveness of the ActaStim-S device for use as an adjunct electrical treatment to primary lumbar spinal fusion surgery for one or two levels. In support of leveraging the clinical dataset for the SpinalPak device, the applicant provided, as discussed above, nonclinical testing results for the ActaStim-S and a compararison of key signal and system characteristics of the ActaStim-S and Spinal Pak devices. The testing provided adequate evidence that the ActaStim-S device and the SpinalPak device deliver closely similar therapeutic signals to the patient. Consequently, the FDA was able to confirm that the clinical study used to support approval of the SpinalPak device under P850022/S009 is applicable to and representative of the safety and effectiveness profiles of the ActaStim-S device for the same indications for use.

A summary of the clinical study of the SpinalPak device is presented below, and additional details of this study are provided in the SSED for P850022/S009 that is available on the CDRH website.This provided adequate evidence that the ActaStim-S device and the SpinalPak device deliver closely similar therapeutic signals to the patient. Consequently, the FDA was able to confirm that the clinical study used to support approval of the SpinalPak device under P850022/S009 is applicable to and representative of the safety and effectiveness profiles of the ActaStim-S device for the same indications for use. A summary of the clinical study of the SpinalPak device is presented below, and additional details of this study are provided in the SSED for P850022/S009 that is available on the CDRH website.

A. Study Design

The capacitively coupled (CC) BGS device clinical study was a concurrent, multi-center, randomized, double-blinded, prospective study. The objective of the study was to determine whether the CC BGS device increased the frequency of overall success when compared to placebo (inactive) units, after primary (first-time) one-level or two-level spinal fusions within L3 to S1.

The study subjects were eligible if they had degenerative disc disease and had undergone one-level or two-level fusions of the lumbar spine within L3 to S1. The surgical procedures qualifying for inclusion were: an interbody fusion, including either a posterior lumbar interbody fusion (PLIF) or anterior lumbar interbody fusion (ALIF); a bilateral posterolateral fusion; or a combination of both procedures. Subjects could also receive either autograft or allograft graft material. Subjects could also receive internal fixation. Subjects were randomized to receive either an active or placebo device within three weeks of surgery.

The study was constructed to demonstrate superiority. Study success was determined by making a comparison between fusions of the lumbar spine, the percentage of active patients in the core group considered to be overall successes (radiographic success and clinical success) and the percentage of placebo patients in the core group considered to be overall successes. The study was to be considered successful if the comparison between the active and placebo core patients considered to be overall successes yielded a statistically significant result (p-value less than or equal to 0.05), in favor of the active device.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the SpinalPak device study under P850022/S009 was limited to patients who met the following inclusion criteria:

- degenerative disc disease
- spine segments: L3/L4, L4/L5, L5/S1, L3/L5, L4/S1
- interbody fusion, either posterior lumbar interbody fusion (PLIF) or anterior lumbar interbody fusion (ALIF), or bilateral posterolateral fusion (with or without fixation hardware)
- primary fusion, within three weeks of enrollment
- one-level or two-level fusion
- autograft or allograft graft material
- closed epiphyses

Patients were not permitted to enroll in the SpinalPak device study under P850022/S009 if they met any of the following exclusion criteria:

- pathologic process at spine level - spondylosis, infection, Paget's disease
- systemic disease that may affect fusion - cancer, diabetes mellitus, renal disease
- osseous trauma of the lumbar spine

- pregnancy
- cardiac pacemaker
- inability of patient to understand or comply with study instructions
- osteoporosis

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 3, 6, 9, and 12 months after the initial use of the device. The subjects were instructed to use the device continuously, except for periods of personal hygiene, until a physician had assessed overall success or for a period of nine months (the period of time allocated for this study). Preoperatively, the Patient Self-Assessment Form (PSAF) was collected. Postoperatively, the objective parameters measured during the study included both assessments of radiographic (x-ray) and clinical status (pain and function).

Radiographic Assessment: Radiographic assessments were gathered in 2 formats:

- Interim Assessments (Follow-Up Case Report Form at 6 weeks and at 3, 6, 9, and 12 months after the initial use of the device).

  Radiographic assessments on the Follow-Up Case Report Forms consisted of checking the appropriate description of the patient's radiographic condition from the following list: Complete; Incomplete - progressing; Incomplete - not progressing; and No Fusion Evident. No additional definitions were provided of these descriptive terms.

  Interim assessments were not used as a determinant of overall success within the approved Investigational Protocol.

- Final Evaluation (Final Success Evaluation Form at the final office visit)

  Radiographic assessments on the Final Success Evaluation Case Report Form were made in the following fashion:

  The following definitions (Table 3A) were used in evaluating the interbody fusion (ALIF and PLIF) and the bilateral posterolateral fusion.

Table 3A – Radiographic Evaluation – Final Success Evaluation

ALIF/PLIF	
a. >75% assimilation of graft and vertebrae	Success
b. 50-75% assimilation of graft and vertebrae	Success
c. 25-50% assimilation of graft and vertebrae	Failure
d. <25% assimilation of graft and vertebrae	Failure
Bilateral Posterolateral	
a. Fusion	Success
b. Incomplete fusion	Failure
a. Absence of fusion mass	Failure

When a subject completed the study and received a radiographic assessment of "success" from the investigator, a series of the subject's radiographs were forwarded to a blinded, independent radiologist for a second opinion. If the independent radiologist agreed with the investigator's evaluation of "success", the investigator's assessment remained as the radiographic outcome. If the independent radiologist disagreed with the investigator, the radiographs were to be sent to a second blinded, independent reviewer. The opinion of this reviewer served as the radiographic outcome. Any subject receiving a negative radiographic assessment from the investigator at the completion of the study was automatically classified as a study failure.

Clinical Rating: Clinical assessments were gathered in 3 formats:

- Interim Assessments (Follow-Up Case Report Forms completed by the attending physician (at 6 weeks and at 3, 6, 9, and 12 months after the initial use of the device).

  Clinical assessments on the Follow-Up Case Report Forms consisted of checking the appropriate description of the patient's clinical condition from the following list: Excellent, Good, Fair, and Poor. No additional definitions were provided for these descriptive terms.

  Interim assessments were not used as a determinant of overall success within the approved Investigational Protocol.

- Final Evaluation (Final Success Evaluation Form completed by the attending physician at the final office visit)

  Clinical assessments on the Final Success Evaluation Case Report Form were made in the following fashion (Table 3B):

Table 3B – Clinical Assessment – Final Success Evaluation

Excellent	Resumption of normal activities; No pain	Success
Good	Resumption of normal or modified activities; Occasional episodes of back or leg pain; Occasional pain medication	Success
Fair	Resumption of activities on a limited basis; Daily back and/or leg pain; Requires frequent pain medication	Failure
Poor	Unable to resume normal or modified activities; Severe back and/or leg pain; Requires daily pain medication.	Failure

- Patient Self-Assessment Form (PSAF) - completed by the patient at baseline, 6 weeks, and at 3, 6, 9, and 12 months after the initial use of the device.

The patient self-assessment questionnaire consisted of 14 questions which described a patient's perception of his/her pain and his/her ability to function. The patient answered each question by providing the degree of his/her symptom. To analyze the results of the questionnaire, each answer was assigned a numeric score, and the sum of the results was used as an indicator of outcome. The highest score, i.e., the worst possible pain and function score, would be 57, while the best score would be zero (0).

The PSAF was not used as a determinant of success within the approved Investigational Protocol.

3. Clinical Endpoints

With regards to safety, every subject entered into the study was analyzed for adverse events.

Patient Success

With regards to effectiveness, a patient was considered to be a success in this study if he/she was considered both clinically and radiographically successful at the time of the final evaluation. Patient progress at the interim (follow-up) visits was not taken into consideration in making the final evaluation.

A radiographic success at the final evaluation was:

For ALIF/PLIF

- 75% assimilation of graft and vertebrae, or
- 50-75% assimilation of graft and vertebrae

For Bilateral Posterolateral:

- "Fusion"

A clinical success at the final evaluation was a determination by the physician of either:

- Excellent: Resumption of normal activities; no pain;
  or
- Good: Resumption of normal or modified activities; occasional episodes of back or leg pain; occasional pain medication.

Study Success

With regard to success/failure criteria, study success was determined by making a comparison between the percentage of active patients in the core group considered to be overall successes (as defined above) and the percentage of placebo patients in the core group considered to be overall successes (as defined above). The study was to be considered successful if the comparison between the active and placebo core patients considered to be overall successes yielded a statistically significant result (p-value less than or equal to 0.05), in favor of the active device.

B. Accountability of PMA Cohort

Table 3C summarizes subject accountability, by "active" and "placebo" group as of a data-cut-off point of December 31, 1997.

Table 3C – Summary of Subject Accountability – All Subjects Enrolled as of 12/31/1997

	All Subjects	Active	Placebo
Enrolled (does not include 4 who received ID No. but not entered)	349	177	172
Not Reached Twelve Months Post Surgery, or Fused	-6	-3	-3
Twelve Months Post Surgery, Potentially Eligible for Evaluation	343	174	169
Withdrawals	-83	-43	-40
Reasons Unknown	(59)	(32)	(27)
Adverse Reaction	(12)	(5)	(7)
Compelled (jail, secondary surgery)	(7)	(4)	(3)
Requested (violated entry criteria)	(5)	(2)	(3)
Twelve Months Post Surgery, Eligible for Evaluation (Intent to Treat Population)	260	131	129
Protocol Deviations (Censored Population)	-45	-21	-24
Twelve Months Post Surgery, Meet Protocol (Core Population)	215	110	105

As Table 3C shows, 349 subjects were initially enrolled in the study and randomized to receive either an active or inactive (placebo) unit. Eighty-three subjects (24%) withdrew from the study and six had not yet completed the study as of the data cutoff date, leaving 260 subjects who completed the study and were available for analysis.

Of the 260 subjects who completed the study (Intent-To-Treat Population), 45 did not meet the entry criteria, had an intervening surgical/medical event that precluded an unbiased evaluation of overall success, or did not have an independent assessment of their radiographs (Censored Population). This left a total of 215 subjects who met all the protocol criteria and completed the study (Core Population).

Different groups of subjects were analyzed to demonstrate the safety and effectiveness of the CC BGS device. The safety analyses included all subjects who used the device at least once and had the potential to experience an adverse event (n=349). The effectiveness analyses focused on the findings from the core group (n=215).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a randomized controlled pivotal study performed in the US of a noninvasive bone growth stimulator for use as an adjunct treatment to spinal fusion surgery.

Clinical Characteristics of Core Subjects (n=215)

The demographic and clinical characteristics of the active and placebo subjects in the core group were comparable. The mean age for the active and placebo groups was 46.54 years and 44.75 years, respectively. The active and placebo groups included an approximately equal number of men and women (active female = 46.4%, active male = 53.6%, placebo female= 51.4%, placebo male= 48.6%). Of the active subjects, 24.5% smoked; 21.0% of the placebo subjects smoked.

A number of subjects had prior (pre-operative) surgeries; 29.1% of the actives, and 36.2% of the placebos. 67% of the actives and 59.1% of the controls had a posterolateral fusion. The remaining subjects had some type of interbody fusion, including a posterior interbody fusion, an anterior interbody fusion, or a combination of an interbody and posterolateral fusion. Approximately, one half of the subjects in both groups had a one-level fusion. Subjects could receive either autograft or allograft graft material; and 26.4% of the actives and 20.0% of the placebos had fusions with internal fixation (hardware). The 99 active core subjects had a baseline summed mean pain and dysfunction score of 31.44 from their 14-question self-assessment form; the 99 placebo subjects had a summed mean of 33.35 at baseline.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on both the active and placebo cohorts of 349 total patients.

Adverse effects that occurred in the PMA clinical study:

Every subject entered into the study was analyzed for adverse events. Of the 349 subjects enrolled in the clinical study and who used the device at least once, nine experienced skin irritation and cited this as a reason to withdraw from the study (2.6%). Of the nine subjects, four were in the active group and five were in the placebo group.

Three other subjects withdrew from the study because of adverse events: one placebo had a wound infection (non-device related); one placebo had back spasms; and, one active was "not progressing." (While lack of progression is normally not considered an adverse event, the investigator reported it that way.)

Eight subjects who completed the study experienced adverse events: (1) leg pain (placebo); (2) recurrent pain due to over-activity (placebo); (3) post-surgical wound seroma (active); (4) superficial wound disruption from a staple reaction (placebo); (5) pedicle fracture - screw removed (placebo); (6) a pedicle screw placement (active); (7) an aneurysm clipping (placebo); and (8) a cluneal nerve neuroma at the graft site (active). These eight subjects continued in the study, and were included in the effectiveness analyses.

2. Effectiveness Results

The analysis of effectiveness was based on the active and placebo 215 evaluable patients of the core group (n=215) at the 12-month time point.

Table 3D compares the frequency of success in the active and placebo subjects of the core group (n=215). An overall success requires an independent confirmation of radiographic successful outcome on the Final Assessment Case Report Form and also a successful clinical outcome on the Final Assessment Case Report. For each group the number of successes is shown. The p-value presented for "Overall Success" indicates statistical significance (a p-value of less than or equal to 0.05 denotes significance). The data were analyzed using a two-tail Fisher exact test.

Table 3D – Frequency of Success in the Core Group, By Treatment (n=215)

	Overall Success (Clinical AND Radiographic Success)	Clinical Success	Radiographic Success	Average PSAF Score Baseline/12 Months
Active (N=110)	87 (79%)	95 (85%)	94 (85%)	31.44/23.03
Placebo (N=105)	64 (61%)	79 (75%)	82 (78%)	33.35/23.44
P-value	0.0018			

Note: A patient was considered to be a success in this study if he/she was considered both clinically and radiographically successful at the time of the final evaluation. Patient progress at the interim (follow-up) visits was not taken into consideration in making the final evaluation.

In the 215-subject core group, 87 active subjects (79%) achieved an overall success (defined as a combination of both physician described clinical success and also a radiographic success at the time of final evaluation) whereas 64 placebo subjects (61%) achieved overall success at the time of final evaluation. This difference in the rates of overall success (18.1%) was statistically significant (p=0.0018).

This trial was not designed to look at either clinical success or radiographic success independently. However, in the 215 core group, 94 of 110 active subjects (85%) were reported by the treating physician as being radiographically successful at the time of final evaluation; whereas 82 of 105 placebo subjects (78%) were reported by the treating physician as being radiographically successful at the time of final evaluation. This difference in the rates of success (7%) was not statistically significant (p=0.0535). In the 215-subject core group, 95 active subjects (85%) achieved clinical success at the time of final evaluation; whereas 79 placebo subjects (75%) achieved a clinical success at the time of final evaluation. This difference in the rates of success (10%) was statistically significant (p=0.0163). However, these values were not adjusted for multiplicity and were also not adjusted for additional confounding factors (e.g., prior surgery, posterolateral fusion, or smoking).

As presented previously, the PSAF was also used to compare treatment groups. At baseline, the active and placebo core treatment groups were similar, with the active core subjects having a summed mean score of 31.44 and the placebos having a mean summed score of 33.35. The 1.91 point difference between core active and placebo mean patient self-assessment scores is not statistically significant (Z= -1.62426). At the time of final evaluation, active core subjects have a mean summed score of 23.03 and placebo core subjects have a mean summed score of 25.44. The point difference between core active and placebo mean patient self-assessment scores is not statistically significant (Z = -0.2675).

Logistic Regression Analysis

A number of subject characteristics and demographics may affect the probability of an overall successful outcome. A logistic regression analysis was conducted to determine if any variable(s) may have affected overall success. A logistic regression analysis tests whether any variable is statistically associated with success after controlling for the other variables, and provides an odds ratio to indicate the nature and strength of the relationship. A logistic regression was conducted using the following 13 variables that may have had an effect on the likelihood of an overall successful outcome:

1. the active device;
2. history of prior surgery (treatment);
3. gender;
4. age;
5. overweight;
6. smoking;
7. use of pre-operative medications, including steroids and NSAIDS
8. a secondary diagnosis of herniated disc pulposus;
9. a secondary diagnosis of spondylolisthesis;
10. occupational type, such as sedentary employment or moderate/heavy labor;

11. type of fusion, such as posterolateral or interbody;
12. level of fusion (single or multiple); and
13. the use of fixation hardware.

The following four variables were associated with overall success and were statistically significant: the active device, a history of prior surgery, fusion type, and smoking. The other variables, including the use of fixation hardware, were not significantly associated with overall success after controlling for the other variables. An analysis was then conducted with only the four identified variables, and is shown below in Table 3E.

Table 3E – Logistic Regression Analysis for the Core Group (n=215)

Variable	Odds Ratio	95% Confidence Interval	p-value
Prior Surgery	0.48	0.25-0.92	0.0276
Posterolateral Fusion	2.40	1.26-4.55	0.0073
Smoker	0.33	0.16-0.68	0.0024
Active Device	2.33	1.21-4.48	0.0110

This analysis showed that subjects with a history of prior surgery were less likely to achieve success, regardless of other factors (odds ratio = 0.48; p=0.0276). Subjects who had a posterolateral fusion were more likely to be overall successes, regardless of the other variables (odds ratio = 2.40, p=0.0073). Subjects who smoked were also less likely to achieve overall success (odds ratio= 0.33, p=0.0024). The subjects in the active group were more likely (odds ratio = 2.33) to achieve overall success regardless of their type of fusion, their prior history of surgery, or smoking. This odds ratio was statistically significant (p=0.0110).

3. Subgroup Analyses

Comparability of Core Groups/Effectiveness Analyses

In order to assure patient withdrawals and losses did not affect study outcome or introduce bias, statistical analyses were performed to determine if patients in the sub-populations (core, censored, and withdrawn) were comparable. First, all active 0and placebo subjects were compared with respect to 63 preoperative demographic and clinical characteristics to determine if there were any significant differences between these treatment groups overall. There were none. This same analysis was performed for the active and placebo subjects in the Censored Population and in the Core Population. Only two statistically significant differences between the active and placebo subjects in the Censored Population were found "race" (p=0.0365) and the recorded use of "preoperative NSAIDs" (p=0.0247)). Then, using the same 63 factors, the withdrawn subjects were compared to the 260 Intent-To-Treat Population. Then the population that withdrew, combined with the Censored Population, was compared to the Core Population. All these analyses established that the comparability of the Core Population treatment groups was not adversely affected by the absence of the withdrawn and censored subjects, and that the active

and placebo subjects in the Core Population had similar demographic and clinical characteristics.

To further establish the comparability of the active and placebo groups in the Core Population summed pain and dysfunction scores from a 14-question PSAF (gathered either pre-operatively or post-operatively) were statistically compared and no significant differences were found at baseline.

4. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

This section is not applicable.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In this PMA the sponsor provided adequate evidence of the sufficient similarity of ActaStim-S and SpinalPak with regard to the delivered therapeutic signal power and waveform characteristics. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for SpinalPak in support of the reasonable assurance of its effectiveness is directly applicable towards establishing reasonable assurance of the effectiveness of ActaStim-S.

As detailed in the SSED for SpinalPak (P850022/S009), a comparative clinical trial of SpinalPak to a placebo control successfully demonstrated and improved clinical and radiographic success of fusion following 12 months of treatment. The treatment group had an overall (clinical and radiographic) success of 79%, compared to the control arm which had a 61% success rate ($p = 0.0018$), demonstrating a statistically significant effect of the treatment.

B. Safety Conclusions

Non-clinical bench testing of the device was provided to demonstrate a similarity in design of the ActaStim-S and the SpinalPak device, including assessment of the generated signal, electrical safety, electromagnetic compatibility, and biocompatibility. This testing was used to provide evidence of the reasonable assurance of the safety of the SpinalPak under P850022/S009 apply equally to the ActaStim-S.

As detailed in the SSED for the SpinalPak, a clinical study was provided which included 349 subjects. Of the 349 enrolled in the clinical study who used the device at least once, nine experienced skin irritation and cited this as a reason to withdraw from the study. Of the nine subjects, four were in the active group and five were in the control group. Three other subjects withdrew from the study because of adverse events; one placebo had a non-device related wound infection, one placebo had back spasms, and one active was "not progressing".

Eight subjects who completed the study experienced adverse events: (1) leg pain (placebo); (2) recurrent pain due to over-activity (placebo); (3) post-surgical wound seroma (active); (4) superficial wound disruption from a staple reaction (placebo); (5) pedicle fracture - screw removed (placebo); (6) a pedicle screw placement (active); (7) an aneurysm clipping (placebo); and (8) a cluneal nerve neuroma at the graft site (active). These eight subjects continued in the study, and were included in the effectiveness analyses.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval of the SpinalPak device. As described above, results of comparative non-clinical testing provided evidence of the sufficient similarity of the SpinalPak and ActaStim-S devices, such that FDA could then apply Section 216 of the FDAMA and cite evidence of clinical effectiveness presented in the SSED for the SpinalPak device in support of a determination of reasonable assurance of the effectiveness of the ActaStim-S device.

As detailed in the SSED for the SpinalPak device (P850022/S009), a comparative clinical trial of the SpinalPak device to a placebo control successfully demonstrated improved clinical and radiographic success of fusion following 12 months of treatment. The treatment group had an overall (clinical and radiographic) success of 79%, compared to the control arm which had a 61% success rate ($p = 0.0018$), demonstrating a statistically significant effect of the treatment with the SpinalPak device compared to a placebo control.

As documented in the SSED for the SpinalPak, the probable risks consisted of various transitory, non-serious adverse events that were observed in the clinical trial. The only clearly device-related event was skin irritation at the treatment site. The probable

risks and safety profile of the ActaStim-S device were demonstrated to be similar to the SpinalPak device with a reasonable assurance through non-clinical testing.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above and its applicability to the ActaStim-S, the data support that for adjunct treatment of lumbar spinal fusion, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application and its applicability to the ActaStim-S support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With regard to reasonable assurance of the safety and effectiveness of the ActaStim-S, the sponsor provided adequate evidence of the sufficient similarity of the ActaStim-S and the SpinalPak devices. This similarity was established through non-clinical side-by-side characterization and testing of the two devices to demonstrate that a closely similar therapeutic signal is generated and delivered to the subject. Additionally, safety was evaluated by demonstration that the ActaStim-S complies with appropriate safety standards including biocompatibility, electrical safety, and electromagnetic compatibility. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the clinical evidence for the SpinalPak device presented in the SSED for P850022/S009 in support of the reasonable assurance of the safety and effectiveness of the SpinalPak device is directly applicable towards establishing a reasonable assurance of the safety and effectiveness of the ActaStim-S device.

XIII. CDRH DECISION

CDRH issued an approval order on December 9, 2020.

The applicant's manufacturing facilities have been determined, through prior on-site inspection and (due to constraints posed by the COVID-19 pandemic) by a review of relevant manufacturing site documentation and compliance history, to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None