P850022/S9

SUMMARY OF SAFETY
AND EFFECTIVENESS INFORMATION

I. General Information

Device Generic Name:	Bone Growth Stimulator
Trade Name:	SpinalPak® Fusion Stimulator
Applicant's Name and Address:	Biolectron, Inc. 25 Commerce Drive Allendale, NJ 07401
Premarket Approval (PMA) Application: Supplement Number:	P850022 S9
Date of Notice of Approval to Applicant:	September 24, 1999

II. Device Description

The SpinalPak® Fusion Stimulator is a bone growth stimulator utilizing capacitive coupling technology. It incorporates the same technological features of Bioelectron's OrthoPak® Bone Growth Stimulator System (P850022, approved February 18, 1996) which is indicated for the treatment of established non-unions acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than half the width of the bone to be treated.

III. Indications

The SpinalPak® Fusion Stimulator is indicated as a noninvasive bone growth stimulator for use as an adjunct electrical treatment to primary lumbar spinal fusion surgery for one or two levels.

IV. Warnings

- Cardiac pacemakers or cardioverters may be adversely affected by the SpinalPak® Fusion Stimulator. The concomitant use of the device and a pacemaker or cardioverter must be assessed on an individual basis, such as with an electrocardiogram, prior to use. The patient should be referred to a cardiologist for monitoring of pacemaker function while wearing the active SpinalPak® device. If there are any observable adverse changes in the pacemaker rhythm or output, the SpinalPak® device should not be used.

- The safety and effectiveness of the SpinalPak® Fusion Stimulator in pregnant women have not been studied, and the effects of the device on the mother or the developing fetus are unknown. A patient who is either pregnant or is intending to become pregnant should be referred to her doctor prior to treatment with the SpinaPak® device.

V. Precautions

- The safety and effectiveness of the SpinalPak® Fusion Stimulator in individuals with the following conditions have not been studied, and therefore the safety and effectiveness of the device in these individuals is therefore unknown:

    - spondylitis, infection, Paget's disease
    - cancer, diabetes mellitus, renal disease
    - trauma of the lumbar spine
    - osteoporosis

- The patient should be instructed to apply the electrode after the skin has been cleaned and dried. If erythema develops at the electrode sites, the electrodes should be relocated either immediately above or below the original sites. If the reaction does not resolve after 48 hours after relocating the electrodes, the patient should be instructed to consult with the physician.

- Do not submerge or expose the SpinalPak® Fusion Stimulator to water. The patient should be instructed to remove the stimulator during bathing, showering or swimming.

- Compliance with the treatment schedule, daily battery changes, proper maintenance of the device, and replacing the electrodes every five to seven days are essential for proper device function.

- The patient should be able to use the device in accordance with the instructions for use. If a patient cannot comply with these instructions for any reason, use of the device is not recommended.

VI. Adverse Events

During a multi-center clinical study of 349 patients treated with the SpinalPak Fusion Stimulator for the indication listed above, skin irritation was the most common adverse effect. It occurred in 9 patients (2.6% of the patient population) – 4 patients treated with the active device and 5 patients treated with the placebo device.

VII. Alternative Practices or Procedures

Alternatives to use of the SpinalPak Fusion Stimulator include physical therapy, medications, external bracing, chiropractic care, exercising, and spinal fusion therapy (with or without instrumentation) and with or without concomitant stimulation. Two other electrical stimulation devices are in commercial distribution and are indicated for "use as an adjunct electrical treatment to primary spine fusion surgery." These other devices utilize different methods to stimulate bone growth and consist of a noninvasive stimulator and an invasive stimulator.

VIII. Summary of the Pre-Clinical Studies

The SpinalPak® Fusion Stimulator device incorporates the same technological features of Bioelectron's OrthoPak® Bone Growth Stimulator System (P850022, approved February 18, 1996) and indicated for the treatment of established non-unions acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than half the width of the bone to be treated. Pre-clinical studies were performed to support the relative safety of this product. Details of the pre-clinical studies gathered using the OrthoPak Bone Growth Stimulator System can be found in the Summary of Safety and Effectiveness for the OrthoPak® Bone Growth Stimulator System (P850022).

IX Summary of Clinical Trial

Clinical data to support the safety and effectiveness of the SpinalPak® Fusion Stimulator were collected as part of multi-center trial.

A. Study Design

The clinical study was a randomized, double-blinded, prospective study conducted at multiple sites. The objective of this study was to determine whether the SpinalPak® Fusion Stimulator increased the frequency of overall success (defined as the combination of both clinical and radiographic success) when compared to placebo (inactive) units, after primary (first-time) one-level or two-level fusions within L3 to S1.

Subjects were eligible if they had degenerative disc disease and had undergone one-level or two-level fusions of the lumbar spine between L3 and 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.

Subjects were to be followed at six weeks, and at three, six, nine 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).

B. Inclusion/Exclusion Criteria

1. Inclusion Criteria

To be included, subjects were to meet the following 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

2. Exclusion Criteria

Subjects who exhibited any of the following conditions were not eligible:

- pathologic process at spine level - spondylisis, 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

C. Outcome Measure

During this trial, assessments of radiographic (x-ray) and clinical status (pain and function) were made.

1. Radiographic Assessment

Radiographic assessments were gathered in 2 formats:

a. Interim Assessments (Follow-Up Case Report Form at 6 weeks and, at three, six, nine 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 patients 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.

b. 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 were used in evaluating the interbody fusion (ALIF and PLIF) and the bilateral posterolateral fusion.

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
c. 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.

2. Clinical Rating

Clinical assessments were gathered in 3 formats:

a. Interim Assessments (Follow-Up Case Report Forms completed by the attending physician (at 6 weeks and, at three, six, nine 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.

b. 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:

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

c. Patient Self Assessment Form (PSAF) – completed by the patient at baseline, 6 weeks, and, at three, six, nine and 12 months after the initial use of the device

The patient self-assessment questionnaire consists of 14-questions which describe a patient's perception of their pain and their ability to function. The patient answered each question, by providing the degree of their symptom. To analyze the results of the questionnaire, each answer was given 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 0.

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

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D. Patient Success

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 either:

ALIF/PLIF
- 75% assimilation of graft and vertebrae
- 50-75% assimilation of graft and vertebrae

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
- Good: Resumption of normal or modified activities; occasional episodes of back or leg pain; occasional pain medication.

E. Study Success

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) as compared to the percentage of placebo patients in the core group considered to be overall successes (as defined above). If the comparison between the active and placebo core patients considered to be successful overall yields a statistically significant result (p-value less than or equal to 0.05), the study is considered to be successful.

F. Study Subject Enrollment and Discontinuation

Table 1 summarizes subject accountability, by "active" and "placebo" group as of a data-cut-off point of December 31, 1997.

Table 1
Summary Of Subject Accountability
All Subjects Enrolled As Of 12/31/97

	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 Reactions	(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 1 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 SpinalPak® Fusion Stimulator. 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).

G. Safety Analyses (All Subjects n=349)

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 irritations 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.

H. Comparability of Core Groups / Effectiveness Analyses

In order to assure patient withdrawals and losses do 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 and 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.

I. Clinical Characteristics of the Core Subjects (n=215)

As described above, the demographic and clinical characteristics of the active and placebo subjects in the core group are 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. Almost all subjects had a 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.

J. Success in the Core Group (n=215)

Table 2 compares 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 2
Frequency Of Success 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 core group, 87 active subjects (79%) achieved an overall success (defined as a combination of both physician described clinical success and also a radiographic successes 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 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 scores of 23.03 and placebo core subjects have a mean summed score of 25.44. The 2.41 point difference between core active and placebo mean patient self-assessment scores is not statistically significant (Z = -0.2675).

K. 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 a 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 spondylolysthesis;
(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 3.

Table 3
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).

X. Conclusions Drawn From Study

All of the data provided in the previous sections describing the pre-clinical, clinical studies provide reasonable assurance of the safety and effectiveness of the SpinalPak Fusion Stimulator when used by trained physicians as a non-invasive bone growth stimulator used as an adjunct electrical treatment to primary lumbar spinal fusion surgery for one or two levels.

XI. Panel Recommendations

This is a PMA supplement which did not require panel review

XII. CDRH Decision

CDRH recommends approval for the SpinalPak Fusion Stimulator as a non-invasive bone growth stimulator used as an adjunct electrical treatment to primary lumbar spinal fusion surgery for one or two levels.

XIII. Approval Specifications

A Post-market Study will not be required for this device. No significant clinical issues of safety and effectiveness remain to be collected which would yield clinically significant information which would necessitate modifications to device indications, adverse events, contra-indications, precautions or warnings.