

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: filler, bone void, synthetic peptide

Device Trade Name: i-FACTOR™ Peptide Enhanced Bone Graft

Device Procode: NOX

Applicant's Name and Address: Cerapedics, Inc.
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140019

Date of FDA Notice of Approval: November 3, 2015

II. INDICATIONS FOR USE

i-FACTOR™ Peptide Enhanced Bone Graft is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels, after failure of at least 6 weeks of conservative treatment. i-FACTOR™ Peptide Enhanced Bone Graft must be used inside an allograft bone ring and with supplemental anterior plate fixation.

III. CONTRAINDICATIONS

i-FACTOR™ Peptide Enhanced Bone Graft should not be used in situations where there is:

- An absence of load bearing structural support at the graft site
- Sensitivity to any components of i-FACTOR™ Peptide Enhanced Bone Graft
- Acute or chronic infections, systemic or at the operative site
- Metabolic or systemic disorders that affect bone or wound healing
- Compromised renal or hepatic function

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the i-FACTOR™ Peptide Enhanced Bone Graft labeling.

V. **DEVICE DESCRIPTION**

i-FACTOR™ Peptide Enhanced Bone Graft (also referred to as i-FACTOR™ Bone Graft or i-FACTOR™ Putty) is a composite bone graft material consisting of multiple components - a synthetic peptide (P-15) adsorbed onto calcium phosphate particles, which are suspended in a hydrogel carrier. The i-FACTOR™ Peptide Enhanced Bone Graft must be used in combination with an allograft ring and a metallic anterior cervical plate.

P-15 peptide component

The synthetic peptide is a short chain peptide consisting of 15 amino acids that mimics the sequence of amino acids found in residues 766-780 of the $\alpha 1$ chain of Type I collagen according to the following sequence:

Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val

It is intended to facilitate attachment of osteogenic cells to the granule component. None of the amino acids used in synthesizing the peptide are animal-derived.

calcium phosphate granule component

The calcium phosphate granules, also known as anorganic bone mineral (ABM), provide a scaffolding and source of calcium for new bone growth. These granules consist of hydroxyapatite that is derived from thermally treated ($> 1000^{\circ}$ C) bovine bone. The thermal processing removes all of the organic material from the source bone. The potential for disease transmission from this component is mitigated by the thermal processing, as well as use of a closed, documented US herd. The granules are irregularly-shaped with a particle diameter range of 250-425 μ and are naturally porous.

hydrogel component

The hydrogel component consists of plant-derived sodium carboxymethylcellulose (NaCMC) in combination with glycerin and water.

The various components are combined in a proportion that delivers the desired handling characteristics and allows the material to be maintained at the surgical site. Prior to being combined with the hydrogel component, the peptide component is adsorbed onto the calcium phosphate granules component. The final composition of I-FACTOR™ Peptide Enhanced Bone Graft is shown in the following table:

Components		Proportion (w/w)
ABM/P-15 particles		51.9 %
Sodium Carboxymethylcellulose	Hydrogel	1.5 %
Glycerin USP		7.0 %
Water For Injection USP		39.6 %

i-FACTOR™ Peptide Enhanced Bone Graft is supplied to the clinician as a sterile device in a single-use, pre-filled syringe containing 5.0cc of graft material. No mixing or other preparation is required. The syringe is removed from the sterile barrier package at time of delivery during the surgery. The clinician removes the syringe cap, and delivers the material to the cavity in the allograft ring before placing the combination into the graft site.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several non-surgical and surgical alternatives for the treatment of cervical degenerative disc disease. Non-surgical alternative treatments may include physical therapy and/or pain relief medications. Surgical alternatives may include cervical fusion with autograft or allograft bone with or without the use of supplemental metallic fixation implants, or artificial cervical disc replacement surgery. Each alternative has its own advantages and disadvantages. A subject should discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

i-FACTOR™ Peptide Enhanced Bone Graft has been available in markets outside of the United States since 2008. The device has not been withdrawn from the market for any reason relating to the safety and effectiveness of the devices. The countries in which i-FACTOR™ Peptide Enhanced Bone Graft is available are as follows: Italy, Spain, Portugal, Belgium, Germany, Netherlands, Luxembourg, Poland, France, England, Scotland, Wales, Ireland, Norway, Sweden, Finland, Denmark, Slovenia, Croatia, Latvia, Russia, Greece, Cyprus, Turkey, Malaysia, Hong Kong, Vietnam, Australia, New Zealand, Canada and Singapore.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

As with any surgery, surgical treatment of cervical degenerative disc disease is not without risk. A variety of complications related to the surgery or the use of i-FACTOR™ Peptide Enhanced Bone Graft may occur. The following is a list of potential adverse events that could be associated with the use of i-FACTOR™ Peptide Enhanced Bone Graft, some of which were identified in the i-FACTOR™ Peptide Enhanced Bone Graft clinical trial results. These adverse events include: (1) those associated with any surgical procedure; (2) those associated with anterior cervical discectomy and fusion (ACDF) surgery; and (3) those that may occur specifically with the use of i-FACTOR™ Peptide Enhanced Bone Graft. These risks may occur singly or in combination and may be

severe and/or negatively impact patient outcomes. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of symptoms. Additional surgery may be required to correct some of the potential adverse effects.

1. Risks associated with any surgical procedure:

- Anesthesia complications including an allergic reaction or anaphylaxis
- Infection (wound, local, and/or systemic) or abscess
- Wound complications including hematoma, site drainage, infection dehiscence and/or necrosis
- Mild to severe swelling, edema
- Soft tissue damage or fluid collections, including hematoma or seroma
- Pain/discomfort at the surgical incision and/or skin or muscle sensitivity over the incision, which may result in skin breakdown, pain, and/or irritation
- Heart or vascular complications including bleeding, hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding, ischemia, myocardial infarction, abnormal blood pressure, venous thromboembolism including deep vein thrombosis and pulmonary embolism, thrombophlebitis, or stroke
- Pulmonary complications including atelectasis or pneumonia
- Impairment of the gastrointestinal system including ileus or bowel obstruction
- Impairment of the genitourinary system including incontinence, bladder dysfunction, or reproductive system complications
- Neurological complications including nerve damage, paralysis, seizures, changes to mental status, or reflex sympathetic dystrophy
- Complications of pregnancy including miscarriage or congenital defects
- Inability to resume activities of daily living
- Death

2. Risks specifically associated with anterior cervical discectomy and fusion (ACDF) surgery, some of which were observed with use of i-FACTOR™ Peptide Enhanced Bone Graft:

- Failure of fusion, with requirement for secondary surgical intervention
- Early or late loosening, breakage or migration of internal fixation and/or graft material
- Vertebral body fracture
- Failure of symptom relief
- Nonunion, malunion or delayed union
- Worsening of neurologic status, arachnoiditis
- Adjacent level degeneration
- External chylorrhea or chylothorax
- Recurrent laryngeal nerve injury with hoarseness
- Superior laryngeal nerve injury and dysphagia

- Tracheal, esophageal, or pharyngeal perforation
 - Dural injury with cerebrospinal fluid leakage, fistula, headache
 - Scar formation or other problems with the surgical incision
 - Vascular injury resulting in stroke, hemorrhage and possible death
3. Potential adverse events that may occur specifically with the use of i-FACTOR™ Peptide Enhanced Bone Graft include:
- Extrusion or migration of the i-FACTOR™ Peptide Enhanced Bone Graft, as is possible with any bone graft, resulting in pain, neural impingement, physical impairment, or loss of function; any of which may require revision surgery
 - Allergic reaction to components of i-FACTOR™ Peptide Enhanced Bone Graft
 - Abnormal bone formation in an unintended location
 - Excessive or incomplete bone formation

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Cell Tumorigenicity

To determine the extent of binding of the ABM/P-15 sequence to tumor/transformed cells relative to that of Type I collagen; and the proliferative or differentiative response of transformed cells bound to ABM/P-15 and of transformed cells bound to Type I collagen sequence. Ten cell lines (osteosarcoma MG-63, SAO-2, G-292, HOS, SGSA-1, U2-OS and HS706.T; chondrosarcoma SW 1353; breast cancer HCC38 and prostate cancer VCaP) were tested for attachment, proliferation, bone phenotype, and maintenance of relevant phenotype. ABM/P-15 has no greater proliferative or differentiative effect on tumor/transformed cells than native collagen.

B. Animal Studies

Goat Cervical Spine Fusion Study

To evaluate the efficacy and biomechanical stability of i-FACTOR™ Peptide Enhanced Bone Graft versus autograft in an allograft ring for anterior instrumented cervical interbody spinal arthrodesis. Single-level cervical fusion procedures were performed on 28 skeletally mature female goats. Evaluations were performed at 6 and 12 months (7 animals per group per time point). The evaluations consisted of fluoro and plain films, CT scans, mechanical testing, high resolution microradiographs and undecalcified histology. The incidence of partial and solid fusion was similar between the two groups at 6 months and markedly better for the i-FACTOR™ Peptide Enhanced Bone Graft group than the autograft group at 12

months. Multidirectional biomechanical flexibility testing of the operative function spinal units demonstrated no statistical differences in the range of segmental motion between the i-FACTOR™ Peptide Enhanced Bone Graft group and the autograft group at either the 6 month interval or the 12 month interval.

Sheep Cervical Spine Immunology/Dose Study

To determine whether the P-15 protein elicits an immune response and if there is a dose response to typical i-FACTOR™ Peptide Enhanced Bone Graft volumes in a cervical spine fusion indication. The study included 36 sheep and five study groups (100% i-FACTOR™ Peptide Enhanced Bone Graft, 67% i-FACTOR™ Peptide Enhanced Bone Graft /33% ABM Putty, 33% i-FACTOR™ Peptide Enhanced Bone Graft /67% ABM Putty, 100% ABM Putty, and empty cages). Thirty sheep (6 per group) were carried out to 13 weeks and six sheep (three 100% i-FACTOR™ Peptide Enhanced Bone Graft and three 100% ABM Putty) were carried out to 26 weeks. Evaluations included serum antibody testing, microCT and histomorphometry. Sheep implanted with up to 1.0cc of 100% i-FACTOR™ Peptide Enhanced Bone Graft did not elicit an immune response to the P-15 peptide present in the i-FACTOR™ Peptide Enhanced Bone Graft at any of the tested dosing levels. i-FACTOR™ Peptide Enhanced Bone Graft did not demonstrate a dose response in bone growth using the volume of product necessary for a single-level fusion procedure.

C. Additional Studies

Biocompatibility

Biocompatibility testing was conducted on i-FACTOR™ Peptide Enhanced Bone Graft in accordance with ISO 10993-1, *Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing*. i-FACTOR™ Peptide Enhanced Bone Graft is an implant device with permanent contact to tissue or bone. The i-FACTOR™ Peptide Enhanced Bone Graft used for the ISO 10993-1 testing was manufactured, packaged, and sterilized in a syringe using the same processes and materials as the i-FACTOR™ Peptide Enhanced Bone Graft used in the U.S. IDE study. The syringe components are composed of UPS Class VI materials. The battery of biocompatibility tests conducted include: Acute Systemic Toxicity (mice), Intracutaneous Reactivity (rabbit), Sensitization (guinea pig), 30-day Implantation - muscle (rabbit), 30-day implantation – femur (rabbit), Cytotoxicity (MEM Elution), 30-Day Subacute Toxicity (mice), Genotoxicity - Ames Mutagenicity, Genotoxicity - In-vitro Mouse Lymphoma Assay, and Genotoxicity - In-Vitro Chromosome Aberration Assay (hamster ovary cells). This testing demonstrated i-FACTOR™ Peptide Enhanced Bone Graft to be nontoxic, nonirritating, nonsensitizing, and nonmutagenic.

Sterilization, Shipping, and Shelf Life

i-FACTOR™ Peptide Enhanced Bone Graft is terminally sterilized by steam autoclave using a validated cycle that provides a sterility assurance level (SAL) of 10^{-6} . The autoclave qualification and sterilization cycle is validated according to guidelines set forth in ISO 17665-1:2006, *Sterilization of health care products* –

Moist heat – Part 1: Requirements for development, validation and routine control of sterilization process for medical devices.

The package integrity was tested through a range of anticipated shipping conditions - bubble leak testing per ASTM F2096-04, seal strength testing per ASTM F88-06, and a visual inspection of the test samples.

i-FACTOR™ Peptide Enhanced Bone Graft is currently specified to have a shelf life of 3 years from the date of sterilization. Results of stability study showed that three-year real-time aged ABM/P-15 stored at ambient room temperature and humidity conditions is stable, and continues to function as designed with regards to its biological activity. There have also been several shelf-life studies performed on the i-FACTOR™ Peptide Enhanced Bone Graft. These studies include both real time and accelerated aging out to 3+ years and support the specified shelf life of 3 years.

Human Sera Immunology Study

In addition to the animal immunology study, an immunology clinical study was performed in Belgium using sera from human subjects implanted with commercially-available i-FACTOR™ Peptide Enhanced Bone Graft. A single clinician performed posterior lumbar interbody fusion procedures by placing i-FACTOR™ Peptide Enhanced Bone Graft was placed inside one interbody fusion cage and autograft was placed inside the contralateral cage in single and two level procedures. Twenty-four (24) single-level, thirteen (13) two-level, one (1) three-level and one (1) four-level fusions procedures were performed. An average of 2.0cc (range of 1.0 to 3.5cc) of i-FACTOR™ Peptide Enhanced Bone Graft was implanted in 40 subjects. Sera were collected at the following time points: preoperatively (within 8 weeks of the surgery) and postoperatively at 2, 6, 12, 26, and 52 weeks. An electrochemiluminescence (ECL)-based assay for anti-P-15 antibodies in human sera was developed and validated prior to the sera analysis. This assay was shown to have a sensitivity of at least 6.3ng/ml when used to measure anti-P-15 antibodies in a positive control preparation of affinity-purified rabbit sera. Testing of the human sera samples showed no detectable anti-P-15 antibodies in any of the samples at any time point. Thus, humans implanted with up to 3.5cc of i-FACTOR™ Peptide Enhanced Bone Graft in lumbar spine fusion procedures did not elicit an immune response to the P-15 peptide present in the i-FACTOR™ Peptide Enhanced Bone Graft.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of anterior cervical discectomy and fusion (ACDF) with i-FACTOR™ Peptide Enhanced Bone Graft placed inside of an allograft ring and stabilized with an anterior plate fixation system for the reconstruction of a degenerated cervical disc at a single spine level (C₃-C₄ to C₆-C₇) following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic

imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. Subjects were required to be skeletally mature and have failed at least 6 weeks of conservative treatment prior to implantation, unless there was a significant or worsening neurologic deficit. The study was performed in the US and Canada under IDE # G050178. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. **Study Design**

Subjects were treated between June 1, 2006 and April 15, 2014. The database for this PMA reflected data collected through May 14, 2014 and included 319 total subjects. There were 19 investigational sites in the US (24 approved, 19 collected data) and 3 in Canada (4 approved, 3 collected data).

The study was a prospective, multi-center, single-blinded (subject), randomized, controlled clinical trial. All of the subjects underwent the standard ACDF procedure using a metallic anterior plate fixation system and allograft ring structural graft. The difference between the groups was the graft material placed within the allograft ring. Subjects were randomized 1:1 between the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups. For the i-FACTOR™ Peptide Enhanced Bone Graft subjects, the central cavity of the allograft was filled with i-FACTOR™ Peptide Enhanced Bone Graft. The filled allograft ring was tapped gently into the prepared disc space. For the subjects in the Control group, the autologous bone created during the procedure (milling and osteophyte removal) was collected and placed into the central cavity of the ring.

There were two aspects of the study that differed from “traditional” clinical study design. The first is that the study employed an adaptive study design wherein an interim analysis was performed after 134 total subjects (67 subjects in each group) had been enrolled and had completed their 12 month evaluation. The result of the analysis was used to modify the sample size or, if certain conditions were met, to end enrollment because the study’s hypothesis had been met. The minimum sample size before the interim analysis was 164 total subjects (increased to 180 subjects to allow for lost-to-follow-up). From the interim analysis, the study did not meet its early stopping conditions and the sample size was increased to 250 total subjects (increased to 278 to allow for lost-to-follow-up).

The second aspect of the study that differed related to blinding. In addition to subject blinding with respect to randomization and treatment, the sponsor, as well as FDA, was blinded with respect to the effectiveness data. During the course of the study, the sponsor and FDA only had access to the demographic, site enrollment/distribution and safety data. Only the Data Safety Monitoring Board (DSMB) were aware of the safety and effectiveness outcomes. The complete database was not opened/presented to the sponsor by the DSMB until after the study had been completed.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to subjects who met the following inclusion criteria:

- age between 18 and 70;
- radiographically determined discogenic origin to include at least one of the following characteristics:
 - degenerated/dark disc on MRI
 - decreased disc height compared to adjacent levels on radiographic film, CT, or MRI
 - disc herniation on CT or MRI;
- radicular symptoms by history and physical exam to include at least one of the following characteristics:
 - arm/shoulder pain
 - decreased reflexes
 - decreased strength
 - abnormal sensation;
- pain level at arm/shoulder >4 on 0-10 Visual Analog Scale (VAS) OR pain level at neck >4 on 0-10 VAS;
- Neck Disability Index (NDI) >30;
- involved disc between C3 and C7;
- undergoing ACDF at a single level;
- failed to gain adequate relief from at least 6 weeks of non-operative treatment;
- able and willing to give consent to participate in study;
- willing and able to participate in the study follow-up according to the protocol;
- willing and able to comply with postoperative management program;
- ability to understand and read English at an elementary level.

Subjects were not permitted to enroll in the study if they met any of the following exclusion criteria:

- systemic infection such as AIDS, HIV or active hepatitis;
- significant metabolic disease that, in the physician's opinion, might compromise bone growth, *e.g.*, osteoporosis or osteomalacia;
- taking medication for the prevention of osteoporosis;
- circulatory, cardiac, or pulmonary problems that could cause excessive surgical risk;
- active malignancy;
- non-discogenic source of symptoms, *e.g.*, tumor, etc.;
- multiple level symptomatic degenerative disc disease;
- previous cervical fusion;
- previous cervical decompression at the same level;

- acute cervical trauma or instability, *i.e.*, subluxation > 3 mm on flexion/extension radiographic film;
- undergoing treatment for tumor or bony traumatic injury to the cervical spine;
- rheumatoid disease of the cervical spine;
- myelopathy;
- pregnant or planning to become pregnant in the next 2 years;
- posterior cervical spine procedure scheduled;
- more than one level to be operated;
- history of substance abuse (recreational drugs, alcohol);
- is a prisoner;
- is currently involved in a study of another investigational product for similar purpose;
- has a disease process that would preclude accurate evaluation, *e.g.*, neuromuscular disease, significant psychiatric disease.

2. Follow-up Schedule

All subjects were followed for 12 months from the day of initial treatment. This included time during initial hospitalization (baseline), unplanned visits and planned follow-up visits which occurred at 6 weeks \pm 2 weeks, 3 months \pm 2 weeks, 6 months \pm 1 month, 9 months \pm 1 month and 12 months \pm 2 months post-operatively. Subjects also were followed at 18 \pm 2 months and 24 \pm 2 months post-operatively. After this initial study period ended, subjects continued to be followed annually at 36 \pm 4 months, 48 \pm 4 months, 60 \pm 4 months, and 72 \pm 4 months. These final four follow-up examinations were referred to by the sponsor as the “Extended Study”.

The evaluations performed in relation to the index procedure pre-operatively, as well as the assessments performed which were used to assess the endpoints post-operatively, are shown in Table 1 below. Adverse events (AEs) and complications were recorded at all visits, including unscheduled visits, as outlined in below.

Table 1: Summary of evaluations and associated evaluation timepoints

domain	scale	instrument	follow-up timepoint									
			BL	post-op	6w	3m	6m	9m	12m	18m ¹	24m ¹	
clinical	pain	VAS (neck)	X	X ³	X	X	X	X	X	X	X	X
		VAS (arm)	X	X ³	X	X	X	X	X	X	X	X
	neuro-logical	clinical exam	X	X	X	X	X	X	X	X	X	X
radiographic	fusion	radiograph	X		X ³	X	X	X	X	X	X	
		CT							X ²			
functional	disease-specific	NDI	X				X	X	X	X	X	
	generic	SF36v2	X				X	X	X	X	X	
complications		list		X	X	X	X	X	X	X	X	

¹ 18 and 24 month follow-ups were performed for all subjects until the last subject reached 12 months follow-up.

² CT scans were applied only in the subjects for whom there was no evidence of fusion on plain radiographs.

³ The VAS (neck and arm) at post-op and the radiographs at 6 weeks were no longer required after the first 236 subjects were enrolled.

3. Clinical Endpoints

All primary endpoints were assessed by blinded reviewers. All subjects remained blinded unless they withdrew early.

The study had three co-primary efficacy endpoints - fusion status, Neck Disability Index (NDI) and neurological success. The study also had one primary safety endpoint, the complication rate. The primary endpoints were evaluated at the 12 month follow-up.

Efficacy success was defined as follows:

- The fusion success rate in the i-FACTOR™ Peptide Enhanced Bone Graft group at 12 months is non-inferior to the fusion success rate in the Control group, and
- The mean change in NDI score from baseline in the i-FACTOR™ Peptide Enhanced Bone Graft group at 12 months is non-inferior to the mean change in NDI score from baseline in the Control group, and
- The neurological success rate in the i-FACTOR™ Peptide Enhanced Bone Graft group at 12 months is non-inferior to the neurological success rate in the Control group.

Safety success was defined as follows:

- The complication rate in the i-FACTOR™ Peptide Enhanced Bone Graft group is not significantly different from the complication rate in the Control group, or
- The complication rate in the i-FACTOR™ Peptide Enhanced Bone Graft group is significantly lower than the complication rate in the Control group.

In order to be considered a success, a subject had to be a success for each of the individual primary endpoint elements, as well as have experienced no subsequent surgical interventions or serious product-related AEs. Overall study success was achieved if both the primary efficacy endpoints and the primary safety endpoint met the pre-defined success criteria.

Secondary endpoints evaluated during the study included the following:

- neck pain and arm pain, as measured by a 10-point Visual Analog Scale (VAS);
- kyphosis, assessed using measurements from preoperative and subsequent postoperative films;
- quality of life, assessed using the SF36v2 questionnaire; and
- surgical success in relieving pre-operative symptoms, assessed using modified Odom’s criteria.

B. Accountability of PMA Cohort

At the time of database lock, of 319 subjects enrolled in the PMA study, 85.6% of the investigational and 92.2% of the control subjects are available for analysis at the completion of the study, the 12 month post-operative visit. They were subdivided into the following populations:

- Intent-to-Treat (ITT):
all subjects randomized and enrolled/treated regardless of degree of follow-up
- Modified Intent-to-Treat (mITT):
all enrolled subjects who had any follow-up (identical to the ITT); prospectively identified as the population for the safety analysis
- Completed Cases (CC):
all subjects randomized and enrolled/treated with 12 month follow-up
- Per-Protocol (PP):
the ITT population minus 6 subjects who had major protocol deviations

Table 2: Distribution of subjects by study group and analysis population

	i-FACTOR	Control	total
Intent-to-treat (ITT) set	165	154	319
Modified ITT (mITT) set	165	154	319
Completed Cases (CC) set	137	141	278
Per-Protocol (PP) set	161	152	313

At the 12 month follow-up, a total of 22 subjects were lost-to-follow-up (15 investigational and 7 control). This increased to 36 total subjects (23 investigational and 13 control) by the 24 month post-op follow-up. A small number of subjects were determined to be ineligible during the post-op period (1

investigational and 0 control at 12 months post-op and 0 investigational and 2 control at 24 months post-op). No subjects died or were withdrawn for non-compliance over the 24 month post-op period.

Subject accountability is shown below (Table 3) for all 319 subjects who were randomized into the study (the intent-to-treat (ITT) population). All randomized subjects received the assigned treatment, except that two subjects randomized to i-FACTOR™ Peptide Enhanced Bone Graft received a combination of i-FACTOR™ Peptide Enhanced Bone Graft and autograft. Follow up (regardless of visit window) at 12 months, was 85.6% and 92.2% for the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups, respectively. The lack of complete data from the three i-FACTOR Peptide Enhanced Bone Graft subjects that had not completed their 12 month follow-up as of the date of database closure was addressed through pre-specified imputation procedures. These analyses determined that these missing data had no effect on the study outcome.

Table 3: Subject accounting by visit and study arm– ITT population

		Baseline	6W	3M	6M	9M	12M ¹	18M ²	24M ³
Enrolled	i-FACTOR	165	165	165	165	165	165	165	165
	Control	154	154	154	154	154	154	154	154
Treated	i-FACTOR	165	165	165	165	165	165	165	165
	Control	154	154	154	154	154	154	154	154
Patient self-withdrawn	i-FACTOR	0	0	0	0	2	2	6	8
	Control	0	0	0	1	1	1	2	5
Visits in window, endpoints obtained	i-FACTOR	164 (99.4%)	151 (91.5%)	139 (84.2%)	137 (83.0%)	114 (69.9%)	132 (82.5%)	106 (73.6%)	94 (71.2%)
	Control	153 (99.4%)	138 (89.6%)	123 (79.9%)	132 (86.3%)	117 (76.5%)	135 (88.2%)	113 (79.6%)	102 (77.3%)
Any visit	i-FACTOR	165 (100%)	161 (97.6%)	158 (95.8%)	148 (89.7%)	131 (80.4%)	137 (85.6%)	111 (77.1%)	103 (78.0%)
	Control	154 (100%)	147 (95.5%)	141 (91.6%)	145 (94.8%)	127 (83.0%)	141 (92.2%)	118 (83.1%)	112 (84.8%)

¹Three (3) i-FACTOR subjects without 12 month follow-up who were not overdue at the time of data base closure are not included.

²Three (3) i-FACTOR subjects and 3 Control subjects without 18 month data who were not overdue at the time of data base closure are not included; 12 i-FACTOR subjects and 7 Control subjects who were not yet due for the 18 month visit at the time of data base closure are not included.

³Five (5) i-FACTOR subjects and 1 Control subjects without 24 month data who were not overdue at the time of data base closure are not included; 20 i-FACTOR subjects and 16 Control subjects who were not yet due for the 24 month visit at the time of data base closure are not included.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the US. There were no significant differences in baseline characteristics between groups with respect to age, gender, height, weight, body mass index (BMI), race/ethnicity

and smoking status. There was a difference in height which is not believed to be clinically significant.

The operative characteristics that were recorded during the study included length of cervical level operated, length of surgery, length of radiographic screening and blood loss (Table 4 below.) There were no significant between-group differences.

Table 4: Surgery characteristics by treatment arm – ITT population

	i-FACTOR	Control
Location of Surgery (level), n (%)		
C3/C4	5 (3.0)	4 (2.6)
C4/C5	20 (12.1)	12 (7.8)
C5/C6	71 (43.0)	76 (49.4)
C6/C7	69 (41.8)	64 (40.3)
Length of Surgery (min)		
n	165	153
Mean ± SD	91.4 ± 40.4	92.3 ± 32.5
Range	26 - 270	12 – 190
Total Radiographic Screening Time (sec)		
n	162	151
Mean	145.2 ± 368.3	162.6 ± 389.8
Range	1 - 1800	0 – 1800
Blood Loss (mL)		
n	164	154
Mean	41.4 ± 37.8	46.0 ± 62.0
Range	0 - 300	9 - 500

D. Safety and Effectiveness Results

1. Safety Results

As prospectively specified in the protocol, the analysis of safety was based on the mITT cohort of 319 subjects available for the 12 month evaluation. The key safety outcomes (adverse events) for this study are presented below in Tables 5 to 10.

The proportion of subjects with any reported adverse event at 12 months is shown in **Table 5** below. The proportion of subjects with any adverse event was 83.6% in the i-FACTOR™ Peptide Enhanced Bone Graft group and 82.5% in the Control group. The difference in any adverse event rate between the groups was not statistically significant. Thus, the i-FACTOR™ Peptide Enhanced Bone Graft group met the statistical criterion for safety.

Table 5: Any adverse event at 12 months by treatment arm – mITT population

Any AE within 12 months of surgery	i-FACTOR (N=165)	Control (N=154)	p-value	Success Criteria Met
Yes	138/165 (83.6%)	127/154 (82.5%)		
No	27/165 (16.4%)	27/154 (17.5%)	0.8814	Yes
Total	165	154		

Table 6 describes the number of specific adverse events by event type. The number of these individual types of adverse events was comparable between groups throughout the study.

Table 6: Summary of specific adverse events queried in the case report form over entire course of study – mITT

Number (%) of patients	i-FACTOR (n=165)		Control (n=154)	
	Subject ¹	Event	Subject ¹	Event
Any adverse event	146 (88.5)	684	137 (89.0)	705
Other ²	114 (69.1)	377	114 (74.0)	396
Axial pain (nuchal or periscapular pain or neck fatigue)	75 (45.5)	98	65 (42.9)	84
Postoperative radiculopathy/radiculitis	37 (22.4)	49	33 (21.4)	42
Dysphagia	32 (19.4)	33	30 (19.5)	31
New radiculopathy	23 (13.9)	40	36 (23.4)	65
Adjacent segment degeneration	21 (12.7)	29	25 (16.2)	26
New intractable neck pain	16 (9.7)	17	20 (13.0)	25
Nonunion/Pseudarthrosis	21 (12.8)	21	22 (14.3)	22
Dysphonia	6 (3.6)	6	3 (1.9)	3
Superficial infection	6 (3.6)	6	1(0.6)	1
Worsening of neurological status	2 (1.2)	2	4 (2.6)	4
Reoperation/subsequent surgical intervention at index level	4 (2.4)	4	6 (3.8)	6
Dural tear	1 (0.6)	1	0	0
Retropharyngeal hematoma/airway obstruction	0	0	1 (0.6)	1
Horners syndrome	0	0	1 (0.6)	1
Progression of myelopathy	1 (0.6)	1	0	0
Cardiopulmonary event	1 (0.6)	1	0	0
Screw malposition	0	0	1 (0.6)	2

¹ Each subject is counted only once in the respective category.

² The "Other" category consists of the following types of events (in descending order according to the total number of events) that occurred in both the i-FACTOR™ Peptide Enhanced Bone Graft group and the Control group: musculoskeletal and connective tissue disorders; nervous system disorders; injury, poisoning and procedural complications; infections and infestations; general disorders and administrative site conditions; respiratory, thoracic and mediastinal disorders; surgical and medical procedures; gastrointestinal disorders; psychiatric disorders; endocrine disorders; skin and subcutaneous tissue disorder; neoplasms benign, malignant and unspecified (including cysts and

polyps); renal and urinary; metabolism and nutrition disorders; vascular disorders; eye disorders; investigations; immune system disorders; cardiac disorders; ear and labyrinth disorders; and reproductive system and breast disorders. The “Other” category also contains an event falling within pregnancy, puerperium and perinatal conditions, but this type of event only presented in the Control group.

Adverse Events by Time of Occurrence

Table 7 shows the number of adverse events by category and time of occurrence. The number of these adverse events was comparable between groups throughout the study.

Table 7: Summary of specific adverse events queried in the case report form and time of occurrence over entire course of study – mITT population

Number of Events	Treatment	PreOp	0-42 ¹ Days	43-90 Days	91- 180 Days	181- 365 Days	366- 730 Days	>730 Days
Any adverse event	i-FACTOR	2	161	72	92	174	169	13
	Control	3	181	78	101	179	144	18
Other	i-FACTOR	2	73	44	53	102	93	9
	Control	1	98	30	62	113	80	11
Axial pain (nuchal or periscapular pain or neck fatigue)	i-FACTOR	0	28	13	14	26	16	1
	Control	2	30	15	10	14	11	2
New radiculopathy	i-FACTOR	0	1	2	5	18	14	0
	Control	0	4	14	9	20	16	2
Postoperative radiculopathy/radiculitis	i-FACTOR	0	19	8	6	8	8	0
	Control	0	18	7	6	3	7	1
Dysphagia	i-FACTOR	0	25	3	3	1	1	0
	Control	0	21	2	4	4	0	0
Adjacent segment degeneration	i-FACTOR	0	0	0	3	9	16	1
	Control	0	0	1	4	8	12	1
New intractable neck pain	i-FACTOR	0	2	0	3	2	8	2
	Control	0	4	3	5	7	5	1
Nonunion/Pseudarthrosis	i-FACTOR	0	3	2	4	5	7	0
	Control	0	2	4	1	8	7	0
Superficial infection	i-FACTOR	0	6	0	0	0	0	0
	Control	0	1	0	0	0	0	0
Dysphonia	i-FACTOR	0	5	0	1	0	0	0
	Control	0	2	1	0	0	0	0
Hypothyroidism	i-FACTOR	1	0	0	0	0	4	1
	Control	0	0	0	0	1	0	0
Worsening of the neurological status	i-FACTOR	0	0	0	0	0	2	0
	Control	0	0	1	0	1	2	0
All subsequent surgical intervention ²	i-FACTOR	0	0	0	2	1	7	5
	Control	0	0	0	3	3	4	6
Screw malposition	i-FACTOR	0	0	0	0	0	0	0

Number of Events	Treatment	PreOp	0-42 ¹ Days	43-90 Days	91- 180 Days	181- 365 Days	366- 730 Days	>730 Days
	Control	0	0	0	0	0	2	0
Cardiopulmonary event	i-FACTOR	0	1	0	0	0	0	0
	Control	0	0	0	0	0	0	0
Dural tear	i-FACTOR	0	1	0	0	0	0	0
	Control	0	0	0	0	0	0	0
Horners syndrome	i-FACTOR	0	0	0	0	0	0	0
	Control	0	1	0	0	0	0	0
Progression of myelopathy	i-FACTOR	0	0	0	0	1	0	0
	Control	0	0	0	0	0	0	0
Retropharengal hematoma/airway obstruction	i-FACTOR	0	0	0	0	0	0	0
	Control	0	1	0	0	0	0	0

¹ Day 0 is a day of surgery. ² Includes revisions, removals, supplemental fixations and disc arthroplasty
NOTE: Time of occurrence missing for two events.

Study-Related Adverse Events

Table 8 shows adverse events by relatedness to the study. The rates of adverse events in all categories were similar in the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups.

Table 8: Summary of study-related adverse events by case report form query over entire course of study –MITT population

	Main Study to 24 months		Extension to 72 months	
	i-FACTOR	Control	i-FACTOR	Control
	165	154	86	92
Pseudarthrosis/Non union	21 (13)	21 (13)	16 (9)	17 (11)
Hardware failure	--	--	--	--
Screw malposition	0	1 (1)	--	--
Postoperative radiculopathy/radiculitis	37 (22)	33 (21)	6 (4)	9 (6)
Axial pain*	75 (46)	65 (43)	16 (10)	17 (11)
New intractable neck pain	16 (10)	20 (13)	2 (1)	8 (5)
Adjacent segment degeneration	21 (13)	25 (16)	2 (1)	1 (1)
Instability	--	--	--	--
Reoperation/Subsequent surgical intervention	2 (1)	3 (2)	0	1(1)
Dural tear	1 (1)	0	--	--
Epidural hematoma	--	--	--	--
Retropharyngeal hematoma/airway obstruction	0	1 (1)	--	--
Horner's syndrome	0	1(1)	--	--
Partial or complete vocal cord paralysis/Dysphonia (hoarseness)	6 (4)	3 (2)	2 (1)	0
Deep infection	--	--	--	--
Superficial infection	6 (4)	0	1 (1)	0
Graft site pain > 6 months post-op	--	--	--	--
Dysphagia	32 (19)	30 (20)	8 (5)	10 (6)

	Main Study to 24 months		Extension to 72 months	
	i-FACTOR	Control	i-FACTOR	Control
Progression of myelopathy	1 (1)	0	--	--
New radiculopathy	23 (14)	36 (23)	7 (4)	6 (4)
Perioperative worsening of myelopathy	--	--	--	--
Graft dislodgement/migration	--	--	--	--
Graft subsidence	0	0	0	0
Graft site pain	--	--	--	--
Postoperative kyphosis	--	--	--	--
Cardiopulmonary event	1 (1)	0	--	--
Worsening of Neurological status	2 (1)	4 (3)	0	1 (1)
Signs of potential immunologic response	--	--	--	--
Other	114 (69)	114 (74)	22 (13)	27 (18)

* Axial pain = nuchal, periscapular, or neck pain

There were a small number of adverse events that occurred at different rates in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to the Control group. However, these adverse event rate differences did not result in clinical outcome differences:

- superficial infection (6 cases or 3.6% in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to 1 case or 0.6% in the Control group);
- hypothyroidism (6 cases or 3.6% in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to 1 case or 0.6% in the Control group); and
- new radiculopathy (23 cases or 13.9% in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to 36 cases or 23.4% in the Control group).

Subsequent Surgical Interventions

As shown in **Table 9**, there were 14 subjects (15 events) in the i-FACTOR™ Peptide Enhanced Bone Graft group and 16 subjects (16 events) in the Control group with secondary surgical interventions. Seven subjects (8 events) in the i-FACTOR™ Peptide Enhanced Bone Graft group and 13 subjects (13 events) in the Control group had subsequent surgical interventions that included the index surgery level. The most common type of secondary surgical intervention was supplemental fixation in the i-FACTOR™ Peptide Enhanced Bone Graft group and revision in the Control group. There were 4 reoperations at the index level in the i-FACTOR™ Peptide Enhanced Bone Graft group, and 6 in the Control group.

Table 9: Summary of subsequent surgical interventions – mITT population

	i-FACTOR (n=165)	Control (n=154)	Total
Subjects with any subsequent surgery	14	16	30
Subsequent surgery	15	16	31

	i-FACTOR (n=165)	Control (n=154)	Total
Same level as index (%)	4 (26.6)	6 (37.5)	9 (30.0)
Procedures			
	15	20	35
Removal	1(6.7)	4 (20.0)	5 (14.2)
Revision Reoperation	2 (13.3)	7 (35.0)	9 (25.7)
Supplemental fixation	2 (13.3)	2 (10.0)	3 (8.6)
Other	4 (26.6)	1 (5.0)	5 (14.2)
	6 (42.9)	6 (30.0)	12 (34.3)

Serious Adverse Events

Table 10 shows all serious adverse events by category. Forty-five (45) i-FACTOR™ Peptide Enhanced Bone Graft subjects (27.3%) reported a serious adverse event compared to 35 Control subjects (22.7%), and the i-FACTOR™ Peptide Enhanced Bone Graft group reported 70 serious adverse events compared to 60 serious adverse events reported by the Control group. There were 4 reoperations at the index level in the i-FACTOR group, and 6 in the Control group. The incidence of Serious Adverse Events was not statistically significantly different between the treatment groups (p=0.368).

**Table 10: Summary of serious adverse events by category over entire course of study
— MITT population**

	i-FACTOR (n=165)		Control (n=154)		p-value²
	Subjects¹	Events	Subjects¹	Events	
Any adverse event	45 (27.3)	70	35 (22.7)	59	0.368
Other ³	33 (20.0)	47	26 (16.9)	38	0.564
Adjacent segment degeneration	7 (4.2)	7	7 (4.5)	7	1.000
New radiculopathy	6 (3.6)	6	6 (3.9)	6	1.000
Pseudarthrosis	3 (1.8)	3	3 (1.9)	3	1.000
Reoperation/subsequent surgical intervention at index level	4 (2.4)	4	6 (3.8)	6	0.675
Superficial infection	6 (3.6)	6	1 (0.6)	1	0.499
New intractable neck pain	1 (0.6)	1	1 (0.6)	1	1.000
Retropharyngeal hematoma/airway obstruction	0	0	1 (0.6)	1	0.483
Progression of myelopathy	1 (0.6)	1	0	0	1.000
Postoperative radiculopathy/radiculitis	0	0	1 (0.6)	1	0.483
Axial pain (nuchal or periscapular pain or neck fatigue)	1 (0.6)	1	0	0	1.000

¹ Each subject is counted only once in the respective category.

² Fisher's exact test between i-FACTOR™ Peptide Enhanced Bone Graft and Control group.

³ The “Other” category consists of the following types of events (in descending order according to the total number of events) that occurred in both the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups: musculoskeletal and connective tissue disorders; nervous system disorders; surgical and medical procedures; infections and infestations; neoplasms benign, malignant and unspecified (incl cysts and polyps); injury, poisoning and procedural complications; respiratory, thoracic and mediastinal disorders; gastrointestinal disorders; and skin and subcutaneous tissue disorders. The “Other” category also contains events characterized as cardiac disorders, investigations, and reproductive system and breast disorders, which presented only in the i-FACTOR™ Peptide Enhanced Bone Graft group, as well as general disorders and administrative site conditions, and renal and urinary disorders, which only presented in the Control group.

2. Effectiveness Results

Primary Effectiveness Analysis:

As pre-specified by the study Statistical Analysis Plan, primary analyses of primary efficacy endpoints were performed on the PP population. The PP population excluded 6 subjects with major protocol deviations with the potential to impact the primary endpoint results. The PP population included 313 subjects available for analysis of the primary endpoints at 12 months (161 randomized i-FACTOR™ Peptide Enhanced Bone Graft subjects and 152 Control subjects). Key effectiveness outcomes are presented in Tables 11 to 17.

Fusion Rate

Fusion status at 12 months is shown in **Table 11**. The fusion rate was 88.97% in the i-FACTOR™ Peptide Enhanced Bone Graft group and 85.82% in the Control group. The i-FACTOR™ Peptide Enhanced Bone Graft group fusion rate was non-inferior to the Control group fusion rate at 12 months (p=0.0004), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 11: Fusion status at 12 months – PP population

Fusion Status	i-FACTOR (n=161)	Control (n=152)	difference (95% CI) i-FACTOR – Control	non-inferiority margin
Fused	129/145 (88.97%)	121/141 (85.82%)		
No evidence of fusion	16/145 (11.03%)	20/141 (14.18%)	3.15% (-4.54%, 10.84%)	-10%

The table below (**Table 12**) shows fusion success based on the number of PP subjects with fusion status determination, i.e., evaluable imaging. Favorable trends of increasing fusion success rates over time were demonstrated in both treatment groups at the 18 month (93.0% i-FACTOR™ Peptide Enhanced Bone Graft 92.8% Control) and 24 month (96.8% i-FACTOR™ Peptide Enhanced Bone Graft, 95.1% Control) visits. There was no statistically significant difference between the two groups at any time point.

Table 12: Summary of fusion success by follow-up visit and study arm – PP population

Visit		i-FACTOR (n=161)	Control (n=152)	p-value
6M	Subjects with fusion status determination	138	140	0.516
	Subjects with successful fusion (%)	45 (32.6)	40 (28.6)	
9M	Subjects with fusion status determination	121	119	0.897
	Subjects with successful fusion (%)	69 (57.0)	69 (58.0)	
12M	Subjects with fusion status determination	145	141	0.478
	Subjects with successful fusion (%)	129 (89.0)	121 (85.8)	
18M	Subjects with fusion status determination	100	111	1.000
	Subjects with successful fusion (%)	93 (93.0)	103 (92.8)	
24M	Subjects with fusion status determination	93	103	0.724
	Subjects with successful fusion (%)	90 (96.8)	98 (95.1)	

Proportion is based on the number of subjects with non-missing fusion status.

Variable analyzed using Fisher’s exact test.

Missing fusion success at 12 month and later visits has been imputed using last value carry on of the most recent non-missing fusion status starting from the 6 month visit.

Neck Disability Index

Table 13 shows least square estimated mean changes in imputed sample NDI, adjusted for baseline NDI, in the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups. The mean change (improvement) in the i-FACTOR™ Peptide Enhanced Bone Graft group at 12 months was 28.8 (95% CI 25.8, 31.7) and the mean change in the Control group was 27.4 (95% CI 24.4, 30.5). Subjects treated with i-FACTOR™ Peptide Enhanced Bone Graft had non-inferior NDI outcomes at 12 months compared to the Control group (p<0.0001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 13: Mean change in Neck Disability Index (NDI) at 12 months, adjusted for baseline NDI – PP population

NDI	i-FACTOR (n=134)	Control (n=137)	Difference (95% CI) i-FACTOR - control	non- inferiority margin	p-value
12 month mean change (95% CI)	28.8 (25.8, 31.7)	27.4 (24.4, 30.5)	1.35 (-2.8, 5.5)	-11	<0.0001

Neurological Outcomes

Neurological success status at 12 months is shown in **Table 14**. The neurologic success rate was 93.71% in the i-FACTOR™ Peptide Enhanced Bone Graft group and 93.01% in the Control group. Subjects treated with i-FACTOR™ Peptide Enhanced Bone Graft had non-inferior neurological outcomes at 12 months, compared to the Control group ($p < 0.0001$), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 14: Neurological success at 12 months – PP population

Neurological Success	i-FACTOR (n=161)	Control (n=152)	difference (95% CI) i-FACTOR – Control	non-inferiority margin
Yes	134/143 (93.71%)	133/143 (93.01%)		
No	9/143 (6.29%)	10/143 (6.99%)	0.70% (-5.07%, 6.47%)	-15%
Total¹	143	143		

¹Total is the number of observed subjects.

Overall Success

Table 15 shows results of the overall success (responder analysis) at 12 months by treatment group in the PP population. For the composite endpoint of overall success, which required success on all four primary endpoints, the proportion of subjects responders was significantly higher in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to the Control group (68.75% and 56.94%, respectively, Chi-square $p=0.0382$). The difference in overall success was 11.81% in favor of the i-FACTOR™ Peptide Enhanced Bone Graft group.

Table 15: Responder analysis at 12 months – PP population

Component	Value	i-FACTOR n (%)	Control n (%)	p-value
Fusion success	No evidence of fusion	16 (11.03%)	20 (14.18%)	0.4220
	Fused	129 (88.97%)	121 (85.82%)	
NDI success	NDI improved ≤ 15 from baseline	29 (20.57%)	36 (25.90%)	0.2907
	NDI improved > 15 from baseline	112 (79.43%)	103 (74.10%)	
Neurological success	Yes	134 (93.71%)	133 (93.01%)	0.8123
	No	9 (6.29%)	10 (6.99%)	
Safety success	No	4 (2.48%)	7 (4.61%)	0.3085
	Yes	157 (97.52%)	145 (95.39%)	
Overall success	Overall Failure	45 (31.25%)	62 (43.06%)	0.0382
	Overall Success	99 (68.75%)	82 (56.94%)	

Secondary Effectiveness Results:

As pre-specified by the study Statistical Analysis Plan, primary analyses of secondary efficacy endpoints were performed on the PP population. **Table 16** shows secondary outcomes by treatment arm in the PP population. On average, there was a significant improvement at 12 months compared to baseline in both treatment arms in all secondary outcomes represented in the table.

The significance of difference in secondary endpoints between the two arms was evaluated by an ANCOVA test applied on multiply imputed samples between the two treatment arms. There were no significant differences in outcomes between the i-FACTOR™ Peptide Enhanced Bone Graft group and Control group

Table 16: Changes in secondary endpoints at 12 months by treatment arm - PP population

Endpoint	i-FACTOR (n=161) mean change (95% CI)	Control (n=152) mean change (95% CI)	t -test	Pr > t ¹
VAS Arm _{b-12m}	4.89 (4.44 to 5.34)	4.85 (4.40 to 5.30)	0.12	0.9010
VAS Neck _{b-12m}	4.45 (4.00 to 4.90)	4.39 (3.96 to 4.82)	0.22	0.8257
SF36v2 PCS _{12m-b}	10.02 (8.39 to 11.66)	9.95 (8.25 to 11.65)	0.06	0.9520
SF36v2 MCS _{12m-b}	8.33 (6.66 to 10.01)	8.21 (6.48 to 9.95)	0.10	0.9204

¹ ANCOVA adjusted for the baseline value of the endpoint

PCS = PHYSICAL HEALTH COMPONENT SCORE;

PCS = MENTAL HEALTH COMPONENT SCORE;

b-12m = value is the difference between the pre-operative and 12 months value;

12m-b = value is the difference between the 12 months value and pre-operative.

Values are least square estimated means and corresponding 95% Confidence Intervals

Table 17 shows Odom’s Criteria of success at 12 months by treatment arm. Over 80% of subjects in each arm reported excellent or good outcomes. There were no differences in Odom’s Criteria for success at 12 months between the i-FACTOR™ Peptide Enhanced Bone Graft and Control arms (Chi-square p=0.9929, Fisher exact = 1.000).

Table 17: Odom’s Criteria at 12 months by treatment arm – PP population

Category	i-FACTOR (n=161)	Control (n=152)
Excellent: Improvement ≥ 80% Deterioration < 10%	80/129 (62.02%)	80/129 (62.02%)
Good: Improvement ≥ 70% Deterioration < 15%	25/129 (19.38%)	25/129 (19.38%)
Fair: Improvement ≥ 50% Deterioration < 20%	16/129 (12.40%)	15/129 (11.63%)
Poor: Improvement < 50% Deterioration > 20%	8/129 (6.20%)	9/129 (6.98%)

Extended Study Follow-Up Data:

To provide continuous follow-up of enrolled subjects and to gather longer-term data, the IDE protocol was amended to add annual follow-up through 72 months. The available data through the 60 month follow-up visit are discussed below.

In the extended study, very high fusion rates were observed in both treatment arms, with consistently higher fusion rates in the i-FACTOR™ Peptide Enhanced Bone Graft group compared to the Control group at each extended study visit. At 60 months, the fusion rate in the i-FACTOR™ Peptide Enhanced Bone Graft group was 100% and in the Control group was 88.5%. Consistent with the results reported for the 12 month primary endpoint visit, longer term follow-up through 60 months continued to demonstrate comparable NDI improvement between the treatment arms.

In terms of secondary endpoints, mean VAS arm pain and mean VAS neck pain during the extended study period, for both groups, were consistent with the earlier results. The mean SF36v2 MCS and PCS scores were comparable for the i-FACTOR™ Peptide Enhanced Bone Graft and Control groups at all extended study follow-up visits.

The total number of subjects experiencing an adverse events was similar for the i-FACTOR™ Peptide Enhanced Bone Graft group (20 subjects (23.3%)) and the Control group (25 subjects (27.2%)); however, the number of adverse events in the Control group (94 events) was greater than that in the i-FACTOR™ Peptide Enhanced Bone Graft group (54 events). Most categories of adverse events occurred at similar rates in the two treatment groups, and the most common categories were musculoskeletal and connective tissue disorders (i-FACTOR™ Peptide Enhanced Bone Graft, 14 subject (16.3%); Control, 17 subjects (18.5%)) and nervous system disorders (i-FACTOR™ Peptide Enhanced Bone Graft, 8 subjects (9.3%); Control, 18 subjects (19.6%)). During the extended study, only one i-FACTOR™ Peptide Enhanced Bone Graft subject and two Control subjects underwent subsequent surgical intervention.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes (fusion status, NDI score and neurological status):

- age (< or \geq 50)
- gender
- litigation
- ever smoking (\leq or $>$ 100 cigarette)
- current smoking (yes vs. no)
- NDI score at baseline (< or \geq 40)
- use of NSAIDs at baseline
- financial interest of the investigator
- type of cervical fixation plate used.

There were no statistically significant differences associated with any of these factors.

Although there was not a significant interaction between treatment group and the factors of “current smoking” or “ever smoking” with respect to fusion, there was an overall effect of lower fusion success rates in both treatment groups considered together by approximately 13% points for “current smoking” and 11% points for “ever smoking”, and both factors were significant in separate multivariate models for fusion which included treatment group. It is not unexpected that smoking could have an effect on fusion outcome. Similar results were observed for NDI, but “current smoking” and “ever smoking” were not significant predictors of neurological success or AEs. However, after adjusting for these factors, there continued to be statistical non-inferiority for the effectiveness endpoints.

Gender was another factor with an overall effect, with overall fusion rates at 12 months of 83.2% among females and 93.8% among males. However, there was no interaction between treatment group and gender on fusion outcome ($p = 0.8308$). Gender was not a significant predictor of NDI, neurological status or AEs. As with “current smoking” and “ever smoking”, non-inferiority was maintained after adjusting for gender.

The sponsor also performed a logistic regression analysis of pre-operative factors associated with lack of fusion at 12 months. The significant factors were “ever smoking”, female gender and older age. Treatment group was not a significant factor.

A multiple regression analysis of predictors of change in NDI was also performed. Pre-operative NDI, litigation, duration of symptoms, VAS pain at arm and shoulder and SF36v2 PCS and MCS were significant predictors (using the cut-off point $\alpha = 0.1$.) “Duration of symptoms” was highly significant (p -value < 0.0001).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 100 investigators of which none were full-time or part-time employees of the sponsor and five (5) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 3

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

i-FACTOR™ Peptide Enhanced Bone Graft is a composite bone graft material consisting of multiple components - a synthetic peptide (P-15) adsorbed onto calcium phosphate particles, which are suspended in a hydrogel carrier. The i-FACTOR™ Peptide Enhanced Bone Graft must be used in combination with an allograft ring and a metallic anterior cervical plate.

The scientific evidence presented in the preceding sections provides reasonable assurance that i-FACTOR™ Peptide Enhanced Bone Graft is a safe and effective alternative to autograft in single level anterior cervical discectomy and fusion (ACDF) procedures using an allograft ring and metallic anterior plate supplemental stabilization for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic

imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels in patients who have failed at least 6 weeks of conservative treatment prior to implantation

Non-clinical studies provide support for the safety of i-FACTOR™ Peptide Enhanced Bone Graft, including local and systemic biocompatibility studies, as well as cell tumorigenicity. Animal studies were conducted to evaluate i-FACTOR™ Peptide Enhanced Bone Graft's role in spinal fusion. Additional animal studies evaluated dose-based immunogenicity of the product. Human clinical data were also used to characterize immunogenicity.

These studies show that i-FACTOR™ Peptide Enhanced Bone Graft is biocompatible, non-tumorigenic and non-immunogenic. The product also demonstrated a similar fusion response when compared to autograft bone. No evidence of ectopic or heterotopic bone formation has been demonstrated in these animal studies.

i-FACTOR™ Peptide Enhanced Bone Graft demonstrated a reasonable assurance of safety and effectiveness as a substitute for autograft bone in a randomized clinical trial involving 319 subjects. These conclusions are based upon clinical and radiographic measurements.

A. Effectiveness Conclusions

In the pivotal trial, 319 subjects were enrolled and treated. The control group for the clinical trial received local autograft bone within the allograft ring compared to the investigational group which received i-FACTOR™ Peptide Enhanced Bone Graft. Clinical and radiographic effectiveness were assessed at 12 months post-operatively. These primary endpoint evaluations included radiographic assessment of fusion, changes in the Neck Disability Index (NDI) score from baseline and neurological success. Specifically, effectiveness success was defined the presence of radiographic fusion, an increase in NDI score of more than 15 points and maintenance or improvement in neurological status. Analysis of subject demographics showed no differences between the treatment groups. According to the pre-defined analyses, the effectiveness of the subjects treated i-FACTOR™ Peptide Enhanced Bone Graft was non-inferior to that of the subjects treated with autograft bone for each of the primary effectiveness endpoints.

Secondary endpoints evaluated during the study included neck pain and arm pain, as measured by a 10-point Visual Analog Scale (VAS); kyphosis, assessed using measurements from preoperative and subsequent postoperative films; quality of life, assessed using the SF36v2 questionnaire; and surgical success in relieving pre-operative symptoms, assessed using Modified Odom's criteria. There were no significant differences in outcome between the two study groups for the secondary effectiveness endpoints.

In conclusion, the clinical trial data indicate that, at 12 months postoperatively, i-FACTOR™ Peptide Enhanced Bone Graft is non-inferior to the autograft control treatment for the population and indications studied in this investigation.

B. Safety Conclusions

The key safety conclusions from the trial are that subjects treated with i-FACTOR™ Peptide Enhanced Bone Graft had overall similar types and rates of adverse events (AEs) compared to subjects treated with autograft. The clinical trial revealed several AEs that occurred at higher rates. Superficial infections and hypothyroidism occurred at a higher rate in the i-FACTOR™ Peptide Enhanced Bone Graft group, while the rate of new radiculopathy was higher in the control group. These differences did not have a detrimental impact on clinical outcome for either group.

With the limited exceptions noted above, the data demonstrate that use of i-FACTOR™ Peptide Enhanced Bone Graft resulted in a similar safety profile when compared to autograft.

C. Benefit-Risk Conclusions

The probable benefits of i-FACTOR™ Peptide Enhanced Bone Graft are based on data collected in the clinical trial as described above. Benefits of i-FACTOR™ Peptide Enhanced Bone Graft demonstrated over the 12 month evaluation period studied include:

i-FACTOR™ Peptide Enhanced Bone Graft and autograft control subjects achieved comparable clinical and radiographic effectiveness. Regarding risk, subjects treated with i-FACTOR™ Peptide Enhanced Bone Graft had overall similar rates of AEs compared to subjects treated with autograft with the few exceptions noted above. When overall success, defined as success for each of the individual primary effectiveness measurements and safety success, was assessed, the subjects implanted with i-FACTOR™ Peptide Enhanced Bone Graft had significantly greater overall success rates compared to the control group.

In conclusion, the data support that the probable clinical benefits of i-FACTOR™ Peptide Enhanced Bone Graft for single level ACDF procedures using an allograft ring and supplemental anterior fixation stabilization outweigh the probable risks through 12 months of follow-up.

D. Overall Conclusions

The preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of i-FACTOR™ Peptide Enhanced Bone Graft when used in accordance with the indications for use when compared to autograft. Based on the clinical trial results, the clinical benefits of the use of i-FACTOR™ Peptide Enhanced Bone Graft outweigh the risks in terms of clinical and radiographic outcome when

used in the intended population in accordance with the directions for use, and as compared to the autograft control treatment in the same intended population. The valid scientific evidence presented in the preceding sections provides reasonable assurance that i-FACTOR™ Peptide Enhanced Bone Graft is a safe and effective alternative to autograft for use in single level ACDF procedures when the product is placed within an allograft ring and stabilized with supplemental anterior fixation hardware.

XIII. CDRH DECISION

CDRH issued an approval order on November 3, 2015. The final conditions of approval cited in the approval order are described below.

1. Conduct a post approval clinical study that follows the subjects enrolled under IDE G050178 for a total of 72 months post-op. The proposed post-approval clinical study plan is described in Attachment IV-4.22 in the original PMA submission and repeated below:

“...In order to assess the long-term performance of P-15 Putty, Cerapedics plans to conduct a post-approval study to obtain a total of 6 years of postoperative data from a statistically-justified number of patients treated with this device. The study will be open to all patients in the IDE study at the time of device approval. All sites with subjects reaching the 2-year follow up period have been asked to participate. Of the 22 sites that enrolled subjects, 17 sites have agreed to participate in the post-approval study. These sites have asked all IDE patients to consent to the study through 6-year follow-up. Subjects are already enrolled into extended follow-up under the current FDA approved IDE Protocol addendum. The post-approval study will continue to follow these patients according to the approved protocol addendum (see **Attachment IV-4.6**).

A statistical justification based on the current sample size follows. Cerapedics expects to enroll 220 subjects into the post-approval study. A conservative estimate of expected number of subjects at 6 years follow-up is 170 subjects (i.e. loss of 10 subjects per year due to withdrawals, death and other causes). Further, Cerapedics expects up to 70% follow-up rate at all follow-ups. Thus, Cerapedics expects 154 subjects at year 3 and 120 subjects at year 6 years. The working study hypothesis is that P-15 Putty will be non-inferior to autologous bone. This working hypothesis will be tested by a non-inferiority approach as follows. In order to be a success, non-inferiority structured H0 for each primary efficacy endpoint has to be rejected. Three independent hypotheses will be tested, for each of the primary endpoints using the same non-inferiority margins as in the main study. The hypotheses will

be tested with one-sided and two-sided 95% C.I. For the fusion and neurological success primary endpoints, the exact binomial confidence interval will be created. For the change in NDI primary endpoint, the confidence intervals for the differences in mean change between the groups adjusting for baseline NDI value will be created. If the confidence interval does not include non-inferiority margin, the H0 will be rejected. Cerapedics will evaluate a need to adjust the analysis for possible differences between the groups.

Statistical power.

- We estimate that the fusion rate will be between 98% and 100% at all follow-ups based on the main study results. At 3 years, the study will have 99% power and at 6 years it will have 98% power to reject non-inferiority H0 with non-inferiority margin of 10%.
- The study will have 97% power at 3 years and 93% power at 6 years to reject H0 for the change in NDI outcome under the standard deviation assumption of 19 (based on the main study) and a non-inferiority margin of 11.
- The study will have 95% power at 3 years and 90% power at 6 years to reject non-inferiority H0 for neurological success outcome under the assumption of a neurological success rate of 93% as observed in the main study and a non-inferiority margin of 15%.

The rate of adverse events will be compared between the P-15 Putty and the control arm using the Fisher exact test and superiority approach, in the same way as in the original IDE study. Failure to reject H0 or, rejection of H0 in favor of P-15 group will meet safety success. We will also compare the rate of subsequent surgical interventions at the index level.

The data from the post-approval study will be submitted to FDA as part of the annual report and will include the following data collected annually for each patient:

1. A description of any surgical interventions, which will include reoperations, removals, revisions, and supplemental fixations;
2. A radiographic assessment of fusion using the same criteria employed in the original IDE study;
3. An assessment of neurological outcomes;

4. An assessment of pain and function using the same criteria employed in the original IDE study (*i.e.*, change in NDI and change in neck and arm VAS for pain);
 5. Other primary and secondary endpoints not specified in items 1-3 above, as specified in the IDE study protocol addendum...”
2. Comply with the following stability commitments:
- a. Conduct bioactivity stability test for the first 3 production batches of i-FACTOR™ Peptide Enhanced Bone Graft product manufactured and packaged according to the commercialized manufacturing process. The stability study should be performed at the long term controlled storage condition of 25°C/60%RH with test frequency of 0, 6, 12 months for the 1st year, every 6 months for the 2nd year and annually thereafter through the shelf life. The stability data report should be submitted as a “Report – Other” due at the same time as the annual report, but submitted separately from the annual report.
 - b. Place a minimum one commercial batch of the finished product into long-term stability testing at 25°C/60% RH through the shelf life on an annual basis if manufactured.
 - c. Withdraw from the market, any batches that fail to meet the approved specifications for the putty product during long-term stability evaluations.

The applicant’s manufacturing facilities have been inspected and found 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.