INSTRUCTIONS FOR USE

CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician.

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 conjunction with an allograft ring or a polyether ether ketone (PEEK), titanium alloy or PEEK/titanium interbody fusion device cleared by FDA and a metallic anterior cervical plate.

i-FACTOR Peptide Enhanced Bone Graft 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 α1 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° 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 250-425µm and are naturally porous.

Hydrogel component

The hydrogel component consists of plant-derived sodium carboxymethycellulose (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 the 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 of the allograft ring.

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, or a PEEK, titanium alloy or PEEK/titanium interbody fusion device cleared by FDA for use in the cervical spine and with supplemental anterior plate fixation.

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

WARNINGS:

- i-FACTOR Peptide Enhanced Bone Graft is designed for single patient use only. Attempting to reuse the putty will adversely affect product sterility and physical handling characteristics. DO NOT attempt to re-sterilize or re-use. Discard unused contents.
- Women of childbearing potential should avoid becoming pregnant for one year after being treated with i-FACTOR Peptide Enhanced Bone Graft. The influence of i-FACTOR Peptide Enhanced Bone Graft on pregnant women and on fetal development is unknown.
- The effect of i-FACTOR Peptide Enhanced Bone Graft on nursing women has not been evaluated. It is not known if i-FACTOR Peptide Enhanced Bone Graft is excreted in human milk.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft when mixed with any additional components, e.g., autograft, allograft, other bone grafting materials, blood, saline or bone marrow aspirate, has not been established.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft used with implants other than allograft bone rings or FDA cleared PEEK, titanium alloy or PEEK/titanium interbody fusion devices and anterior cervical plates have not been established.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft applied in anatomic

sites other than the cervical spine have not been established.

- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft applied in anatomic sites other than the cervical spine have not been established.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft has not been established in patients with pathology at more than one level and/or pathology not localized to the disc space.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft in patients who are not skeletally mature has not been established.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft in patients with hepatic or renal impairment has not been established.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft has not been established for volumes out of the range of 0.15cc to 4.0cc.
- The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft in patients with metabolic bone disease has not been established.
- As with any surgical procedure, care should be exercised in treating individuals with pre-existing conditions that may affect the success of the surgical procedure.
    - *Bleeding disorders of any etiology:* The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft has not been established in patients with bleeding disorders of any etiology.
    - *Long-term steroidal therapy:* The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft has not been established in patients who have had long term steroidal therapy.
    - *Immunosuppressive therapy or high dosage radiation therapy:* The safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft has not been established in patients who have had immunosuppressive therapy or high dosage radiation therapy.

PRECAUTIONS:

- i-FACTOR Peptide Enhanced Bone Graft should only be used by physicians who are experienced with anterior cervical spinal procedures and are familiar with the implant components, instruments, appropriate selection criteria, biomechanics, and risks associated with such procedures. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, including neurological complications.
- DO NOT USE IF STERILE PACKAGING IS OPENED OR DAMAGED. Discard or return damaged packaging and all contents.
- Do not use after the printed expiration date on the label.
- i-FACTOR Peptide Enhanced Bone Graft should only be used in surgical procedures where it can be adequately contained in the allograft ring or FDA cleared interbody fusion device. Avoid overfilling the allograft ring or fusion device. Avoid pressurizing the treatment site. While it was not observed during the clinical study used to support marketing use in the cervical spine, inadequate containment of i-FACTOR Peptide Enhanced Bone Graft could result in product migration from the intended implantation site, as for any graft material. If product migration occurs, clinical outcomes may be compromised by the lack of bone graft material in the appropriate space. Potential patient adverse events caused by inadequate containment and migration of i-FACTOR Peptide Enhanced Bone Graft could include, but are not limited to, the following: heterotopic bone formation, pain, neural impingement, physical impairment, or loss of mobility function; any of which may require revision surgery.
- i-FACTOR Peptide Enhanced Bone Graft is not intended to provide load bearing structural support during the healing process. i-FACTOR Peptide Enhanced Bone Graft should only be used inside an allograft ring or FDA(k) cleared interbody fusion device. Use of metallic anterior plate fixation is required to assure stabilization of the construct in all planes.

- Patients with significant vascular impairment may be at increased risk of non-union.
- A sheep study conducted to determine whether i-FACTOR Peptide Enhanced Bone Graft elicits an immune response showed no detectable anti-P-15 antibodies in any of the study animals. In a small clinical study (n = 40), i-FACTOR Peptide Enhanced Bone Graft did not elicit an immune response in humans implanted with up to 3.5cc of i-FACTOR Peptide Enhanced Bone Graft.

POTENTIAL ADVERSE EVENTS:

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 more detailed information on the specific adverse effects that occurred during the clinical trial, please refer to the Safety Results Section below (Summary of IDE Clinical Study).

SUMMARY OF IDE CLINICAL STUDY:

Overview of The Clinical Study

The i-FACTOR Peptide Enhanced Bone Graft in Anterior Cervical Fusion with Instrumentation Study was a multi-center, single-blinded (subject), randomized, controlled trial. The objective of the study was to evaluate whether i-FACTOR Peptide Enhanced Bone Graft is non-inferior to local autologous bone when applied in instrumented anterior cervical discectomy and fusion (ACDF) with use of a structural allograft ring in subjects with degenerative cervical disc disease.

Subjects were enrolled according to the inclusion/exclusion criteria outlined below. Subjects were required to meet all of the inclusion and none of the exclusion criteria.

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.

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 boney 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.

Study Design/Methods

All of the subjects underwent standard ACDF using a metallic anterior plate fixation system and bone allograft ring structural graft. The difference between the groups was the graft material placed within the bone allograft ring. Subjects were randomized 1:1 between the i-FACTOR Peptide Enhanced Bone Graft and Control groups. For i-FACTOR Peptide Enhanced Bone Graft subjects, the central cavity of the bone allograft ring was filled with i-FACTOR Peptide Enhanced Bone Graft. 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. The filled bone allograft ring was inserted into the prepared disc space.

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 consisted of 6 weeks ± 2 weeks, 3 months ± 2 weeks, 6 months ± 1 month, 9 months ± 1 month and 12 months ± 2 months. Subjects also were followed at 18 ± 2 months and 24 ± 2 months. After this initial study period ended, subjects continued to be followed annually at 36, 48, 60, and 72 months.

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 also outlined in **Table 1** 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	24m
Clinical	Pain	VAS (neck)	X	X[2]	X	X	X	X	X	X	X
		VAS (arm)	X	X[2]	X	X	X	X	X	X	X
	Neuro-logical	Clinical exam	X	X	X	X	X	X	X	X	X
Radiographic	Fusion	Radiograph	X		X[2]	X	X	X	X	X	X
		CT							X[1]		
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] CT scans were applied only in the subjects for whom there was no evidence of fusion on plain radiographs.

[2] 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.

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) was aware of the safety and effectiveness outcomes. The complete, unblinded database was not opened and presented to the sponsor until after the 12-month follow-up for the subjects in the study had been completed.

Subject Accountability

Subjects were enrolled at 19 sites in the US and at 3 sites in Canada (a total of 55 Canadian subjects were enrolled.) A pooling analysis allowed for pooling across US sites and between US and Canadian sites. This resulted in a total of 319 subjects (165 investigational and 154 control). Several populations were defined:

- 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)
- 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

	Investigational	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 in **Table 2** below 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 at 12 months was 85.3% and 92.2% for the i-FACTOR Peptide Enhanced Bone Graft and Control groups, respectively. Follow up at 24 months was 77.9% and 84.2% for the i-FACTOR Peptide Enhanced Bone Graft and Control groups, respectively.

Table 2: Subject accounting by visit and study arm– ITT population

		Baseline	6W	3M	6M	9M	12M	18M	24M
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
Subject self-withdrawn	i-FACTOR	0	0	0	0	2	2	8	11
	Control	0	0	0	1	1	1	1	2
Visits in window, endpoints obtained	i-FACTOR	164 (99.4%)	150 (90.9%)	139 (84.2%)	134 (81.2%)	113 (69.3%)	134 (82.2%)	110 (70.1%)	106 (68.8%)
	Control	153 (99.4%)	136 (88.3%)	122 (79.2%)	130 (85.0%)	114 (74.5%)	132 (86.3%)	120 (78.4%)	117 (77.0%)
Any visit	i-FACTOR	165 (100%)	161 (97.6%)	158 (95.8%)	148 (89.7%)	131 (80.4%)	139 (85.3%)	119 (75.8%)	120 (77.9%)
	Control	154 (100%)	147 (95.5%)	141 (91.6%)	145 (94.8%)	127 (83.0%)	141 (92.2%)	128 (83.7%)	128 (84.2%)

The analysis populations included: the Intent to Treat (ITT) population (n=319), comprised of all randomized subjects; the Per-Protocol population, comprised of all randomized subjects without major protocol deviations (n=313); and the modified ITT (mITT) population (n=319), which was prospectively specified as the primary population for safety analysis. The mITT population is identical to the ITT population.

Demographics and Baseline Characteristics
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.

Clinical Endpoints
Subjects were masked to treatment assignment. All primary endpoints were assessed by blinded reviewers.

The study had three co-primary efficacy endpoints – (i) Fusion Status, (ii) Neck Disability Index (NDI), and (iii) Neurological Success. The study also had one primary safety endpoint, the complication rate. The primary endpoints were evaluated at the 12-month follow-up visit for primary effectiveness analysis and again at the 24-month visit.

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 efficacy endpoint elements, as well as have experienced no subsequent surgical interventions or serious product-related AEs. Overall study success was achieved if both the co-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;
- health-related quality of life, assessed using the SF-36v2 questionnaire; and
- surgical success in relieving pre-operative symptoms, assessed using Modified Odom's criteria.

Surgery and Operative Characteristics

The operative characteristics that were recorded during the study included length of cervical level operated, duration of surgery, duration of radiographic screening and blood loss (**Table 3**). There were no between-group differences.

Table 3: Surgery characteristics by treatment arm – ITT population

	i-FACTOR (n=165)	Control (n=154)
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)
Duration of Surgery (min)		
n	165	153
Mean	91.4	92.3
SD	40.4	32.5
Range	26 - 270	12 – 190
Total Radiographic Screening Time (sec)		
n	162	151
Mean	145.2	162.6
SD	368.3	389.8
Range	1 - 1800	0 – 1800
Blood Loss (mL)		
n	164	154
Mean	41.4	46.0
SD	37.8	62.0
Range	0 - 300	9 - 500
Amount of i-FACTOR Used, cc		
n	162	
Mean	0.777	
SD	0.596	
Range	0.15-4.00	

Safety Results

The proportion of subjects with any reported adverse event at 12 months and 24 months are shown in **Tables 4** and **5**, respectively. 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 at 12 months. The proportion of subjects with any adverse event was 88.5% in the i-FACTOR Peptide Enhanced Bone Graft group and 89.6% in the Control group at 24 months. The difference in *any* adverse event rate between the groups was not statistically significant at either 12 months or 24 months. Thus, the i-FACTOR Peptide Enhanced Bone Graft group met the statistical criterion for safety.

Table 4: 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 5: Any adverse event at 24 months by treatment arm – mITT population

Any AE within 24 months of surgery	i-FACTOR (N=165)	Control (N=154)	p-value	Success Criteria Met
Yes	146/165 (88.5%)	138/154 (89.6%)		
No	19/165 (11.5%)	27/154 (10.4%)	0.8581	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 over entire course of study – mITT

	i-FACTOR (n=165)		Control (n=154)	
Number (%) of Subjects	**Subject[1]**	**Event**	**Subject[1]**	**Event**
Any adverse event	150 (90.9)	960	142 (92.2)	990
Other[2]	127 (69.1)	574	127 (82.5)	591
Axial pain (nuchal or periscapular pain or neck fatigue)	82 (49.7)	120	73 (47.4)	103
Postoperative radiculopathy/radiculitis	39 (23.6)	56	34 (22.1)	44
Dysphagia	33 (20.0)	35	30 (19.5)	31
New radiculopathy	36 (21.8)	58	42 (27.3)	97
Adjacent segment degeneration	35 (21.2)	47	38 (24.7)	41
New intractable neck pain	23 (13.9)	28	30 (19.5)	40
Nonunion/Pseudarthrosis	21 (12.8)	21	27 (17.5)	29
Dysphonia	1 (0.6)	1	2 (1.3)	2
Superficial infection	6 (3.6)	6	0 (0.0)	0
Worsening of neurological status	2 (1.2)	2	4 (2.6)	4
Reoperation/subsequent surgical intervention at index level	2 (1.2)	2	3 (1.9)	3
Dural tear	1 (0.6)	1	0 (0.0)	0
Retropharyngeal hematoma/airway obstruction	0	0 (0.0)	1 (0.6)	1
Horner's syndrome	0	0 (0.0)	1 (0.6)	1
Progression of myelopathy	1 (0.6)	1	0 (0.0)	0
Cardiopulmonary event	1 (0.6)	1	0 (0.0)	0
Screw malposition	0	0 (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 by 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	163	75	93	176	190	269
	Control	5	180	79	102	186	172	265
Other	i-FACTOR	2	74	45	54	106	112	184
	Control	3	97	31	62	118	100	179
Axial pain (nuchal or periscapular pain or neck fatigue)	i-FACTOR	0	28	13	14	26	17	22
	Control	2	30	15	10	15	13	18
New radiculopathy	i-FACTOR	0	1	2	5	17	14	19
	Control	0	4	15	10	20	18	30
Postoperative radiculopathy/radiculitis	i-FACTOR	0	19	8	6	8	9	6
	Control	0	18	7	6	3	6	4
Dysphagia	i-FACTOR	0	25	3	3	1	1	2
	Control	0	21	2	4	4	0	0
Adjacent segment degeneration	i-FACTOR	0	0	0	3	9	16	24
	Control	0	0	1	4	8	12	16
New intractable neck pain	i-FACTOR	0	2	0	3	2	9	12
	Control	0	4	2	5	7	8	14
Nonunion/Pseudarthrosis	i-FACTOR	0	3	2	4	5	7	0
	Control	0	2	4	1	9	9	3
Superficial infection	i-FACTOR	0	4	0	0	0	2	0
	Control	0	0	0	0	0	0	0
Dysphonia	i-FACTOR	0	5	0	1	0	0	0
	Control	0	2	1	0	0	0	0
	i-FACTOR	1	0	0	0	0	4	1

Number of Events	Treatment	PreOp	0-42[1] Days	43-90 Days	91-180 Days	181-365 Days	366-730 Days	>730 Days
Hypothyroidism	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
	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
Horner's 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	1	0	0	0	0
	Control	0	0	0	0	0	0	0
Retropharyngeal 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 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	--	--	--	--

	Main Study to 24 months		Extension to 72 months	
	i-FACTOR	Control	i-FACTOR	Control
	165	154	86	92
Superficial infection	6 (4)	0	1 (1)	0
Graft site pain > 6 months post-op	--	--	--	--
Dysphagia	32 (19)	30 (20)	8 (5)	10 (6)
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. 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 0 cases or 0.0% 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 19 subjects (23 events) in the i-FACTOR Peptide Enhanced Bone Graft group and 25 subjects (28 events) in the Control group with secondary surgical interventions. Eleven subjects (15 events) in the i-FACTOR Peptide Enhanced Bone Graft group and 19 subjects (21 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	19	25	44
Subsequent surgery	23	28	51
Same level as index (%)	4 (17.4)	8 (28.6)	12 (23.5)
Different from index surgery level	8 (34.8)	7 (25.0)	15 (29.4)
Includes index surgery level and different surgery level(s)	11 (47.8)	13 (46.4)	24 (47.1)
Procedures	25	35	60
Removal	7 (28.0)	7 (20.0)	14 (23.3)
Revision	3 (12.0)	9 (25.7)	12 (20.0)
Reoperation	1 (4.0)	3 (8.6)	4 (6.7)
Supplemental fixation	5 (20.0)	6 (17.1)	11 (18.3)
Other	9 (36.0)	10 (28.6)	19 (31.7)

Serious Adverse Events

Table 10 shows all serious adverse events by category. Fifty-six (56) i-FACTOR Peptide Enhanced Bone Graft subjects (33.9%) reported a serious adverse event compared to 60 Control subjects (39.0%), and the i-FACTOR Peptide Enhanced Bone Graft group reported 107 serious adverse events compared to 102 serious adverse events reported by the Control group. There were 2 reoperations at the index level in the i-FACTOR group, and 3 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-value[2]
	Subjects[1]	Events	Subjects[1]	Events	
Any adverse event	56 (33.9)	107	60 (39.0)	102	0.368
Other[3]	48 (29.1)	81	50 (32.5)	74	0.545
Adjacent segment degeneration	9 (5.5)	9	13 (8.4)	13	0.378
New radiculopathy	6 (3.6)	6	6 (3.9)	6	1.000
Pseudarthrosis	2 (1.2)	2	5 (3.2)	5	0.269
Reoperation/subsequent surgical intervention at index level	2 (1.2)	2	3 (1.9)	3	0.675
Superficial infection	2 (1.2)	2	0	0	0.499
New intractable neck pain	4 (2.4)	4	2 (1.3)	2	0.686
Retropharyngeal hematoma/airway obstruction	0	0	1 (0.6)	1	0.483
Progression of myelopathy	1 (0.6)	1	0	0	1.000

	i-FACTOR (n=165)		Control (n=154)		p-value[2]
	Subjects[1]	Events	Subjects[1]	Events	
Postoperative radiculopathy/radiculitis	0	0	1 (0.6)	1	0.483
Nonunion	1 (0.6)	1	0	0	1.00

[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.

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 (161 randomized i-FACTOR Peptide Enhanced Bone Graft subjects and 152 Control subjects).

Fusion Rate

Fusion status at 12 months is shown in **Table 11**. The fusion rate at 12 months was 89.7% in the i-FACTOR Peptide Enhanced Bone Graft group and 85.8% 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	130/145 (89.7%)	121/141 (85.8%)		
No evidence of fusion	16/145 (10.3%)	20/141 (14.2%)	3.9% (-4.5%, 10.8%)	-10%

Fusion status at 24 months is shown in **Table 12**. The fusion rate at 24 months was 97.3% in i-FACTOR Peptide Enhanced Bone Graft group and 95.8% in the Control group. The i-FACTOR Peptide Enhanced Bone Graft group fusion rate was non-inferior to the Control group fusion rate at 24 months (p=0.001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 12: Fusion status at 24 months – PP population

Fusion Status	i-FACTOR (n=161)	Control (n=152)	Difference (95% CI) i-FACTOR – Control	Non-inferiority Margin
Fused	144/148 (97.3%)	136/142 (95.8%)		
No evidence of fusion	4/148 (2.7%)	6/142 (4.2%)	2.2% (-2.7%, 5.7%)	-10%

Table 13 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 (94.5% i-FACTOR Peptide Enhanced Bone Graft, 93.0% Control) and 24-month (97.3% i-FACTOR Peptide Enhanced Bone Graft, 95.8% Control) visits. There was no statistically significant difference between the two groups at any time point.

Table 13: Summary of fusion success by follow-up visit and study arm – PP population

Visit		i-FACTOR (n=161)	Control (n=152)	p-value[1]
6M	Subjects with fusion status determination	139	140	0.517
	Subjects with successful fusion (%)	45 (32.4)	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 (%)	130 (89.7)	121 (85.8)	
18M	Subjects with fusion status determination	146	143	0.634
	Subjects with successful fusion (%)	138 (94.5)	133 (93.0)	
24M	Subjects with fusion status determination	148	142	0.534
	Subjects with successful fusion (%)	144 (97.3)	136 (95.8)	

[1] Fisher's exact test.

Missing fusion status for 12 months or later was imputed based on the principle that, once fusion was achieved, the status of "fused" could be carried forward.

Neck Disability Index

Table 14 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 at 12 months. 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 14: Mean change in Neck Disability Index (NDI) at 12 months, adjusted for baseline NDI – PP population

NDI	i-FACTOR (n=161)	Control (n=152)	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

NDI was imputed by multiple imputation procedure

Table 15 shows least square estimated mean changes in imputed sample NDI, adjusted for baseline NDI, in the i-FACTOR Bone Graft and Control groups at 24 months. The mean change (improvement) in the i-FACTOR Bone Graft group was 28.8 (95% C.I. 25.3, 32.2) and the mean change in the Control group was 26.6 (95% C.I. 23.4, 29.8). Subjects treated with i-FACTOR Peptide Enhanced Bone Graft had non-inferior NDI outcomes at 24 months compared to the Control group (p<0.0001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 15: Mean change in Neck Disability Index (NDI) at 24 months, adjusted for baseline NDI – PP population

NDI	i-FACTOR (n=161)	Control (n=152)	Difference (95% CI) iFACTOR - Control	Non-inferiority Margin	p-value
24 month mean change (95% CI)	28.8 (25.3, 32.2)	26.6 (23.4, 29.8)	2.18 (-2.39, 6.75)	-11	<0.0001

NDI was imputed by multiple imputation procedure

Neurological Outcomes

Neurological success status at 12 months is shown in **Table 16**. The neurologic success rate was 93.7% in the i-FACTOR Peptide Enhanced Bone Graft group and 93.0% 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 16: 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 (93.7%)	133/143 (93.0%)		
No	9/143 (6.3%)	10/143 (7.0%)	0.70% (-5.1%, 6.5%)	-15%

Neurological success data were not imputed

Neurological success status at 24 months is shown in **Table 17**. The neurologic success rate was 94.9% in the i-FACTOR Peptide Enhanced Bone Graft group and 93.7% in the Control group. Subjects treated with i-FACTOR Peptide Enhanced Bone Graft had non-inferior neurological outcomes at 24 months, compared to the Control group ($p < 0.0001$), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 17: Neurological success at 24 months – PP population

Neurological Success	i-FACTOR (n=117)	Control (n=127)	Difference (95% CI) i-FACTOR – Control	Non-inferiority margin
Yes	111/117 (94.9%)	119/127 (93.7%)		
No	6/117 (5.1%)	8/127 (6.3%)	1.17% (-4.65%, 6.99%)	-15%

Neurological success data were not imputed

Overall Success

Table 18 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 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 18: Responder analysis at 12 months – PP population

Component	Value	i-FACTOR n (%)	Control n (%)	p-value
Fusion success	No evidence of fusion	15 (10.3%)	20 (14.2%)	0.369
	Fused	130 (89.7%)	121 (85.8%)	
NDI success	NDI improved =<15 from baseline	29 (20.57%)	36 (25.90%)	0.2907

Component	Value	i-FACTOR n (%)	Control n (%)	p-value
	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%)**	

Table 19 shows results of the overall success (responder analysis) at 24 months by treatment group in the PP population. Once again, the proportion of subjects with overall success was significantly higher in the i-FACTOR Peptide Enhanced Bone Graft group compared to the Control group (68.91% and 55.04%, respectively, Chi-square p=0.0269). The difference in overall success was 13.87% in favor of the i-FACTOR Peptide Enhanced Bone Graft group.

Table 19: Responder analysis at 24 months – PP population

Component	Value	i-FACTOR n (%)	Control n (%)	p-value
Fusion success	No evidence of fusion	4 (2.70%)	6 (4.23%)	0.5343
	Fused	144 (97.30%)	136 (95.77%)	
NDI success	NDI improved =<15 from baseline	30 (23.81%)	41 (31.06%)	0.2112
	NDI improved >15 from baseline	96 (76.19%)	91 (68.94%)	
Neurological success	Yes	111 (94.87%)	119 (93.70%)	0.5349
	No	6 (5.13%)	8 (6.30%)	
Safety success	No	19 (11.52%)	16 (10.39%)	0.8581
	Yes	146 (88.48%)	138 (89.61%)	
Overall success	**Overall Failure**	**37 (31.09%)**	**58 (44.96%)**	**0.0269**
	Overall Success	**82 (68.91%)**	**71 (55.04%)**	

Subgroup Analyses

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

- age (< or ≥ 50 years)
- gender
- litigation
- ever smoking (≤ or > 100 cigarette)
- current smoking (yes vs. no)
- NDI score at baseline (< or ≥ 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 between the i-FACTOR Peptide Enhanced Bone Graft and the Control groups.

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% for "current smoking" and 11% 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 occurrence of 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).

Secondary Effectiveness Results

As pre-specified by the study Statistical Analysis Plan, primary analyses of secondary efficacy endpoints were performed on the PP population. **Tables 20 and 21** show secondary outcomes by treatment arm in the PP population at 12 months and 24 months, respectively. 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 at either 12 months or 24 months.

Table 20: 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
VAS $Arm_{b\text{-}12m}$	4.88 (4.42 to 5.34)	4.83 (4.39 to 5.27)	0.88
VAS $Neck_{b\text{-}12m}$	4.48 (4.05 to 4.92)	4.38 (3.96 to 4.81)	0.74
SF36v2 $PCS_{12m\text{-}b}$	10.01 (8.37 to 11.65)	10.19 (8.52 to 11.86)	0.88
SF36v2 $MCS_{12m\text{-}b}$	8.18 (6.53 to 9.84)	8.08 (6.37 to 9.78)	0.93

PCS = PHYSICAL HEALTH COMPONENT SCORE;
MCS = 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 21: Changes in secondary endpoints at 24 months by treatment arm– PP population

Endpoint	i-FACTOR (n=161) mean change (95% CI)	Control (n=152) mean change (95% CI)	t -test
VAS $Arm_{b\text{-}12m}$	5.41 (4.93 to 5.89)	5.01 (4.59 to 5.44)	0.27
VAS $Neck_{b\text{-}12m}$	4.81 (4.36 to 5.26)	4.38 (3.93 to 4.83)	0.18
SF36v2 $PCS_{12m\text{-}b}$	10.39 (8.59 to12.20)	10.06 (8.27 to 11.85)	0.79
SF36v2 $MCS_{12m\text{-}b}$	7.76 (5.96 to 9.56)	7.64 (5.87 to 9.41)	0.93

PCS = PHYSICAL HEALTH COMPONENT SCORE;
MCS = MENTAL HEALTH COMPONENT SCORE;
b-24m = value is the difference between the pre-operative and 24 months value;
24m-b = value is the difference between the 24 months value and pre-operative.
Values are least square estimated means and corresponding 95% Confidence Intervals

Tables 22 and 23 show Odom's criteria of success at 12 months and 24 months by treatment arm. There were no differences in Odom's criteria for success at either 12 months or 24 months between the i-FACTOR Peptide Enhanced Bone Graft and Control arms (Chi-square p=0.9929 and p=0.1986, respectively).

Table 22: 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%)

Table 23: Odom's criteria at 24 months by treatment arm – PP population

Category	i-FACTOR (n=161)	Control (n=151)
Excellent: Improvement ≥ 80% Deterioration < 10%	79 (69.3%)	75 (60.5%)
Good: Improvement ≥ 70% Deterioration < 15%	20 (17.5%)	20 (16.1%)
Fair: Improvement ≥ 50% Deterioration < 20%	7 (6.1%)	17 (13.7%)
Poor: Improvement < 50% Deterioration > 20%	8 (7.0%)	12 (9.7%)
Odom Not Performed	47 (29.2%)	27 (17.9%)

POST-APPROVAL STUDY (PAS)

A post approval study (PAS) was performed on a subset of the subjects enrolled in the original IDE study.

Study Objectives

The objective of the PAS was to provide longer-term data on the safety and effectiveness of i-FACTOR Bone Graft. The study compared the long term (up to 6 years) safety and effectiveness of i-FACTOR Bone Graft versus local autologous bone in subjects undergoing a single level anterior cervical discectomy and fusion.

Study Design

The PAS provided extended follow up on the subjects originally randomized and enrolled in the pivotal IDE trial. All subjects enrolled in the IDE trial were invited to participate. The additional follow-up schedule included 3-year, 4-year, 5-year and 6-year visits. Subject evaluation at each visit was identical to those performed at the original IDE trial 2-year visit.

Study Population

The study population included all subjects enrolled in the IDE trial who consented to be in the PAS. The study population of the original IDE study included male and female subjects aged 18-70 years with clinical and radiological confirmation of single level cervical degenerative disc disease as defined in the inclusion and exclusion criteria.

Data Source

The PAS subjects were all originally randomized and enrolled in the pivotal IDE trial. Data for the PAS was collected from the 3-year, 4-year, 5-year and 6-year visits. Subject evaluation at each visit was identical to those performed at the original IDE trial 2-year visit.

Key Study Endpoints

The study co-primary endpoints were as follows: fusion, change in Neck Disability Index (NDI), neurological success, and the proportion of subjects with adverse events.

The study secondary endpoints were as follows: pain at neck, pain at arm (measured by VAS), health-related quality of life (measured by SF-36v2), success (measured by Modified Odom's criteria) and a composite Overall Success endpoint (comprised of fusion success, NDI success, neurological success and no reoperations at the index level, no device explantations and no device-related serious adverse events).

Total number of Enrolled Study Sites and Subjects/Follow up Rate

Of 319 subjects originally enrolled in the pivotal study, 220 subjects from 17 investigational sites were enrolled into PAS. The subject accountability for the PAS is provided in **Table 24**.

Table 24: Subject Accounting by Visit – PAS ITT population

		Baseline	6W	3M	6M	9M	12M	18M	24M	36M	48M	60M	72M
Enrolled	i-FACTOR	106	106	106	106	106	106	106	106	106	106	106	106
	Control	114	114	114	114	114	114	114	114	114	114	114	114
Treated	i-FACTOR	106	106	106	106	106	106	106	106	106	106	106	106
	Control	114	114	114	114	114	114	114	114	114	114	114	114
Theoretical	i-FACTOR	106	106	106	106	106	106	106	106	106	106	106	106
	Control	114	114	114	114	114	114	114	114	114	114	114	114
Subject self-withdrawn	i-FACTOR	0	0	0	0	0	0	0	0	6	9	10	11
	Control	0	0	0	0	0	0	0	0	2	9	12	13
Expected	i-FACTOR	106	106	106	106	106	106	106	106	100	97	96	95
	Control	114	114	114	114	114	114	114	114	112	105	102	101
Any Visit	i-FACTOR	106 (100.0)	104 (98.1)	104 (98.1)	100 (94.3)	96 (90.6)	100 (94.3)	95 (89.6)	99 (93.4)	80 (80.0)	80 (82.5)	77 (80.2)	74 (77.9)
	Control	114 (100.0)	111 (97.4)	107 (93.9)	113 (99.1)	104 (91.2)	111 (97.4)	104 (91.2)	105 (92.1)	91 (81.3)	90 (85.7)	81 (79.4)	78 (77.2)

The number of subjects in each of the analysis populations is shown in **Table 25**.

Table 25: Analysis Populations for PAS

	Subjects, n (%)		
Population	**i-FACTOR (N=106)**	**Control (N=114)**	**Total (N=220)**
Intention-to-Treat (ITT) set	106 (100.0%)	114 (100.0%)	220 (100.0%)
Modified Intention-to-Treat (mITT) set	106 (100.0%)	114 (100.0%)	220 (100.0%)
Per-Protocol (PP) set	105 (99.1%)	112 (98.2%)	217 (98.6%)
Completed Cases (CC) set	74 (69.8%)	78 (68.4%)	152 (69.1%)

Study visits and length of follow-up

The PAS visits included 3 years, 4 years, 5 years and 6 years post-surgery. The length of follow-up was six (6) years.

SUMMARY OF POST-APPROVAL STUDY (PAS) RESULTS:

Final safety findings (key endpoints)

The AE rate at 72 months is provided for the PP Population in **Table 26**. The proportion of subjects with any AEs was 96.2% in the i-FACTOR Bone Graft Group and 97.4% in the Control Group. The difference in the proportion of subjects with any AEs between the groups was not statistically significant (p=0.714). In addition, there was no difference in the type of AEs between the groups. Thus, the i-FACTOR Bone Graft Group reached the statistical criterion for safety endpoint at 72 months.

A summary of adverse events over the entire course of the pivotal and PAS studies for the PAS group is provided in **Table 27**. A summary of study-related adverse events over the entire course of the pivotal and PAS studies for the PAS group is provided in **Table 28**. A summary of subsequent surgical interventions for the PAS group is provided in **Table 29**. A summary of serious adverse events over the entire course of the pivotal and PAS studies for the PAS group is provided in **Table 30**.

Table 26: Complications Success at 72 Months – PAS PP Population

Any AE within 72 months past surgery, n (%)	i-FACTOR (N=106)	Control (N=114)	p-value	Success Criteria Met
Yes	102 (96.2%)	111 (97.4%)		
No	4 (3.8%)	3 (2.6%)	0.714	Yes

Table 27: Summary of adverse events over entire course of pivotal and PAS studies – PAS ITT Population

	i-FACTOR (N=106)		Control (N=114)	
Adverse Event	**Subjects[1]**	**Events**	**Subjects[1]**	**Events**
Any adverse event	102 (96.2)	847	111 (97.4)	892
Other	95 (89.6)	507	106 (93.0)	547
Axial pain (nuchal or periscapular pain or neck fatigue)	59 (55.7)	94	57 (50.0)	85
New radiculopathy	34 (32.1)	56	38 (33.3)	93
Adjacent segment degeneration	34 (32.1)	46	35 (30.7)	39
Postoperative radiculopathy/radiculitis	34 (32.1)	51	29 (25.4)	38
Dysphagia	23 (21.7)	26	25 (21.9)	26
New intractable neck pain	22 (20.8)	27	26 (22.8)	35
Pseudarthrosis	8 (7.5)	9	12 (10.5)	13
Nonunion	11 (10.4)	11	9 (7.9)	9
Partial or complete vocal cord paralysis (hoarseness)	4 (3.8)	4	1 (0.9)	1
Superficial infection	5 (4.7)	5	0	0
Worsening of the neurological status	2 (1.9)	2	2 (1.8)	2
Reoperation/subsequent surgical intervention	2 (1.9)	2	1 (0.9)	1
Dysphonia	1 (0.9)	1	1 (0.9)	1
Graft subsidence	2 (1.9)	2	0	0
Cardiopulmonary event	1 (0.9)	1	1 (0.9)	1
Dural tear	1 (0.9)	1	0	0
Horner's syndrome	0	0	1 (0.9)	1
Deep infection	1 (0.9)	1	0	0
Progression of myelopathy	1 (0.9)	1	0	0

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

Table 28: Summary of Study-Related Adverse Events over entire course of pivotal and PAS studies – PAS ITT Population

	i-FACTOR (N=106)		Control (N=114)	
Adverse Event	**Subjects[1]**	**Events**	**Subjects[1]**	**Events**
Any adverse event	37 (34.9)	103	42 (36.8)	130
Other	18 (17.0)	45	26 (22.8)	58
Axial pain (nuchal or periscapular pain or neck fatigue)	12 (11.3)	14	12 (10.5)	15
Nonunion	11 (10.4)	11	8 (7.0)	8
New radiculopathy	8 (7.5)	9	9 (7.9)	10
New intractable neck pain	6 (5.7)	6	9 (7.9)	11
Dysphagia	4 (3.8)	4	8 (7.0)	9
Postoperative radiculopathy/radiculitis	4 (3.8)	4	7 (6.1)	8
Pseudarthrosis	2 (1.9)	3	7 (6.1)	7
Adjacent segment degeneration	3 (2.8)	3	4 (3.5)	4
Graft subsidence	2 (1.9)	2	0	0

	i-FACTOR (N=106)		Control (N=114)	
Adverse Event	**Subjects[1]**	**Events**	**Subjects[1]**	**Events**
Partial or complete vocal cord paralysis (hoarseness)	1 (0.9)	1	0	0
Superficial infection	1 (0.9)	1	0	0

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

Table 29: Summary of subsequent surgical interventions – PAS ITT Population

	i-FACTOR (N=106)	Control (N=114)	Total (N=220)
Subject with any subsequent surgery	20	23	43
Subsequent surgery	24	26	50
Different from index surgery level	9 (37.5)	7 (26.9)	16 (32.0)
Same as index surgery level	4 (16.7)	6 (23.1)	10 (20.0)
Includes index surgery level and different surgery level(s)	11 (45.8)	13 (50.0)	24 (48.0)
Procedures	26	35	61
Removal	7 (26.9)	7 (20.0)	14 (23.0)
Revision	3 (11.5)	7 (20.0)	10 (16.4)
Reoperation	1 (3.8)	4 (11.4)	5 (8.2)
Supplemental fixation	5 (19.2)	7 (20.0)	12 (19.7)
Other	10 (38.5)	10 (28.6)	20 (32.8)

Table 30: Summary of Serious Adverse Events over entire course of pivotal and PAS studies – PAS ITT Population

	i-FACTOR (N=165)		Control (N=154)	
Serious Adverse Event	**Subjects[1]**	**Events**	**Subjects[1]**	**Events, n**
Any serious adverse event	7 (6.6)	9	7 (6.1)	9
New radiculopathy	1 (0.9)	1	3 (2.6)	3
Other	2 (1.9)	2	2 (1.8)	2
Pseudarthrosis	1 (0.9)	1	2 (1.8)	2
Adjacent segment degeneration	2 (1.9)	2	1 (0.9)	1
New intractable neck pain	1 (0.9)	1	1 (0.9)	1
Superficial infection	1 (0.9)	1	0	0
Nonunion	1 (0.9)	1	0	0

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

Final effectiveness findings (key endpoints)

Fusion Rate

Fusion status at 72 months is provided for the PP Population in **Table 31**. The 72-month fusion rate was 98.6% in the i-FACTOR Bone Graft Group and 97.3% in the Control Group. The i-FACTOR Peptide Enhanced Bone Graft Group fusion rate was non-inferior to the Control Group fusion rate at 72 months (p<0.0001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 31: Summary of Fusion Success at 72 Months (LOCF) - PAS PP Population

Fusion Status, n (%)	i-FACTOR (N=105)	Control (N=112)	Difference (95% CI) i-FACTOR – Control	p-value	Non-inferiority margin	Success Criteria Met
No evidence of fusion	1/72 (1.4%)	2/75 (2.7%)				
Fused	71/72 (98.6%)	73/75 (97.3%)	0.01 (-0.033, 0.058)	<.0001	-10	Yes

Abbreviations: LOCF= last observation carried forward

Note: p-Value is for non-inferiority hypothesis (H0: i-FACTOR's Fused percentage at 6-Year - Control's ≤ -0.1).

Change in NDI

The least square estimated mean changes in multiply imputed sample for NDI, adjusted for baseline NDI, in the i-FACTOR Bone Graft and Control Groups are summarized for the PP Population in **Table 32**. Subjects treated with i-FACTOR Peptide Enhanced Bone Graft had non-inferior NDI outcomes at 72 months compared to the Control group (p<0.0001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 32: Mean Change in NDI at 72 Months – PAS PP Population

NDI Change	i-FACTOR (N=105)	Control (N=112)	Difference (95% CI) i-FACTOR - Control	p-value (one-sided)	Non-inferiority Margin	Success Criteria Met
LS Mean (SE) (95% CI)	28.56 (1.923) (24.79, 32.33)	29.17 (1.890) (25.46, 32.88)	-0.61 (2.793) (-6.10, 4.88)	< .0001	-11	Yes

Neurological Success

Neurological success status at 72 months is shown in **Table 33**. The neurologic success rate was 95.9% in the i-FACTOR Bone Graft Group and 93.3% in the Control Group. Subjects treated with i-FACTOR Peptide Enhanced Bone Graft had non-inferior neurological outcomes at 72 months, compared to the Control group (p <0.0001), meeting the statistical criterion for this co-primary effectiveness endpoint.

Table 33: Summary of Neurological Success (Adjudicated) at 72 Months – PAS PP Population

Neurological Success	i-FACTOR (N=105)	Control (N=112)	Difference (95% CI) i-FACTOR – Control	p-value (one-sided)	Non-inferiority Margin	Success Criteria Met
Yes	70 (95.89%)	70 (93.70%)				
No	3 (4.11%)	5 (6.67%)	2.6% (-4.70%, 9.81%)	< .0001	-15%	Yes

Overall Success

The Overall Responder Rate for the PAS at 72-month follow-up was 63.5% (47/74) and 53.8% (42/78) in the i-FACTOR Bone Graft and Controls groups, respectively. The proportion of subject with overall success was higher in the i-FACTOR Bone Graft Group that the Control Group (+9.7%) but the difference was not statistically significant.

PAS Study Strengths and Weaknesses

The PAS was a continued follow-up of a significant subset of the subjects originally randomized in the pivotal trial (220 of 319 subjects). Therefore, the strengths of the pivotal study were continued: prospective, randomized trial; subjects blinded to the treatment group; radiological evaluators and neurological outcome evaluators blinded to the treatment group. In addition, the PAS visit evaluations included all primary and secondary inputs evaluated in the pivotal study.

Not unexpectedly, not all the pivotal trial sites and subjects agreed to participate in the PAS. Although the follow up rates of the PAS subjects were adequate to demonstrate statistical success, the follow-up rates were lower in the PAS than the pivotal trial.

CONCLUSIONS DRAWN FROM THE PIVOTAL AND POST-APPROVAL STUDY DATA:

The clinical data demonstrate the safety and effectiveness of i-FACTOR Peptide Enhanced Bone Graft when used in accordance with the indications for use. All primary endpoints of the study were satisfied at 12 months, 24 months, and 72 months. Based on the clinical study results, the clinical benefits of the use of i-FACTOR Peptide Enhanced Bone Graft outweigh the risks associated with the device and surgical procedure.

HOW SUPPLIED:

The i-FACTOR Peptide Enhanced Bone Graft is provided in a pre-filled syringe. The syringe is comprised of the syringe barrel, plunger rod, plunger tip, and syringe cap. The pre-filled syringe of i-FACTOR Peptide Enhanced Bone Graft is packaged in an outer sterile barrier chevron-style peel pouch and inner vapor barrier foil pouch. The syringe barrel and plunger tip are lubricated with a thin layer of Dow Corning 360 Medical Fluid - 1000 CST (polydimethylsiloxane).

STORAGE:

The product should be stored in its original packaging at ambient room temperature.

DOSAGE AND ADMINISTRATION:

i-FACTOR Peptide Enhanced Bone Graft is supplied to the clinician as a sterile device in a single-use, pre-filled syringe containing the graft material. No mixing or other preparation is required. The clinician

simply removes the syringe from the sterile barrier package, removes the syringe cap, and dispenses the material.

DIRECTIONS FOR USE:

The clinician should remove the syringe cap and dispense i-FACTOR Peptide Enhanced Bone Graft by depressing the syringe plunger. i-FACTOR Peptide Enhanced Bone Graft may be dispensed directly into the allograft ring, FDA cleared PEEK, titanium alloy, or PEEK/titanium interbody fusion device with an internal volume range of 0.15cc to 4.0cc, or into a separate sterile receptacle where it can be transferred using traditional surgical instrumentation or by hand. The entire central cavity of the allograft ring or fusion device should be completely filled with i-FACTOR Peptide Enhanced Bone Graft. The i-FACTOR Bone graft must be in contact with the vertebral endplates. With the exception of filling the allograft cavity or fusion device with i-FACTOR Peptide Enhanced Bone Graft, a standard instrumented ACDF technique should be followed.

NOTE: Refer to the manufacturer's Instructions for Use for the specific interbody fusion device being used.

i-FACTOR Peptide Enhanced Bone Graft should only be placed in an allograft ring or fusion device where it can be contained adequately. Standard surgical techniques should be used to ensure containment.

NOTE: When opening the foil pouch containing the i-FACTOR Peptide Enhanced Bone Graft syringe, a very small amount of water may be retained within the pouch. This is a normal part of the steam sterilization process and does not affect the integrity or sterility of the product.

WARRANTIES:

All warranty rights are lost if repairs or modifications are made to this product. The manufacturer does not take responsibility for any effects on safety, reliability or performance of the product if the product is not used in conformity with the instructions for use.

PRODUCT COMPLAINTS:

Any health care professional (e.g. customer or user of this system), who has complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effectiveness and or performance, should notify Cerapedics. Further, if any of the implanted product ever "malfunctions," (i.e. does not meet any of its performance specifications or otherwise does not perform as intended), or may have caused or contributed to the death or serious injury of a patient, Cerapedics should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component(s) name and catalog number, lot number(s), your name and address, and the nature of the complaint.

FURTHER INFORMATION:

If further information is required, please contact Cerapedics at the address below.

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