InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Important Medical Information

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training.

DESCRIPTION:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of two components containing three parts– a tapered metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. The InFUSE™ Bone Graft component is inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component to form the complete InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. **These components must be used as a system. The InFUSE™ Bone Graft component must not be used without the LT-CAGE™ Lumbar Tapered Fusion Device component.**

LT-CAGE™ Lumbar Tapered Fusion Device component

The LT-CAGE™ device consists of a hollow, perforated, machined cylinder with opposing flat sides. The cage has a tapered design with an angle of 8.8° and is available in diameters ranging from 14mm to 18mm at the narrow end of the taper, 17mm to 22 mm at the wide end of the taper and in lengths ranging from 20mm to 26mm. There are two holes on each of the two flat sides. On each of the two rounded aspects, there is a single rounded slot. The implants have a helical screw thread on the outer surface. One end of the device is closed. The other end is open to be filled with the InFUSE™ Bone Graft component.

The LT-CAGE™ implants are made from implant grade titanium alloy (Ti-6Al-4V) described by such standards as ASTM F136 or its ISO equivalent.

The LT-CAGE™ Lumbar Tapered Fusion Device component is sold separately from the InFUSE™ Bone Graft component, however, these two components must be used together. The package labeling for the LT-CAGE™ Lumbar Tapered Fusion Device contains complete product information for this component.

InFUSE™ Bone Graft component

InFUSE™ Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). The InFUSE™ Bone Graft component induces new bone tissue at the site of implantation. Based on data from non-clinical studies, the bone

formation process develops from the outside of the implant towards the center until the entire InFUSE™ Bone Graft component is replaced by trabecular bone.

rhBMP-2 is the active agent in the InFUSE™ Bone Graft component. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3.7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5, and is clear, colorless and essentially free from plainly visible particulate matter.

The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

Three sizes of the InFUSE™ Bone Graft component are available based on the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device component that is selected. The table below lists the appropriate InFUSE™ Bone Graft kit for the corresponding LT-CAGE™ Lumbar Tapered Fusion Device component size:

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device Combinations				
LT-CAGE™ Lumbar Tapered Fusion Device		**Appropriate InFUSE™ Bone Graft Kit**		
Part #	Size (lead diameter, mm x length, mm)	Part #	Kit name (size in cc)	Reconstituted rhBMP-2/ACS graft volume
8941420	14x20	7510200	Small (2.8)	2.8ml
8941423	14x23	7510200	Small (2.8)	2.8ml
8941620	16x20	7510200	Small (2.8)	2.8ml
8941623	16x23	7510400	Medium (5.6)	5.6ml
8941626	16x26	7510400	Medium (5.6)	5.6ml
8941823	18x23	7510400	Medium (5.6)	5.6ml
8941826	18x26	7510600	Large Pre-Cut (8.0)	8.0ml
8941826	18x26	7510800	Large II (8.0)	8.0ml

Each kit contains all the components necessary to prepare the InFUSE™ Bone Graft component: the rhBMP-2 which must be reconstituted, sterile water, absorbable collagen sponges, syringes with needles, this package insert and

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instructions for preparation. The number of each item may vary depending on the size of the kit.

The rhBMP-2 is provided as a lyophilized powder in vials delivering either 4.2 mg or 12 mg of protein. After appropriate reconstitution, both configurations result in the same formulation and concentration (1.5 mg/mL) of rhBMP-2. The solution is then applied to the provided absorbable collagen sponge(s). The InFUSE™ Bone Graft component is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before placement inside of the LT-CAGE™ Lumbar Tapered Fusion Device components. The Instructions for Preparation contain complete details on preparation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

No warranties, express or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

INDICATIONS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L_4-S_1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device. The InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach.

CONTRAINDICATIONS

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in the vicinity of a resected or extant tumor.

- InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be implanted in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

WARNINGS:

- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, 2/277 (0.7%) patients treated with InFUSE™ Bone Graft component and 1/127 (0.8%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

- Women of childbearing potential should be advised not to become pregnant for one year following treatment with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

- The safety and effectiveness of the InFUSE Bone Graft component with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established. When degenerative disc disease was treated by a posterior lumber interbody fusion procedure with cylindrical threaded cages, posterior bone formation was observed in some instances.

- The implantation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device using an anterior laparoscopic surgical approach is associated with a higher incidence of retrograde ejaculation when compared to implantation using the an anterior open surgical approach.

PRECAUTIONS:

General

- The safety and effectiveness of repeat applications of the InFUSE™ Bone Graft component has not been established.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device, for anterior laparoscopic and/or anterior open procedures.

- Two LT-CAGE™ Lumbar Tapered Fusion Device components should be implanted side by side at the surgical level whenever possible.

- The LT-CAGE™ Lumbar Tapered Fusion Device components and instruments must be sterilized prior to use according to the sterilization instructions provided in the package insert for that component, unless supplied sterile and clearly labeled as such.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is intended for single use only. Discard unused product and use a new device for subsequent applications.

- Prior to use, inspect the packaging, vials and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials and contact a Medtronic Sofamor Danek representative.

- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Geriatrics

- Clinical studies of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger subjects.

Bone formation

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with metabolic bone diseases.

- While not specifically observed in the clinical study, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with autoimmune disease.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to the InFUSE™ Bone Graft component. The immune response to the InFUSE™ Bone Graft components was evaluated in 349 investigational patients and 183 control patients receiving lumbar interbody fusions.

    - *Anti-rhBMP-2 antibodies:* 2/349 (0.6%) patients receiving the InFUSE™ Bone Graft component developed antibodies vs. 1/183 (0.5%) in the control group.

    - *Anti-bovine Type I collagen antibodies:* 18.1% of patients receiving the InFUSE™ Bone Graft component developed antibodies to bovine Type I collagen vs. 14.2% of control patients. No patients in either group developed anti-human Type I collagen antibodies.

    - The presence of antibodies to rhBMP-2 was not associated with immune mediated adverse events such as allergic reactions. The neutralizing capacity of antibodies to rhBMP-2 is not known.

- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to the InFUSE™ Bone Graft component with the incidence of antibodies to other products may be misleading.

ADVERSE EVENTS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device was implanted in 288 investigational patients and compared to 139 control patients who received an LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft. The investigational patients were implanted with the device via either an open anterior surgical approach or a laparoscopic anterior surgical approach. The control patients were implanted only via the open anterior surgical approach.

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Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

ADVERSE EVENTS

(INFUSE™ Bone Graft/LT-Cage™ Device data combined from all experience with the device)

	Surgery		Postoperative (1 day - <4 Weeks)		6 Weeks (≥4 Wks - <9 Weeks)		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos - <9 Months)		12 Months (≥9 Mos - <19 Months)		24 Months (≥19 Mos - <30 Months)		# of Patients Reporting & Total adverse events	
Complication	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Investigational # (% of 288) total events	Control #(% of 139) total events
Anatomical/Technical Difficulty	10	3	0	0	0	0	0	0	0	0	0	0	0	0	10 (3.5) 10	3 (2.2) 3
Back and/or Leg Pain	0	0	1	4	11	5	10	5	14	4	20	7	6	8	65 (22.6) 72	30 (21.6) 33
Cancer	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1 (0.3) 1	1 (0.7) 1
Cardio/Vascular	2	0	4	5	6	2	1	3	2	1	3	2	0	1	15 (5.2) 18	12 (8.6) 14
Death	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Dural Injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Gastrointestinal	1	0	38	22	2	0	5	1	7	1	9	3	4	5	53 (18.4) 67	27 (19.4) 32
Graft Site Related	0	0	0	0	0	8	0	0	0	0	0	0	0	0	0 (0.0) 0	8 (5.8) 8
Implant Displacement/ Loosening	0	0	1	1	3	0	1	0	0	0	0	0	0	0	5 (1.7) 5	1 (0.7) 1
Infection	0	0	19	9	8	4	4	1	5	1	3	0	0	2	35 (12.2) 39	16 (11.5) 17
Malpositioned Implant	5	0	0	0	0	0	0	0	0	0	0	0	0	0	5 (1.7) 5	0 (0.0) 0
Neurological	0	0	7	5	7	3	5	2	5	2	10	3	5	7	36 (12.5) 39	21 (15.1) 22
Non-Union *	0	0	0	0	0	0	1	0	1	3	2	0	1	1	5 (1.7) 5	4 (2.9) 4
Non-Union **	0	0	0	1	0	1	3	0	3	4	4	6	1	1	11 (3.8) 11	13 (9.4) 13
Other	6	6	17	11	7	2	3	4	8	4	14	8	9	8	50 (17.4) 64	37 (26.6) 43
Other Pain	0	0	1	1	2	0	4	2	5	1	7	6	6	3	21 (7.3) 25	12 (8.6) 13
Respiratory	0	0	3	2	1	0	0	0	1	0	0	1	0	1	5 (1.7) 5	4 (2.9) 4
Retrograde Ejaculation	0	0	4	1	5	0	1	0	0	0	2	0	0	0	11 (7.9)[1] 12	1 (1.4)[2] 1
Spinal Event	0	0	1	2	0	0	6	2	8	3	8	8	4	2	24 (8.3) 27	16 (11.5) 17
Subsidence	0	0	3	2	2	0	1	0	1	0	0	0	0	0	7 (2.4) 7	2 (1.4) 2
Trauma	0	0	4	4	5	3	11	6	14	5	27	9	11	7	60 (20.8) 72	29 (20.9) 34
Urogenital	1	0	20	5	2	0	2	2	6	1	2	1	4	2	33 (11.5) 37	10 (7.2) 11
Vascular Intra-Op	15	5	0	0	0	0	0	0	0	0	0	0	0	0	14 (4.9) 15	5 (3.6) 5
Vertebral Fracture	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1 (0.3) 1	0 (0.0) 0
Any Adverse Event															214 (74.3)	114 (82.0)

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* Non-union adverse events that have not resulted in a second surgery.

** Non-union adverse events that have resulted in a second surgery.

[1] Percent of 140 males.

[2] Percent of 70 males.

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The reported rates of several adverse events were high, but similar, in both the investigational and control groups. These events included back and leg pain, neurological events, gastrointestinal events, spinal events, cardiovascular events and infection.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention was 10.4% (30/288) in the investigational groups and 13.7% (19/139) in the control group. The majority of supplemental fixations were due to painful nonunion.

Urogenital events occurred with greater frequency in the investigational groups (11.5%) compared to the control group (7%). Retrograde ejaculation rates were greater in the investigational groups (11 subjects) compared to the control group (1 subject) with the majority of events occurring in the early postoperative period.

The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups compared to the control group. The rates of these events were low, however, and may be partially attributed to a learning curve associated with the laparoscopic surgical approach. The rate of nonunion requiring secondary surgery in the investigational groups was comparable to that of the control group. One death was reported - a control group subject with cardiovascular disease.

Potential Adverse Events:

The following is a list of potential adverse events which may occur with spinal fusion surgery with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. Some of these adverse events may have been previously reported in the adverse events table.

- Bone fracture.
- Bowel or bladder problems.
- Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- Change in mental status.
- Damage to blood vessels and cardiovascular system compromise.
- Damage to internal organs and connective tissue.
- Death.

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- Development of respiratory problems.
- Disassembly, bending, breakage, loosening, and/or migration of components.
- Dural tears.
- Ectopic and/or exuberant bone formation.
- Fetal development complications.
- Foreign body (allergic) reaction.
- Gastrointestinal complications.
- Incisional complications.
- Infection.
- Insufflation complications.
- Neurological system compromise.
- Nonunion (or pseudarthrosis), delayed union, mal-union.
- Postoperative change in spinal curvature, loss of correction, height, and/or reduction.
- Retrograde ejaculation.
- Scar formation.
- Tissue or nerve damage.

Note: Additional surgery may be necessary to correct some of these potential adverse events.

CLINICAL RESULTS:

Clinical data to support the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device were collected as part of a prospective, multi-center pivotal study that consisted of randomized and non-randomized arms. The randomized arm contained two groups, one investigational and one control. The control group was implanted with the LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft bone, while the investigational group was implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. In both

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cases, the surgical approach was an open anterior approach. The non-randomized arm contained only an investigational group, where subjects were implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device through a laparoscopic anterior approach. The control group from the randomized arm was used as the control for the non-randomized arm.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site resulting from the need to collect the iliac crest grafts. The potential for investigator bias in the clinical outcome parameters was reduced by having the subjects rate their outcome using objective self-assessments. The radiographic outcome parameters were performed by independent radiologists who were blinded to treatment. These were the only radiographic evaluations used for determining radiographic success.

The indication studied was degenerative disc disease (DDD) accompanied by back pain with or without leg pain at a single level between L_4 and S_1 confirmed by history and radiographic studies.

Clinical and radiographic effectiveness parameters

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12 and 24 months and biennially thereafter until the last subject enrolled in the study had been seen for their 24 month evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation timepoint, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 24 months of follow-up. Antibodies to rhBMP-2 and bovine Type I collagen were assessed preoperatively and at 3 months post-operatively. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Primary and secondary clinical and radiographic effectiveness outcome parameters were evaluated for all treated subjects at all follow-up evaluation timepoints identified above. The primary clinical parameters assessed were of pain, function and neurological status. The secondary clinical outcome parameters assessed were general health status, back and leg pain, donor site pain (control subjects only), patient satisfaction and patient global perceived effect of the treatment. The primary radiographic outcome parameter consisted of evaluations of fusion, while the secondary radiographic assessment was disc height.

Fusion was evaluated at 6, 12 and 24 months post-op using plain radiographs (AP, lateral and flexion/extension films) and high resolution thin-slice CT scans (1mm slices with 1mm index on axial sagittal and coronal reconstructions). Fusion was defined as the presence of bridging bone connecting the inferior and superior

vertebral bodies; a lack of motion on flexion/extension (≤ 3mm of translation and < 5° of angulation); and no evidence of radiolucencies over more that 50% of either implant. Fusion success was defined as the presence of all of these parameters plus the lack of a second surgical intervention resulting from a non-union. All assessments were made from the plain films except for the assessment of bridging bone, which was made using the CT scans only if bridging bone could not be visualized on the plain film.

Pain and function were measured using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15 point improvement in the Oswestry score from the pre-op baseline score.

Neurological status consisted of measurements of four parameters - motor, sensory, reflexes, and straight leg raise (SLR). Neurological status success was defined as maintenance or improvement of the pre-op baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

Patient demographics and accountability

A total of 143 open approach investigational and 136 control patients were enrolled in the randomized arm of the study and received the device. A total of 134 subjects were enrolled in the non-randomized arm of the study and received the device. For the majority of the demographic parameters, there were no differences in pre-op demographics across the three populations.

Surgical results and hospitalization

Surgical and hospitalization information			
	Investigational Open Surgical Approach	**Control Open Surgical Approach**	**Investigational Laparoscopic Surgical Approach**
mean operative time (hrs)	1.6	2.0	1.9
mean EBL (ml)	109.8	153.1	146.1
hospitalization (days)	3.1	3.3	1.2

statistically different from control

Clinical and radiographic effectiveness evaluation

Individual subject success was defined as success in each of the primary clinical and radiographic outcome parameters. Success for these parameters included:

1. the presence of radiographic fusion;
2. an improvement of at least 15 points from the baseline Oswestry score;
3. maintenance or improvement in neurological status;
4. the presence of no serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
5. no additional surgical procedure classified as "Failure."

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for the individual primary outcome parameters and overall success. All success rates were based on the data from the 24 month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods.

Posterior Probabilities of Success at 24 Months			
Primary outcome variable	**Investigational Open Surgical Approach**	**Control Open Surgical Approach**	**Investigational Laparoscopic Surgical Approach**
	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)
Fusion	92.8% (88.5%, 96.9%)	88.1% (82.6%, 99.3%)	93.0% (87.9%, 97.5%)
Oswestry	71.0% (63.4%, 78.7%)	70.9% (63.1%, 79.1%)	83.0% (75.6%, 90.5%)
Neurologic	81.0% (74.5%, 87.9%)	81.7% (74.9%, 88.7%)	89.0% (83.1%,94.8%)
Overall success	57.1% (49.2%, 65.7%)	56.7% (48.3%, 65.0%)	68.0% (59.3%, 76.5%)

The probability (also called the posterior probability) that the 24 month overall success rate for the investigational groups was equivalent to the 24 month success rate for the control group was 99.4% for the open surgical approach investigational group and almost 100% for the laparoscopic surgical approach investigational group.

For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the open anterior surgical approach, the chance (the predictive probability) of overall success at 24 months would be 57.1% for the open surgical approach. Given the results of the trial, there is a 95% probability that the chance of success ranges from 49.2% to 65.7%. For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the anterior laparoscopic surgical approach, the chance of overall success at 24 months would be 68.0%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 59.3% to 76.5%. For a future patient receiving the control treatment, the chance of overall success at 24 months would be 56.7%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 48.3% to 65.0%.

Safety and immune response evaluation

The assessment of safety consisted of an evaluation of the reported adverse events, as well as an evaluation of antibodies to rhBMP-2, bovine Type I collagen and human Type I collagen. The complete list of complications, adverse events and subsequent interventions is described in the Adverse Events section above. The presence of antibodies were assessed at the pre-op and 3 month post-op visits using ELISA. If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. The screening ELISA cutpoint for positive

antibody responses was set to 5 times the standard deviation of sera from normal human donors. Subjects were considered to have an elevated immune response if the preoperative test was negative (titer < 50) and postoperative test was positive (titer ≥ 50) or if the preoperative test was positive and the postoperative test was positive with a three-fold higher titer than the preoperative test.

There were 3 subjects who had positive antibody responses to rhBMP-2 – 1 subject in each of the study groups. The rates of positive antibody response to rhBMP-2 were 0.7% in the open surgical approach investigational group and 0.8% in the laparoscopic surgical approach investigational and open surgical approach control groups. While there is a theoretical possibility that antibodies to rhBMP-2 could neutralize endogenous BMP-2, thereby interfering with subsequent bone healing, this was not observed during the course of the study.

Sixty-six subjects were considered to have an authentic elevated antibody response to bovine Type I collagen - 18 open surgical approach investigational subjects, 32 laparoscopic surgical approach investigational subjects and 16 control subjects. No subjects had positive responses to human Type I collagen.

An evaluation was performed on the impact of a positive antibody response on overall success and fusion success. There was very little difference in overall and individual success when antibody status was taken into consideration.

During the course of the study, 6 pregnancies were reported – one in the control group and five in the investigational groups. Two of the four pregnancies that occurred in the laparoscopic approach group resulted in first trimester miscarriages. The other three pregnancies in the investigational groups resulted in live births with no reported complications. None of the pregnant subjects had antibody responses to rhBMP-2 or Type I collagen (bovine or human), that were detectable to the limits of the sensitivity of the assay.

Two cases of cancer were diagnosed during the course of the pivotal study – one in an investigational group and one in the control group. An investigational subject was found to have pancreatic cancer while a control subject was found to have breast cancer. No additional information is available on these subjects, *e.g.*, BMP-2 receptor expression.

HOW SUPPLIED

InFUSE™ Bone Graft component is supplied in three kit sizes containing all the components necessary to prepare this portion of the device, *i.e.*, the collagen sponge(s), a vial with the lyophilized growth factor, a vial with sterile water for reconstituting the growth factor, syringes and needles. The LT-CAGE™ Lumbar

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Tapered Fusion Device component is supplied in seven sizes which must be properly selected based on a specific patient's anatomy.

STORAGE CONDITIONS

Store the InFUSE™ Bone Graft component at room temperature (15 – 25 degrees Centigrade (59 to 77° F)). The LT-CAGE™ Lumbar Tapered Fusion Device component should also be stored at room temperature.

DOSAGE AND ADMINISTRATION

InFUSE™ Bone Graft component is prepared immediately prior to use from a kit containing all necessary components. Once prepared, the InFUSE™ Bone Graft component contains rhBMP-2 at a concentration of 1.5 mg/mL.

The size of the InFUSE™ Bone Graft component kit and the volume of InFUSE™ Bone Graft component to be implanted are determined by the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device components which are utilized. The patient's anatomy will determine the size of the LT-CAGE™ components to be used. The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device surgical technique provides more information on templating to determine the appropriate size LT-CAGE™ Lumbar Tapered Fusion Device component.

DIRECTIONS FOR USE

InFUSE™ Bone Graft component is prepared at the time of surgery in the surgical suite by reconstituting the lyophilized rhBMP-2 with sterile water (See Instructions for Preparation), and then uniformly applying the reconstituted rhBMP-2 solution to the ACS. The InFUSE™ Bone Graft component is then inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component. The complete device is then implanted through an anterior open or laparoscopic surgical approach (See the Surgical Technique manual). If the InFUSE™ Bone Graft component is not used within two hours after reconstitution, it must be discarded.

The InFUSE™ Bone Graft component must not be sterilized by the hospital. The LT-CAGE™ Lumbar Tapered Fusion Device component, if not supplied sterile, should be sterilized before insertion of the InFUSE™ Bone Graft component. Refer to the package insert for the LT-CAGE™ Lumbar Tapered Fusion Device component for information on packaging, cleaning/decontamination and sterilization of this component and its instruments.

PRODUCT COMPLAINTS:

Any health care professional (e.g., customer or user of this system of products), who has any complaints or who has experienced any dissatisfaction in the quality, identification, durability, reliability, safety, effectiveness and/or performance of this product, should notify the distributor, Medtronic Sofamor Danek. Further, if any of the

implanted InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device components ever "malfunction," (i.e., do not meet any of their performance specifications or otherwise do not perform as intended), or are suspected of doing so, the distributor should be notified immediately (1-800-933-2635). If any Medtronic Sofamor Danek product ever "malfunctions" and may have caused or contributed to the death or serious injury of a patient, the distributor should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component name and number, lot number, your name and address, the nature of the complaint and notification of whether a written report from the distributor is requested.

DEVICE RETRIEVAL EFFORTS:

Should it be necessary to remove an InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, please call Medtronic Sofamor Danek prior to the scheduled surgery to receive instructions regarding data collection, including histopathological, mechanical and adverse event information.

IN USA
Customer Service Division **Telephone:** 800-933-2635
Medtronic Sofamor Danek USA, Inc. 800-876-3133
1800 Pyramid Place or 901-396-3133
Memphis, Tennessee 38132 **Telefax:** 901-396-0356
USA or 901-332-3920

Supplied by
Medtronic Sofamor Danek USA, Inc.