SUMMARY OF SAFETY AND EFFECTIVENESS DATA

MAR 9 2007

I. GENERAL INFORMATION

Device Generic Name:	Bone void filler, recombinant human bone morphogenetic protein, collagen scaffold, osteoinduction
Device Trade Name:	INFUSE® Bone Graft
Applicant's Name and Address:	Medtronic Sofamor Danek, Inc. USA 1800 Pyramid Place Memphis, TN 38132
Premarket Approval Application (PMA) Number:	P050053
Date of Panel Recommendation:	November 9, 2006
Date of Notice of Approval of Application:	March 9, 2007

II. INDICATIONS FOR USE

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

III. CONTRAINDICATIONS

INFUSE® Bone Graft is contraindicated in the following:

- For patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.
- In the vicinity of a resected or extant tumor or any active malignancy or patients undergoing treatment for a malignancy.
- In pregnant women.
- In patients with an active infection at the operative site.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the INFUSE® Bone Graft physician labeling.

V. DEVICE DESCRIPTION

INFUSE® Bone Graft consists of two components - recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). **These components must be used as a system for the prescribed indications described above. The bone morphogenetic protein solution component**

must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.

INFUSE® Bone Graft 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 device is replaced by trabecular bone.

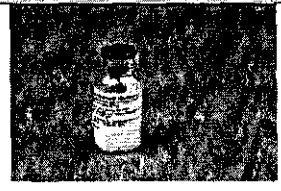
rhBMP-2 is the active agent in INFUSE® Bone Graft. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster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

The 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.

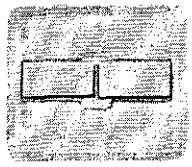
The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

INFUSE® Bone Graft is supplied as part of a kit, which includes a rhBMP-2 vial, an ACS, Sterile Water for Injection vial, and a syringe. Four kit sizes are available, depending on the size of the implant site and the amount of bone growth required. The kits are designated as Small, Medium, Large, and Large II. At least one kit is required for each procedure. INFUSE® Bone Graft kits are stored at room temperature. Prior to implantation, rhBMP-2 is reconstituted with Sterile Water for Injection and the solution is then uniformly applied to the ACS. The table below reflects the INFUSE® Bone Graft kit components, including the labeling documents.

INFUSE® Bone Graft Kit Contents and Description

Part	Number	Brief Description	Photograph
rhBMP-2 Vial	1 or 2 vials per kit	Vial(s) containing 4.9 or 12.7 mg of lyophilized rhBMP-2	
Sterile Water for Injection Vial	1 or 2 vials per kit	5 or 10 mL vial(s) containing Sterile Water for Injection for reconstituting the lyophilized rhBMP-2	

INFUSE® Bone Graft Kit Contents and Description

Part	Number	Brief Description	Photograph
Absorbable Collagen Sponge (ACS)	2, 4, or 6 1"x2" or 1 3"x4" piece per kit	Absorbable Collagen Sponge (ACS); sponge sizes are 1"x2" or 3"x4". The ACS is packaged in a polyvinyl chloride blister pack with a Tyvek lid.	
Syringe	2 or 4 per kit	Used to add the Sterile Water for Injection to rhBMP-2 vial and to place the reconstituted rhBMP-2 on the ACS	
Instructions for Preparation	1 per kit	Detailed procedures for reconstituting rhBMP-2 powder and for applying the reconstituted rhBMP-2 on the ACS	
Package Insert	1 per kit	Provides important medical information about INFUSE® Bone Graft	
Patient Label	1 set per kit	Provides mechanism for recording device information on patient charts, reimbursement forms, hospital records, etc.	
Packaging	1 set per kit	Styrene tray containing vials and syringes; Styrene tray containing ACS; SBS carton containing the two trays	

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-surgical alternatives to performing oral maxillofacial procedures with INFUSE® Bone Graft includes, but may not be limited to, watchful waiting with no intervention.

Surgical alternatives include, but may not be limited to, stimulating bone growth utilizing the following methods:

- Autograft – bone graft taken from one site in the body and placed in a different site of the same individual
- Allograft – bone from a cadaver
- Alloplast – artificial bone
- Distraction Osteogenesis – dividing bone and allowing bone to grow in between.

The above procedures may or may not include the use of a matrix (such as ACS).

VII. MARKETING HISTORY

The INFUSE® Bone Graft has not been marketed in the United States or any foreign country for the indications described in Section II above. INFUSE® Bone Graft is marketed in the United States as a device for both spine and trauma indications. INFUSE® Bone Graft with the LT-CAGE Lumbar Tapered Fusion Device is approved for single-level spinal fusion procedures in skeletally mature patients with degenerative disc disease (P000058). INFUSE® Bone Graft alone is approved for treating acute, open tibial shaft fractures (P000054). INFUSE® Bone Graft has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Adverse Events

In addition to the adverse events identified in the table below, the following potential adverse events may also occur with oral maxillofacial surgery using the INFUSE® Bone Graft:

- Allergic reaction
- Death
- Ectopic and/or exuberant bone formation
- Fetal development complications
- Itching
- Scar formation
- Tissue or nerve damage
- Antibodies to rhBMP-2
- Antibodies to bovine collagen
- Antibodies to human Type I collagen.

Adverse Events for Patients Receiving Autogenous Bone Graft or INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

The table below reflects adverse events that occurred in >5% of the patients who received either (1) bone graft or (2) INFUSE® Bone Graft (1.5mg/mL concentration of rhBMP-2/ACS) in a series of clinical studies involving dental use of the device. The 1.5mg/mL is the commercial concentration. The most frequently occurring adverse events in both groups were edema, erythema, infection, pain, ecchymosis, arthralgia, abnormal gait, and rash. The following adverse events were shown to occur more frequently (i.e., statistically significant) in the bone graft group: edema; infection; pain; nausea; hyperglycemia; hypophosphatemia; arthralgia; hypesthesia; abnormal gait; bronchitis; and rash.

Adverse Events for INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS) vs. Bone Graft Patients: Frequent Adverse Events (>5% of Patients) by Body System and COSTART Term

Body System COSTART Term	INFUSE® Bone Graft Patients (n=120) N (%)	Autogenous Bone Graft Patients (n = 91) N (%)	p-value
Body As A Whole			
Accidental Injury	10 (8.3)	4 (4.4)	0.2817
Back Pain	4 (3.3)	6 (6.6)	0.3340
Dehiscence	6 (5.0)	5 (5.5)	1.0000
Edema	2 (1.7)	34 (37.4)	<0.0001
Face Edema	81 (67.5)	52 (57.1)	0.1500
Flu Syndrome	3 (2.5)	5 (5.5)	0.2950
Headache	14 (11.7)	7 (7.7)	0.3652
Infection	30 (25.0)	39 (42.9)	0.0076
Pain	26 (21.7)	46 (50.5)	<0.0001
Peri-Implantitis	11 (9.2)	4 (4.4)	0.2793
Cardiovascular System			
Hematoma	11 (9.2)	8 (8.8)	1.0000
Hypertension	9 (7.5)	8 (8.8)	0.8011
Digestive System			
Gingivitis	7 (5.8)	5 (5.5)	1.0000
Mouth Pain	102 (85.0)	76 (83.5)	0.8489
Mouth Ulceration	4 (3.3)	6 (6.6)	0.3340
Nausea	4 (3.3)	10 (11.0)	0.0470
Oral Edema	81 (67.5)	59 (64.8)	0.7688
Oral Erythema	57 (47.5)	56 (61.5)	0.0513
Tooth Disorder	10 (8.3)	4 (4.4)	0.2817
Hemic And Lymphatic System			
Anemia	4 (3.3)	9 (9.9)	0.0797
Ecchymosis	19 (15.8)	21 (23.1)	0.2157
Metabolic And Nutritional Disorders			
Healing Abnormal	4 (3.3)	9 (9.9)	0.0797
Hyperglycemia	8 (6.7)	15 (16.5)	0.0270
Hypophosphatemia	2 (1.7)	9 (9.9)	0.0107
SGOT Increased	3 (2.5)	5 (5.5)	0.2950
SGOT Increased	6 (5.0)	6 (6.6)	0.7660
Musculo-Skeletal System			
Arthralgia	14 (11.7)	24 (26.4)	0.0069
Bone Disorder	14 (11.7)	11 (12.1)	1.0000
Nervous System			
Abnormal Gait	0 (0.0)	37 (40.7)	<0.0001
Hypesthesia	5 (4.2)	15 (16.5)	0.0036
Respiratory System			
Bronchitis	0 (0.0)	5 (5.5)	0.0140

Body System COSTART Term	INFUSE® Bone Graft Patients (n=120)	Autogenous Bone Graft Patients (n = 91)	p-value
	N (%)	N (%)	
Epistaxis	7 (5.8)	6 (6.6)	1.0000
Rhinitis	10 (8.3)	6 (6.6)	0.7944
Sinusitis	11 (9.2)	15 (16.5)	0.1390
Skin And Appendages			
Rash	9 (7.5)	34 (37.4)	<0.0001

Serious Adverse Events for All Study Patients Receiving Autogenous Bone Graft or INFUSE® Bone Graft (any concentration)

Although there were no serious adverse events that were determined to be related to the INFUSE® Bone Graft, there were serious adverse events which occurred during the studies. Of the 184 patients treated with all concentrations of INFUSE® Bone Graft, there were 37 serious or life threatening adverse events. Of the 91 patients treated with bone graft, there were 27 severe adverse events. Note that the clinical studies did not assess whether or not adverse events were procedure-related for the bone graft group.

Immune Response

The presence of antibodies was assessed prior to and following use of INFUSE® Bone Graft using Enzyme-Linked ImmunoSorbent Assay (ELISA). If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen.

Four of 184 (2.2%) rhBMP-2/ACS patients had a positive antibody response to rhBMP-2. 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 studies. None of the autogenous bone graft patients developed these antibodies.

There were 37 of 184 (20%) rhBMP-2/ACS patients who were considered to have an authentic elevated antibody response to bovine Type I collagen. There were 28 of 91 (31%) autogenous bone graft patients who were considered to have an authentic elevated antibody response to bovine Type I collagen. No patients had positive responses to human Type I collagen.

There were seven pregnancies, in six women, reported in the clinical studies. Four pregnancies were reported in the rhBMP-2/ACS group and three pregnancies in the autogenous bone graft group. All of these pregnancies resulted in the birth of healthy babies except one in which the patient elected to terminate pregnancy for reasons unrelated to her participation in the clinical study.

Fourteen cases of cancer were diagnosed; 3 in the INFUSE® Bone Graft group, 4 at lower concentrations of rhBMP-2/ACS, and 7 in the autogenous bone graft group. Cancers in the INFUSE® Bone Graft group included 1 gastrointestinal cancer, 1 myeloma and 1 squamous cell carcinoma. Cancers noted at lower concentrations of rhBMP-2/ACS included 1 squamous cell carcinoma, 2 prostate cancers and 1 colon cancer. Cancers in the autogenous

bone graft group included: 2 basal cell carcinoma, 2 squamous cell carcinomas, 1 brain cancer, 1 breast cancer, and 1 fibroadenoma. None of these cancers were considered related to the treatment.

IX. SUMMARY OF NON-CLINICAL LABORATORY STUDIES

A number of preclinical studies for INFUSE® Bone Graft were previously reviewed and found adequate to support approval of rhBMP-2's use in the clinical indications of spinal fusion and tibial long bone healing through PMAs P000054 and P000058. These studies include biocompatibility/toxicity testing; pharmacokinetics and dosing; rhBMP-2 protein and ACS characterization; and stability testing.

The focus of this section is to discuss preclinical testing specific to the clinical indications for this PMA. Testing was conducted in the following categories:

- Preclinical Effectiveness in Oral Maxillofacial Indications
- Comparability of Bone Induction by rhBMP-2 and Autogenous Bone.

Preclinical Effectiveness in Oral Maxillofacial Indications

The preclinical effectiveness studies evaluating oral maxillofacial indications are presented below, stratified by the following categories:

- Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS with Dental Implant Placement
- Maxillary Sinus Floor Augmentation using rhBMP-2/ACS
- Maxillary Sinus Floor Augmentation using rhBMP-2/ACS with Dental Implant Placement.

Study Model	Study Title	Summary
Extraction Socket Augmentation using rhBMP-2/ACS with Dental Implant Placement		
Canine	Evaluation of rhBMP-2/Helistat® Absorbable Collagen Sponge (ACS) using Barrier Membranes and Two-Stage Loading of Dental Implants in a Canine Ridge Augmentation Model	Study investigated the ability of rhBMP-2/ACS-induced bone to support dental implant installation and functional loading. Six animals were treated. There were no statistically significant differences between dental implants placed into rhBMP-2-induced bone and resident bone for any parameter at any observation interval.
Maxillary Sinus Floor Augmentation using rhBMP-2/ACS		
Caprine	Alveolar Bone Augmentation with rhBMP-2/Helistat® Absorbable Collagen Sponge Device (ACS) using a Sinus Floor Elevation Procedure in Goats: Interim Report and Histologic Analysis	These reports show that surgical implantation of rhBMP-2/ACS in a subantral space results in sufficient amounts of augmented bone for the placement and osseointegration of titanium dental implants.

Study Model	Study Title	Summary
Rabbit	Maxillary Sinus Floor Augmentation in Rabbits: A Comparative Histologic-Histomorphometric Study Between rhBMP-2 and Autogenous Bone (Wada, et al, Int J Periodontics Restorative Dent 2001;21:253-236)	Histometric results compared by analysis of variance revealed no statistical difference in the bone volume at augmented areas between the two types of implant ($p>0.05$). Histologic evaluation documented that the trabeculae with a lamellar structure were imbedded in fatty marrow at eight weeks in both implant sites. These results suggest that sinus floor augmentation with rhBMP-2/ACS or autogenous bone induces comparable histologic and histometric evidence of bone formation in rabbits, so the bone formed by rhBMP-2 should support implants similar to autogeneous bone.
Maxillary Sinus Floor Augmentation using rhBMP-2/ACS with Dental Implant Placement		
Non-Human Primate	The Effect of rhBMP-2/ACS on Bone Formation and Osseointegration Following Subantral Augmentation Procedures in Nonhuman Primates	This study evaluated bone formation and osseointegration of dental implants in the subantral space following surgical implantation of rhBMP-2/ACS. In each of four adult Cynomolgus monkeys, one subantral site was implanted with rhBMP-2/ACS with the contralateral site receiving buffer/ACS. This nonhuman primate study provides evidence for considerable vertical bone gain in the subantral space following surgical implantation of rhBMP-2/ACS, allowing placement of dental implants. The newly formed bone appears of similar quality and provides similar possibility for osseointegration as the regional resident bone.

Comparability of Bone Induction by rhBMP-2 and Autogenous Bone in Oral Maxillofacial, Spine, and Trauma Indications

This section summarizes relevant preclinical studies that directly compare the effectiveness of rhBMP-2/ACS to autogenous bone graft at inducing de novo bone formation that is similar in quality to native bone in oral maxillofacial, spine, and trauma indications.

Comparison of Effectiveness between INFUSE® Bone Graft and Autogenous Bone Graft

Study	Species	Results
Mandibular Hemimandibulectomy Defects (Boyne et al. 1999)	Non-human primate	This was a multi-phase study with a bone induction phase, abutment osseointegration phase, and functional loading of the prosthesis. Nine of 9 implants that were placed in the rhBMP-2/ACS bone survived through functional loading while only 4/8 implants from the autograft group survived. Histology comparisons could not be made between the two groups due to the high number of autograft implants lost. The rhBMP-2/ACS bone showed large amounts of trabecular bone undergoing mineralization prior to implantation. After functional loading (at sacrifice), the bone responded like normal bone with thickening of trabeculae and further bony deposition.

Preclinical Conclusions

The preclinical testing, as a whole, supports a reasonable assurance of safety for the product in its intended clinical uses. With respect to the preclinical testing reflected in the two tables above, there were no inflammatory responses seen in the presence of rhBMP-2 and the studies showed that the augmented bone could function in the clinical indications of extraction socket augmentation and sinus augmentation.

X. SUMMARY OF CLINICAL STUDIES

Overview of Clinical Studies

There were five clinical studies that supported the approval of the PMA, three for sinus floor augmentation and two for extraction socket augmentation.

The sinus floor augmentation clinical studies were:

- Pilot Study (short term 9409 and long-term 9410)
- Dosing Study (9531)
- Pivotal Study (9730).

The extraction socket augmentation clinical studies were:

- Pilot Study (short term 9411 and long-term 9412)
- Dosing Study (9514).

A similar study protocol was followed in each of the five studies with the treatment course consisting of study device implantation followed by an osteoinduction phase, dental implant placement followed by an osseointegration phase, and prosthesis placement (functional loading) followed by functional restoration. These studies involved varying dosages of rhBMP-2/ACS and varying control groups.

A total of 312 subjects were enrolled across 5 studies. One hundred eighty four subjects received one of three concentrations of rhBMP-2/ACS (0.43 mg/mL, 0.75 mg/mL, or 1.5 mg/mL); 91 subjects received bone graft, either autogenous bone (autograft) or autogenous bone and allogeneic bone (autograft plus allograft). Two sub-groups were also treated to evaluate no treatment (20 subjects) and a placebo consisting of ACS alone, the carrier for rhBMP-2 (17 subjects).

The five studies are summarized in the tables below.

Sinus Floor Augmentation Study Summaries

Study Description	Pilot Study (9409/9410)		Dosing Study (9531)	Pivotal Study (9730)
	Short-Term (9409)	Long-Term (9410)		
Number of Subjects	12: rhBMP-2/ACS 0.43 mg/mL	(same subjects as 9409)	48 total subjects: • Autogenous bone graft: n=13 • rhBMP-2/ACS 0.75 mg/mL: n=18 • rhBMP-2/ACS 1.5 mg/mL: n=17	160 total subjects: • Autogenous bone graft: n=78 • rhBMP-2/ACS 1.5 mg/mL: n=82
Study Design	Open-label, non-randomized, four-center study	Follow-up study of subjects enrolled in 9409	Randomized multi-center trial (6 centers) of two dosage levels with ACS, or autogenous bone graft alone	Multi-center trial (21 centers) with subjects randomized to rhBMP-2/ACS or autogenous bone graft alone
Follow-Up	16 weeks post-surgery	36 months post-prosthesis	36 months post-prosthesis	24 months post-prosthesis

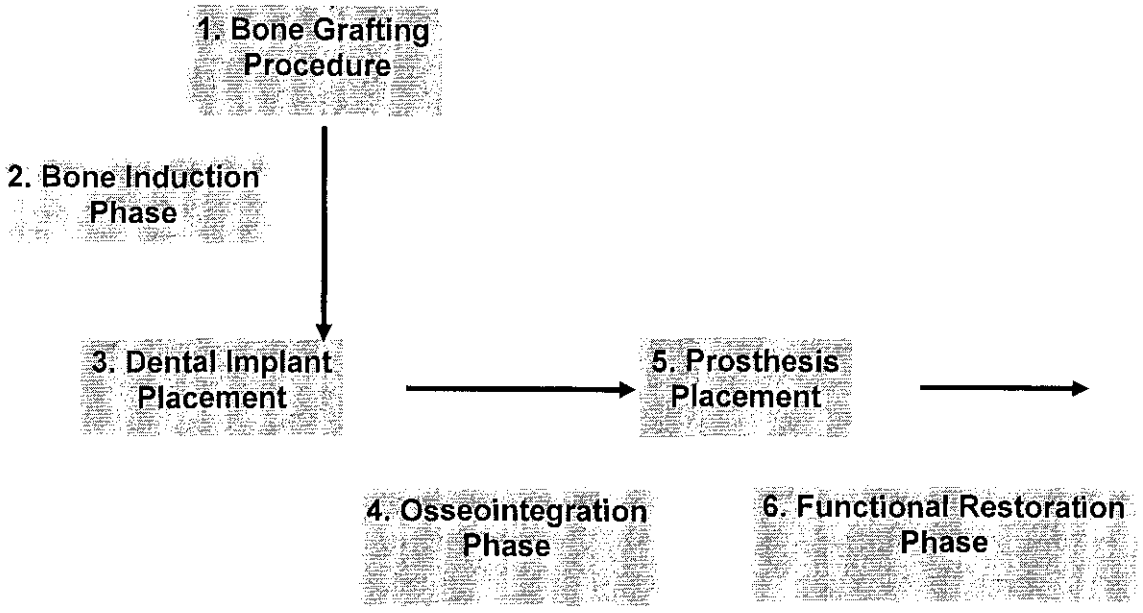
Extraction Socket Augmentation Study Summaries

Study Description	Pilot Study (9411/12)		Dosing Study (9514)
	Short-Term (9411)	Long-Term (9412)	
Number of Subjects	12: rhBMP-2/ACS 0.43 mg/mL	(same subjects as 9411)	80 total subjects: • No treatment: n=20 • ACS alone (no rhBMP-2): n=17 • rhBMP-2/ACS 0.75 mg/mL: n=22 • rhBMP-2/ACS 1.5 mg/mL: n=21
Study Design	Open-label, non-randomized, two-center study	Long-term follow-up of subjects enrolled in 9411	Randomized multi-center trial (8 centers) of two dosage levels with ACS, ACS alone or no treatment
Follow-Up	16 weeks post-surgery	24 months post-surgery	24 months post-prosthesis

Study Design/Methods

The five studies used to support this PMA application were conducted in a similar manner with similar study design and methods used. The treatment course was the same for subjects enrolled in all of the five studies as shown in the Figure below.

Subject Treatment Course Across all Five Studies



Surgery and Evaluation Procedures

Subjects enrolled across the five studies were all candidates for two-stage augmentation procedures. In the first stage, the osteoinductive material is surgically implanted. The second stage is the placement of the dental implant, if applicable, after time has elapsed to allow for osseointegration.

Demographics – All Patients with INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

Demographic data for the 1.5 mg/mL (commercial concentration of INFUSE® Bone Graft) treatment group used for demonstration of effectiveness are summarized below. Age, gender, and race were categorized for all study subjects.

Demographics of INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

Characteristic	Extraction Socket Dosing Study (9514)	Sinus Dosing Study (9531)	Sinus Pivotal Study (9730)	Total
Gender:				
Male	52.4%	35.3%	56.1%	52.5%
Age:				
Mean	47.6	52.1	53.6	52.3
Age Category:				
< 65 yrs	85.7%	88.2%	79.3%	81.7%
Race:				
Black	38.1%	5.9%	6.1%	11.7%
Asian	9.5%	0.0%	1.2%	2.5%
Other	0.0%	0.0%	2.4%	1.7%
Hispanic	9.5%	5.9%	6.1%	6.7%
Caucasian	42.9%	88.2%	84.1%	77.5%

Subject Disposition of All Patients

Across all five studies, the follow-up rate was ≥85%. One death was reported during the conduct of the Extraction Socket Augmentation Dosing study. The death was determined not to be related to the study treatment. Subject withdrawals were both voluntary and withdrawn based on missed follow-ups. As per protocol, subjects who failed to complete their scheduled follow-up were withdrawn. Nine subjects withdrew. Subjects were analyzed in the groups to which they were assigned, not the groups in which they were treated.

Sinus Augmentation Clinical Summary

Overview

Evaluation of the effectiveness for the sinus floor augmentation indication is based primarily on the sinus floor pivotal study (9730). These data are analyzed in accordance with the endpoints and methodology from the sinus floor pivotal study protocol. Because of similarities between studies 9730 and 9531 (sinus floor dosing study), results based on the two studies combined are presented, as well for certain endpoints.

Pivotal Study Endpoints

Primary endpoint:

- Proportion of patients (within the rhBMP-2/ACS treatment group) who have successful dental implant borne restoration after 6 months of functional loading. Subjects who successfully received prosthesis but were lost to follow-up or withdrew anytime thereafter were excluded from the analysis.

Secondary endpoints:

- Proportion of patients (within each treatment group) who have successful dental implant borne restoration after 6, 12, 18, and 24 months of functional loading.
- Proportion of endosseous dental implants (within each treatment group) that once placed into the augmented maxillary sinus(es) achieve clinical osseointegration and maintain functional restoration after 6, 12, 18, and 24 months of functional loading.

Primary Endpoint Analysis

Primary Effectiveness Endpoint Results for Sinus Augmentation Studies 9730 and 9531 with INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

Subjects	Study 9531 (n=17)	Study 9730 (n=82)	Total (n=99)
Received dental implants into newly induced bone without additional augmentation	15 (88.2%)	67 (81.7%)	82 (82.8%)
Received prosthesis (functionally loaded)	14 (82.4%)	65 (79.3%)	79 (79.8%)
After 6 months functionally loaded			
N	**17**	**81**	**98**
Success [a,b]	**14 (82.4%)**	**64 (79.0%)**	**78 (79.6%)**
95% CI of Success[c]	**(56.6, 96.2)**	**(68.5, 87.3)**	**(70.3, 87.1)**
After 12 months functionally loaded			
N	17	80	97
Success [a,b]	14 (82.4%)	63 (78.8%)	77 (79.4%)
95% CI of Success[c]	(56.6, 96.2)	(68.2, 87.1)	(70.0, 87.0)
After 18 months functionally loaded			
N	17	77	94
Success[a,b]	14 (82.4%)	60 (77.9%)	74 (78.7%)
95% CI of Success[c]	(56.6, 96.2)	(67.0, 86.6)	(69.1, 86.5)
After 24 months functionally loaded			
N	17	75	92
Success [a,b]	14 (82.4%)	57 (76.0%)	71 (77.2%)
95% CI of Success[c]	(56.6, 96.2)	(64.7, 85.1)	(67.3, 85.3)

a. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.

b. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.

c. 2-sided 95% exact confidence interval.

Secondary Endpoint Analyses

Number (%) of Subjects Who Received Prosthesis and Maintained Functional Loading in the Sinus Augmentation Pivotal Study (9730)

Subjects	Autogenous Bone Graft (n=78)	INFUSE ® Bone Graft (1.5mg/mL) (n=82)	Difference[a]
Received dental implants into newly induced bone without additional augmentation	74 (94.9%)	67 (81.7%)	
Received prosthesis (functionally loaded)	72 (92.3%)	65 (79.3%)	
After 6 months functionally loaded			
N	76	81	
Success [b,c]	69 (90.8%)	64 (79.0%)	-11.8
95% CI[d]	(81.9, 96.2)	(68.5, 87.3)	(-22.8, -0.8)
After 12 months functionally loaded			
N	76	80	
Success [b,c]	69 (90.8%)	63 (78.8%)	-12.0
95% CI[d]	(81.9, 96.2)	(68.2, 87.1)	(-23.1, -1.0)
After 18 months functionally loaded			
N	76	77	
Success [b,c]	69 (90.8%)	60 (77.9%)	-12.9
95% CI[d]	(81.9, 96.2)	(67.0, 86.6)	(-24.2, -1.5)
After 24 months functionally loaded			
N	76	75	
Success [b,c]	69 (90.8%)	57 (76.0%)	-14.8
95% CI[d]	(81.9, 96.2)	(64.7, 85.1)	(-26.4, -3.1)

a. Difference = INFUSE® – autogenous bone graft.

b. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.

c. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.

d. Exact confidence intervals for success rates in both groups; approximate confidence intervals for the difference.

Number (%) of Subjects Who Received Prosthesis and Maintained Functional Loading in the Sinus Augmentation Pivotal Study (9730) and Dosing Study (9531) Combined

Subjects	Autogenous Bone Graft (n=91)	INFUSE ® Bone Graft (1.5mg/mL) (n=99)	Difference[a]
Received dental implants into newly induced bone without additional augmentation	87 (95.6)	82 (82.8)	
Received prosthesis (functionally loaded)	85 (93.4%)	79 (79.8%)	
After 6 months functionally loaded			
N	89	98	
Success [b,c]	80 (89.9%)	78 (79.6%)	-10.3
95% CI[d]	(81.7, 95.3)	(70.3, 87.1)	(-20.4, -0.2)
After 12 months functionally loaded			
N	87	97	
Success [b,c]	77 (88.5%)	77 (79.4%)	-9.1
95% CI[d]	(79.9, 94.4)	(70.0, 87.0)	(-19.6, 1.4)
After 18 months functionally loaded			
N	87	94	
Success [b,c]	76 (87.4%)	74 (78.7%)	-8.7
95% CI[d]	(78.5, 93.5)	(69.1, 86.5)	(-19.5, 2.2)
After 24 months functionally loaded			
N	87	92	
Success [b,c]	76 (87.4%)	71 (77.2%)	-10.2
95% CI[d]	(78.5, 93.5)	(67.3, 85.3)	(-21.2, 0.9)

a. Difference = INFUSE® – autogenous bone graft.
b. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.
c. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.
d. Exact confidence intervals for success rates in both groups; approximate confidence intervals for the difference.

The tables below show the implant-level success rates after functional loading. Two methods were used to handle missing outcomes (either due to withdrawals or missed visits):

- All patients without documented success were counted as failures (Analysis Method A)
- All patients without documented success were excluded from the calculations (Analysis Method B).

Prosthesis Placement (Baseline - Time 0 Functional Loading)

		Autogenous Bone Graft		INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS)		Statistics		
Method	**Study**	**Success Rate (%)**	**95% CI**	**Success Rate (%)**	**95% CI**	**Odds Ratio**	**95% CI of OR**	**P-value**
A	Both	85.2	(77.2, 90.7)	82.8	(74.1, 88.9)	0.835	(0.398, 1.753)	0.6340
	9531	85.2	(66.1, 94.4)	87.8	(67, 96.2)	1.254	(0.237, 6.632)	0.7903
	9730	84.9	(75.7, 91.1)	81.5	(71.5, 88.5)	0.780	(0.345, 1.763)	0.5504
B	Both	86.7	(78.9, 91.9)	85.6	(77.2, 91.3)	0.913	(0.413, 2.018)	0.8218
	9531	87.9	(66.8, 96.3)	88.6	(68.3, 96.6)	1.074	(0.174, 6.615)	0.9387
	9730	86.1	(77.1, 92)	84.7	(74.9, 91.1)	0.892	(0.374, 2.125)	0.7959

6-month Functional Loading

		Autogenous Bone Graft		INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS)		Statistics		
Method	**Study**	**Success Rate (%)**	**95% CI**	**Success Rate (%)**	**95% CI**	**Odds Ratio**	**95% CI of OR**	**P-value**
A	Both	78.7	(70.4, 85.2)	78.8	(70.1, 85.5)	1.004	(0.531, 1.899)	0.9898
	9531	74.7	(50, 89.7)	81.6	(62, 92.3)	1.501	(0.344, 6.557)	0.5890
	9730	79.5	(70.5, 86.3)	78.4	(68.6, 85.8)	0.939	(0.465, 1.897)	0.8606
B	Both	83.6	(75.4, 89.5)	81.4	(72.7, 87.8)	0.854	(0.419, 1.742)	0.6645
	9531	75.0	(50.4, 89.8)	83.7	(64.2, 93.6)	1.710	(0.379, 7.715)	0.4852
	9730	84.9	(75.9, 91)	80.7	(70.6, 87.9)	0.743	(0.333, 1.657)	0.4679

12-month Functional Loading

		Autogenous Bone Graft		1.5 mg/mL rhBMP-2/ACS		Statistics		
Method	**Study**	**Success Rate (%)**	**95% CI**	**Success Rate (%)**	**95% CI**	**Odds Ratio**	**95% CI of OR**	**P-value**
A	Both	74.8	(66, 82)	72.8	(63.4, 80.5)	0.900	(0.49, 1.652)	0.7332
	9531	51.6	(28.6, 73.9)	63.6	(41.4, 81.3)	1.645	(0.433, 6.246)	0.4643
	9730	78.6	(69.4, 85.6)	74.6	(64.3, 82.8)	0.802	(0.402, 1.599)	0.5304
B	Both	82.8	(74.4, 88.9)	78.7	(69.5, 85.7)	0.766	(0.38, 1.547)	0.4579
	9531	67.4	(40.3, 86.4)	75.8	(52.5, 89.9)	1.514	(0.329, 6.966)	0.5944
	9730	84.7	(75.8, 90.8)	79.1	(68.7, 86.7)	0.681	(0.309, 1.5)	0.3397

18-month Functional Loading

		Autogenous Bone Graft		INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS)		Statistics		
Method	**Study**	**Success Rate (%)**	**95% CI**	**Success Rate (%)**	**95% CI**	**Odds Ratio**	**95% CI of OR**	**P-value**
A	Both	75.6	(66.9, 82.5)	71.2	(62, 79)	0.801	(0.442, 1.452)	0.4653
	9531	58.1	(34.2, 78.6)	78.5	(58.8, 90.3)	2.637	(0.679, 10.233)	0.1611
	9730	78.3	(69.2, 85.3)	69.6	(59.1, 78.4)	0.634	(0.327, 1.229)	0.1771
B	Both	83.4	(74.9, 89.4)	78.4	(69.3, 85.4)	0.722	(0.357, 1.46)	0.3643
	9531	70.1	(44.3, 87.4)	79.4	(59.5, 91)	1.647	(0.387, 7.01)	0.4998
	9730	85.1	(75.9, 91.2)	77.7	(67.1, 85.7)	0.610	(0.274, 1.36)	0.2270

24-month Functional Loading

		Autogenous Bone Graft		INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS)		Statistics		
Method	**Study**	**Success Rate (%)**	**95% CI**	**Success Rate (%)**	**95% CI**	**Odds Ratio**	**95% CI of OR**	**P-value**
A	Both	77.7	(69.2, 84.3)	69.6	(60.3, 77.5)	0.660	(0.362, 1.202)	0.1744
	9531	58.1	(34.3, 78.6)	72.6	(51.9, 86.6)	1.911	(0.508, 7.193)	0.3384
	9730	80.7	(71.8, 87.3)	68.9	(58.4, 77.8)	0.529	(0.269, 1.04)	0.0648
B	Both	83.7	(75.4, 89.6)	76.7	(67.5, 84)	0.642	(0.321, 1.286)	0.2112
	9531	70.1	(44.4, 87.4)	78.1	(57.5, 90.4)	1.520	(0.357, 6.482)	0.5714
	9730	85.4	(76.4, 91.4)	76.1	(65.5, 84.2)	0.544	(0.248, 1.196)	0.1297

Sinus Augmentation Clinical Data Summary

In the Pivotal Study (9730), 79.0% of patients in the INFUSE® group (95% confidence interval: 68.5% – 87.3%) successfully received dental implants without additional augmentation, received a prosthesis, and maintained functional loading for at least six months. The observed success rate at six months post-loading in the autogenous bone graft group was higher by 11.8 percentage points (95% confidence interval: 0.8% – 22.8%). Combining the Pivotal Study (9730) with the Dosing Study (9531) yielded similar results.

However, as seen in the adverse events sections, the bone graft group had a statistically significant higher number of adverse events than the INFUSE® group.

Considering both the safety and effectiveness results for INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) for sinus augmentation, we determined that the benefits (despite success rates being lower than that reported for bone graft) outweigh the risks.

Extraction Socket Clinical Summary

Overview

The evaluation for the extraction socket augmentation procedure is based on the results of the Dosing Study (9514). The treatment groups included:

- No treatment – the extraction socket was allowed to heal on its own
- INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) – ACS with commercial dose of rhBMP-2.

Study Endpoints

The protocol of study 9514 specifies the following endpoints.

Primary endpoint:

- Proportion of patients within each treatment group that have adequate bone formation to support the placement of endosseous dental implants at four months.

Secondary endpoints:

- Proportion of patients that have a prosthesis placed onto the dental implants placed into the study treatment area
- Proportion of patients that maintain a successful prosthesis at 6, 12, 18, and 24 months following loading.

Primary Endpoint Analysis

Number of Patients (%) within each Treatment Group who underwent Dental Implant Placement without Additional Augmentation at 4 months

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	1 (5%)
Withdrew	1 (5%)	0
Succeeded	9 (45%)	18 (85%)
Total	20	21

Because of a withdrawn patient in the No Treatment group, different statistical analyses are possible depending on how this patient is handled. Counting the withdrawn patient as a failure leads to a Fisher exact p-value of 0.0088 for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment. If the withdrawn patient is assumed to be missing completely at random, then it can be excluded from the analysis and the resulting Fisher exact p-value is 0.0171 for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment.

Secondary Endpoint Analyses

Number of Patients (%) within each Treatment Group who underwent Prosthesis Placement without Additional Augmentation (Baseline - Time 0 Functional Loading)

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Withdrew	3 (15%)	0
Succeeded	7 (35%)	16 (76%)
Total	20	21

Again, different methods exist for handling the withdrawn patients. The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.0122 if the patients are counted as failures or 0.0458 if the patients are excluded from the analysis.

The tables below show the proportion of patients that maintain a successful prosthesis at 6, 12, 18, and 24 months following loading. Two methods were used to handle missing outcomes (either due to withdrawals or missed visits):

- to regard all patients without documented success as failures (Analysis Method 1)
- to exclude them from the calculations. (Analysis Method 2).

6-Month Functional Loading

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Withdrew	3 (15%)	0
Missed visit	1 (5%)	2 (10%)
Succeeded	6 (30%)	14 (66%)
Total	20	21

The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.0294 if the patients are counted as failures or 0.0442 if the patients are excluded from the analysis.

12-Month Functional Loading

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Missed Visit	0	3 (14%)
Withdrew	4 (20%)	0
Succeeded	6 (30%)	13 (62%)
Total	20	21

The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.0616 if the patients are counted as failures or 0.0824 if the patients are excluded from the analysis

18-month Functional Loading

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Missed Visit	0	4 (19%)
Withdrew	4 (20%)	1 (5%)
Succeeded	6 (30%)	11 (52%)
Total	20	21

The Fisher exact p-values for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.2082 if the patients are counted as failures or 0.1556 if the patients are excluded from the analysis

24-month Functional Loading

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Missed Visit	0	3 (14%)
Withdrew	4 (20%)	3 (14%)
Succeeded	6 (30%)	10 (48%)
Total	20	21

The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.3408 if the patients are counted as failures or 0.1556 if the patients are excluded from the analysis

Extraction Socket Clinical Data Summary

In the Dosing Study (9514), 85% of the INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) group had grown enough bone at 4 months to receive implants without additional augmentation. Sixty six percent (66%) in the INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) group successfully received dental implants without additional augmentation, received a prosthesis, and maintained functional loading for at least six months. Ten percent (10%) of the patients required augmentation at the time of dental implant placement through six months, 14% of the patients failed through six months, and 10% of the patiens missed their 6-month visit. The observed success rate at six months post-loading in the No Treatment group was 30% and in the ACS with no rhBMP-2 group was 41%. There was a statistically significant difference between the number of patients who were successful in the No Treatment and INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) group at 6 months post-loading.

Adverse Events for All Studies

Adverse events were reported for all subjects across studies. Below is a summary of the adverse events stratified by:

- Serious Adverse Events and Deaths
- Adverse Events for All Patients with INFUSE® Bone Graft (any concentrations of rhBMP-2/ACS) Compared to Autogenous Bone Graft
- Adverse Events for INFUSE® Bone Graft (1.5 mg/mL Concentration of rhBMP-2/ACS) Compared to Autogenous Bone Graft
- Morbidity by Autogenous Bone Graft Harvest Location for the Sinus Augmentation Patients.

Serious Adverse Events and Deaths

The severity of adverse events was assessed according to the World Health Organization (WHO) Recommendations for grading Acute and Subacute Toxic Effects, additional definitions provided in each protocol, and based on the investigator's judgment. Relatedness of adverse events to rhBMP-2/ACS was determined by the investigator on the basis of his/her clinical judgment and definitions of relatedness were defined by the Sponsor.

Serious adverse events from the clinical studies were determined by the investigator based on the following outcomes: death; a life-threatening event; inpatient hospitalization or prolongation of an existing hospitalization; persistent or significant disability or incapacity; cancer; and congenital abnormality.

The serious adverse events reported in the INFUSE® Bone Graft group (any concentration of rhBMP-2/ACS) were death, carcinoma, peri-implantitis, sunburn, edema, arthritis, joint disease, arthralgia, accident, myeloma, gastrointestinal bleeding, abdominal pain, gall stones, dyspepsia, hematoma, nausea, vomiting, constipation, irritable bowel syndrome, anemia, recurrent pelvic organ prolapse, mouth pain, back pain, rash, and oral edema. None were considered related to rhBMP-2/ACS. The life threatening event resulted in death but was not related to rhBMP-2/ACS or the procedure.

The serious adverse events in the autogenous bone graft group were ecchymosis, carcinoma, bradycardia, hypotension, arthralgia, elevated SGOT, abnormal gait, hyperglycemia, bleeding gums, chronic sinusitis, flu, atrial fibrillation, melanoma, pain, edema face, pressure in ears, infection, headache, mouth pain, and asthma. The studies did not collect information on the relatedness of the adverse event to bone graft or the bone graft procedure but collected data strictly on the relatedness to rhBMP-2/ACS.

Adverse Events for All Patients with INFUSE® Bone Graft (any concentrations of rhBMP-2/ACS) Compared to Autogenous Bone Graft

To evaluate the safety of the rhBMP-2/ACS procedure against current available treatments, the adverse events reported for the combined rhBMP-2/ACS subjects were compared to subjects who were randomized to the bone graft treatment group (n=91). The number and percentage of subjects with frequent adverse events (occurring in at least > 5 % of the study subjects) by treatment group, body system, and COSTART term for the entire study period are presented.

Number of Subjects with Frequent Adverse Events (>5% of Subjects) by Treatment Group, Body System, and COSTART Term – Comparing all INFUSE® Bone Graft (any concentration of rhBMP-2/ACS) to Autogenous Bone Graft

Body System Costart Term	All rhBMP-2/ACS Patients (n = 184) N (%)	All Autogenous Bone Graft Patients (n = 91) N (%)	p-value
Body As A Whole			
Accidental Injury	11 (6.0)	4 (4.4)	0.7796
Back Pain	7 (3.8)	6 (6.6)	0.3672
Dehiscence	13 (7.1)	5 (5.5)	0.7970
Edema	12 (6.5)	34 (37.4)	<0.0001
Face Edema	99 (53.8)	52 (57.1)	0.6094
Flu Syndrome	4 (2.2)	5 (5.5)	0.1625
Headache	22 (12.0)	7 (7.7)	0.3063
Infection	45 (24.5)	39 (42.9)	0.0022
Inflammation	10 (5.4)	4 (4.4)	1.0000
Pain	30 (16.3)	46 (50.5)	<0.0001
Peri-Implantitis	15 (8.2)	4 (4.4)	0.3173
Cardiovascular System			
Hematoma	14 (7.6)	8 (8.8)	0.8140
Hypertension	10 (5.4)	8 (8.8)	0.3071
Digestive System			
Gingivitis	10 (5.4)	5 (5.5)	1.0000
Mouth Pain	159 (86.4)	76 (83.5)	0.5862
Mouth Ulceration	5 (2.7)	6 (6.6)	0.1872
Nausea	6 (3.3)	10 (11.0)	0.0139
Oral Edema	113 (61.4)	59 (64.8)	0.5992
Oral Erythema	80 (43.5)	56 (61.5)	0.0069
Tooth Disorder	11 (6.0)	4 (4.4)	0.7796
Hemic And Lymphatic System			
Anemia	6 (3.3)	9 (9.9)	0.0437
Ecchymosis	29 (15.8)	21 (23.1)	0.1832
Metabolic And Nutritional Disorders			
Healing Abnormal	9 (4.9)	9 (9.9)	0.1259
Hyperglycemia	8 (4.3)	15 (16.5)	0.0018
Hypophosphatemia	2 (1.1)	9 (9.9)	0.0010
SGOT Increased	4 (2.2)	5 (5.5)	0.1625
SGPT Increased	9 (4.9)	6 (6.6)	0.5793
Musculo-Skeletal System			
Arthralgia	16 (8.7)	24 (26.4)	0.0002
Bone Disorder	21 (11.4)	11 (12.1)	0.8444
Nervous System			
Abnormal Gait	0 (0.0)	37 (40.7)	<0.0001
Hypesthesia	8 (4.3)	15 (16.5)	0.0018
Respiratory System			
Bronchitis	2 (1.1)	5 (5.5)	0.0418
Epistaxis	9 (4.9)	6 (6.6)	0.5793
Rhinitis	16 (8.7)	6 (6.6)	0.6417

Body System Costart Term	All rhBMP-2/ACS Patients (n = 184) N (%)	All Autogenous Bone Graft Patients (n = 91) N (%)	p-value
Sinusitis	16 (8.7)	15 (16.5)	0.0680
Skin And Appendages			
Rash	11 (6.0)	37 (37.4)	<0.0001

Overall, some of the most frequent adverse events reported for both the rhBMP-2/ACS treatment group and the bone graft treatment group were: mouth pain (86.4% vs. 83.5%); oral edema (61.4% vs. 64.8%); face edema (53.8% vs. 57.1%); and oral erythema (43.5% vs. 61.5%).

However, subjects in the bone graft group had a statistically significantly greater amount of: pain (50.5% vs. 16.3%); infection (42.9% vs. 24.5%); abnormal gait (40.7% vs. 0%); arthralgia (26.4 vs. 8.7%); edema (37.4% vs. 6.5%); rash (erythema) (37.4% vs. 6%); nausea (11% vs. 3.3 %); oral erythema (61.5% vs. 43.5%); anemia (9.9% vs. 3.3%); hyperglycemia (16.5% vs. 4.3%); hypophosphatemia (9.9% vs. 1.1%); hypesthesia (16.5% vs. 4.3%); bronchitis (5.5% vs. 1.1%); and rash (37.4% vs. 6.0%) compared to those in the INFUSE® Bone Graft treatment group. The high incidence of pain, infection, abnormal gait, and arthralgia in the bone graft group is expected for the procedure and reflects the morbidity associated with bone graft harvesting.

The combined INFUSE® Bone Graft treatment group experienced 1636 adverse events in 184 patients for an average of 8.9 events/patient. 80% (1309/1636) of the adverse events were mild, 17% (286/1636) were moderate, 2% (36/1636) were reported as severe, and 0.06% (1/1636) were considered life-threatening in severity (though unrelated to rhBMP-2/ACS).

The bone graft treatment group experienced 1249 adverse events in 91 patients for an average of 13.7 events/patient. Among the 91 subjects who received a bone graft (See Tables in the two sections following for the most frequent events), 1249 adverse events were reported. 82.8% (1034/1249) were mild, 14.7% (184/1249) were moderate, and 2.16 (27/1249) were severe.

Adverse Events for INFUSE® Bone Graft (1.5 mg/mL Concentration of rhBMP-2/ACS) Compared to Autogenous Bone Graft

Of subjects who received INFUSE® Bone Graft, 120 subjects from the sinus studies and extraction socket studies received a concentration of 1.5 mg/mL of rhBMP-2/ACS. To evaluate the safety of the proposed commercial concentration of rhBMP-2/ACS versus bone graft, adverse events for the two treatment groups were compared. The results are presented in the table provided in Section VIII above.

The most frequent adverse events reported for both the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group and the bone graft group were: mouth pain (85.0% vs. 83.5%); oral edema (67.5% vs. 64.8%); face edema (67.5% vs. 57.1%); and oral erythema (47.5% vs. 61.5%). Although, not statistically significant, face edema is

greater in the INFUSE® Bone Graft group and is most likely due to the recruitment of fluid and cells into the treatment area.

Subjects in the autogenous bone graft group showed a significantly greater amount of adverse events versus the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group. Specifically, the following adverse events occurred significantly more often in the bone graft group: pain (50.5% vs. 21.7%); infection (42.9% vs. 25%); abnormal gait (40.7% vs. 0); arthralgia (26.4% vs. 11.7%); nausea (11% vs. 3.3%), hyperglycemia (16.5% vs. 6.7%); hypophosphatemia (9.9% vs. 1.7%); edema (37. 4% vs. 1.7%); rash (erythema) (37.4% vs. 7.5%); hypesthesia (decreased sensation) (16.5% vs. 4.2%); and bronchitis (5.5% vs. 0.0%). As noted, none of the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) subjects reported abnormal gait or gait disturbance compared to 41% of bone graft subjects.

The 120 patients in the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group experienced 1184 adverse events for an average of 9.9 events/patient. 79.1% (936/1184) were mild; 18.3% (217/1184) were moderate; 2.4% (29/1184) were severe and 0.01% life threatening (1/1184).

The bone graft group had an average of 13.7 events/patient, as shown in the previous section. Among the 91 subjects who received a bone graft, 1249 adverse events were reported. 82.8% (1034/1249) were mild, 14.7% (184/1249) were moderate and 2.16 (27/1249) were severe. The increased frequencies of these events are expected in bone graft treatments because of the harvest procedure; these adverse events reflect the morbidity associated with the procedure which is not required with the INFUSE® Bone Graft treatment.

Morbidity by Autogenous Bone Graft Harvest Location for the Sinus Augmentation Patients
Subjects in the Sinus Dosing Study (9531) and Sinus Pivotal Study (9730) were randomized into the INFUSE® Bone Graft or the bone graft treatment group.

With respect to the bone graft treatment group, the harvest locations used in the studies were the iliac crest, tibial plateau, intra-oral bone and other (usually the "other" harvest site was intra-oral bone from the surgical site). The most frequent adverse events reported among the subjects who were randomized to bone graft were pain; arthralgia, abnormal gait, and decreased sensation. The duration of the adverse events per harvest site are summarized over a 6 month post-surgery period. Pain was still significant at 10 days post-surgery for more than a third of bone graft subjects and sensory loss and gait disturbance were reported for some subjects after 2 months post-surgery.

An evaluation of adverse events by harvest site was performed to assess the most frequent adverse events reported for each site. Three sites were used most frequently for bone harvest in the sinus studies: iliac crest; tibial plateau; and intra-oral bone. The table below reports the results of adverse events by harvest site. The tibial plateau site was associated with frequent pain and gait disturbance; the iliac crest site had the highest reported pain as well as reports of later sensory loss. Intra-oral bone sites were associated with sensory loss in 33% subjects out to 6 months post-surgery.

In the Sinus Pivotal Study, one or more harvest site may have been utilized to gather bone. In 77 patients, the following harvest sites were used: 17.9% chin; 21.8% mandible; 5.1% tuberosity; 34.6% tibial plateau; and 17.9% iliac crest. While bone graft was shown to be an effective treatment, the harvest procedure resulted in prolonged pain, additional surgery time, prolonged sensory loss, and gait disturbance.

Adverse Events Reported by Harvest Site in Autogenous Bone Graft Subjects

Variable	Harvest Site	2 days	10 days	1 month	2 months	4 months	6 months
Pain	Iliac Crest	88.9%	44.4%	5.6%	5.6%	0.0%	0.0%
	Tibial Plateau	66.7%	51.5%	24.2%	9.1%	6.1%	6.3%
	Intra-Oral Bone	73.3%	46.7%	6.7%	0.0%	0.0%	0.0%
	Other	46.2%	7.7%	0.0%	0.0%	0.0%	0.0%
Sensory Loss	Iliac Crest	0.0%	0.0%	11.1%	11.1%	11.1%	11.1%
	Tibial Plateau	0.0%	3.0%	3.0%	3.0%	0.0%	0.0%
	Intra-Oral Bone	40.0%	60.0%	46.7%	33.3%	33.3%	33.3%
	Other	15.4%	7.7%	0.0%	0.0%	0.0%	0.0%
Gait Disturbance	Iliac Crest	55.6%	44.4%	16.7%	0.0%	5.6%	5.6%
	Tibial Plateau	72.7%	45.5%	18.2%	6.1%	3.0%	3.1%

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The preclinical testing performed specific to the use of the INFUSE® Bone Graft for sinus augmentation and extraction socket augmentation showed no new safety concerns. Aside from not showing any inflammatory responses, adequate bone for dental implant placement formed in the expected location in all the animal studies.

For the sinus augmentation clinical studies, although the bone graft group showed higher rates of successful functional loading, the INFUSE® Bone Graft group still had a clinically meaningful outcome in terms of functional loading of dental implants. For those patients who received a prosthesis for sinus augmentation, the functional loading success rates ranged from 76%-79% for INFUSE® Bone Graft and was 91% for bone graft across all postoperative evaluation timepoints. In addition, the INFUSE® Bone Graft group showed fewer adverse events than the bone graft group, which offset concerns about lower effectiveness.

Although the extraction socket augmentation clinical study was designed to address dosing, it also showed successful functional loading; however, the patient population was too small to determine statistical significance. The functional loading success rates for INFUSE® Bone Graft ranged from 48%-66% across all postoperative evaluation timepoints. In addition, the collective data for the INFUSE® Bone Graft group (all concentrations) showed fewer adverse events than the autogenous bone graft group, which offset concerns about lower effectiveness. Clinical success was shown because this type of defect is one of the most challenging types to restore and the case reports presented showed that dental implants could be successfully placed in the extraction sockets treated with the device.

XII. PANEL RECOMMENDATION

The Dental Products Panel (the Panel) met on November 9, 2006 to make a recommendation to the FDA on the approvability of the Medtronic Sofamor Danek INFUSE® Bone Graft, P050053. The Panel considered FDA's questions of whether the possible reduction in morbidity associated with INFUSE® outweighs the potential reduction in effectiveness for sinus augmentation when compared to autograft, and whether the data submitted for ridge augmentation for tooth extraction sites are sufficient to arrive at a clinically meaningful conclusion in respect to device effectiveness.

The Panel determined that there was a reasonable assurance that the device is safe under the conditions for use and that there was a reasonable assurance that the device is effective but only with strict labeling. The Panel voted six to zero to recommend that FDA approve the PMA with a labeling condition. The recommended condition of approval was that the labeling note the limitations of the study population as follows: "The labeling should note that in regards to the ridge augmentation at tooth extraction sites indication, this device has not been tested in the molar regions of the mouth, or in the mandible."

XIII. CDRH DECISION

The PMA was filed on February 24, 2006.

CDRH agreed with the Panel's recommendation for INFUSE® Bone Graft (approval with a condition) and determined that this would be best addressed as a precaution in the labeling. The applicant adequately submitted all information requested by CDRH for their PMA, including labeling with the condition requested by the Panel.

The applicant's manufacturing facilities were inspected and were found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on March 9, 2007.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.

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