

**FDA Executive Summary**

**Prepared for the November 9, 2006 Dental Products Panel**

Company: Medtronic Sofamor Danek  
Device: InFuse® Bone Graft  
Document No.: P050053  
Date: October 4, 2006

InFuse® Bone Graft is a combination product consisting of a device and a biologic drug. FDA has determined that InFuse® will be reviewed as a PMA device/drug with consulting reviews from the Center for Drug Evaluation and Research (CDER).

InFuse® Bone Graft is identical to that currently commercially available in the United States through P000054 (InFuse® Bone Graft) and P000058 (InFuse® Bone Graft/LT Cage® Lumbar Tapered Fusion Device).

**DEVICE DESCRIPTION**

Each InFuse® Bone Graft Kit contains one or two vials of recombinant human bone morphogenic protein 2 (rhBMP-2), 1, 2, or 4 pieces of absorbable collagen sponges (ACS), and one or two 5 or 10 ml vials water for injection to reconstitute the lyophilized rhBMP-2 and place the reconstituted rhBMP-2 on the ACS.

The active agent, rhBMP-2, is a recombinant human bone morphogenic protein consisting of a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. The Recombinant Human Bone Morphogenetic Protein (rhBMP-2) is secreted from cultures of Chinese Hamster Ovary cells encoding rhBMP-2 protein gene.

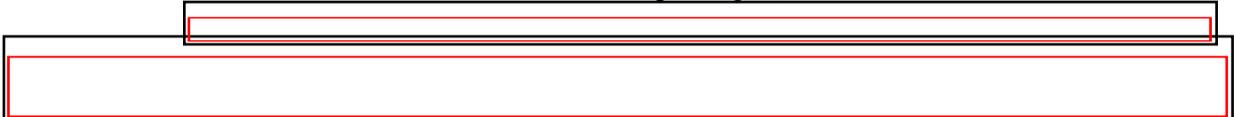
The rhBMP-2 will be

The collagen sponge (ACS) is made of bovine deep flexor (Achilles) tendon collagen from USDA approved sources. It acts as both a bone void filler and a carrier for the rhBMP-2 component. The ACS was originally approved as Helistat® Absorbable Collagen Hemostatic Sponge under P850010. Helistat is indicated for use in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical. It was not recommended for use in neurological, urological, or ophthalmological procedures.

During surgical procedures, the two device components, rhBMP-2 and ACS, are combined with the water for injection to form a cohesive implant that is placed into a bony defect.

InFuse® Bone Graft is intended to be used in the craniofacial region for sinus augmentation and for localized alveolar ridge augmentations for defects associated with extraction sockets, where space maintenance is present. The presence of space maintenance is defined by the sponsor as any location where there is minimal tissue pressure placed on a graft site. The sponsor claims that the use of InFuse® eliminates the need for using allogenic bone grafting materials and the morbidity associated with harvesting autogenous bone to be used as bone grafting material. The rhBMP-2 component is believed to act by inducing cellular chemotaxis, cellular proliferation and cellular differentiation. The collagen sponge is resorbed over time.

Medtronic Sofamor Danek USA, Inc. assembles, packages, and releases the InFuse® Bone



### **PROPOSED INDICATIONS FOR USE**

- Sinus augmentation.
- Localized alveolar ridge augmentations for defects associated with extraction sockets

### **PROPOSED CONTRAINDICATIONS**

- For patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2 or bovine Type I collagen
- In the vicinity of a resected or extant tumor or any active malignancy or patients undergoing treatment for a malignancy.
- In patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- In pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- In patients with an active infection at the operative site.

### **PROPOSED WARNINGS**

Women of childbearing potential should be advised that [redacted] uence of rhBMP-2 on fetal development has not been assessed. In the clinical trials [redacted] 2%) patients treated with InFuse® Bone Graft developed antibodies to rhBMP, while [redacted] (21.9%) patients treated with bone graft bone developed antibodies to rhBMP.

The effect of maternal antibodies to rhBMP-2, might be present for several months following device implantation. The effect on the unborn fetus did not cause fetal abnormalities in rabbit studies. Additionally, it is known from rabbit studies that fetal expression of BMP-2 which could re-expose mothers who were previously antibody positive, did not elicit a more powerful immune response to BMP-2 with adverse consequences for the fetus.

The safety and effectiveness of InFuse® Bone Graft 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 InFuse® Bone Graft.

### **PROPOSED PRECAUTIONS**

The safety and effectiveness of repeat applications of InFuse® Bone Graft has not been established.

- InFuse® Bone Graft should only be used by surgeons or dentists who are experienced in oral maxillofacial surgery.
- Prior to use, inspect the packaging, vials and stoppers for visible damage. If damage is visible, do not use the product.
- Do not use after the printed expiration date on the label.
- The safety and effectiveness of InFuse® Bone Graft in patients with hepatic or renal impairment has not been established.
- The safety and effectiveness of InFuse® Bone Graft has not been demonstrated in patients with metabolic bone diseases.
- While not specifically observed in the clinical studies, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.
- The safety and effectiveness of InFuse® Bone Graft has not been demonstrated in patients with autoimmune disease or suppressed immune systems.
- As with all therapeutic proteins, there is a potential for immune responses to be generated to a component of InFuse® Bone Graft. The immune response to InFuse® Bone Graft components was evaluated in  investigational patients and  control patients during human clinical trials of InFuse® Bone Graft.
- 2.2% patients receiving InFuse® Bone Graft component developed antibodies vs. 0.0% in the control group.
- 20% of patients receiving InFuse® Bone Graft developed antibodies to bovine Type I collagen vs. 31% 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. The incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications and underlying disease.

### **InFuse® Kit Specifications**

The InFuse® Bone Graft kits presented for approval in P050053 are the same kits approved in two previous PMAs (P000054 and P000058). The Sponsor indicates that there have been no changes in the kit components, specifications, manufacturing processes (including

sterilization) or packaging. The only difference is the additional indication for use which will result in an additional package insert, specific to the use of InFuse® Bone Graft for oral maxillofacial bone grafting procedures. Approval is being sought by Medtronic Sofamor Danek [REDACTED]

[REDACTED] Between [REDACTED] [REDACTED] initiated [REDACTED] clinical studies for oral maxillofacial indications, the last of which was concluded in February 2004. The rhBMP-2 component of the devices used in these studies was produced by manufacturing processes which preceded the current commercial manufacturing process. However, comparability of rhBMP-2 drug product used in these studies to the current commercial product was established during review of P000054 and P000058. P000054, InFuse® Bone Graft for treatment of open tibial fractures and P000058, InFuse® Bone Graft/LT-Cage Lumbar Tapered Fusion Device for single level spinal fusion procedures, were approved in April 2004 and July 2002, respectively. Because patient exposure to rhBMP-2 during oral maxillofacial bone grafting procedures, tibial fracture treatment and spinal fusion procedures is expected to be similar, additional safety studies and studies to support the comparability of rhBMP-2 used in the oral maxillofacial clinical studies to the current commercial rhBMP-2 product were not deemed to be necessary.

### **Treatment Alternatives**

Surgical alternatives include the following procedures:

- Autograft – bone graft taken from one site in the body and placed in a different site of the same individual.
- Allograft – calcified or decalcified bone from human or bovine sources.
- Alloplast – artificial bone.
- Periodontal membrane – collagen or alloplastic materials placed over bone defects to prevent ingrowth of connective and epithelial cells into bone defect.
- Demineralized bone matrix – particulate, paste, or putty composed of human cortical and corticocancellous bone.

### **PRECLINICAL STUDIES**

Preclinical studies have been conducted to support the use of InFuse® Bone Graft in humans for oral indications, using canine, goat, and primate as models. These animal models were used to evaluate rhBMP-2 in mandibular reconstructions, critical sized defects, and implant placement. Please note that device components and not InFuse® Bone Graft in its final form was used in these studies.

A number of animal model studies were conducted that included mandibular critical size defects and alveolar ridge defects that were repaired using Guided Bone Regeneration (GBR). The studies investigating GBR plus rhBMP-2 included a number of materials, e.g., ePTFE, glycolide polymer, HA (hydroxyl apatite). The evaluations found that space maintenance could be enhanced by rhBMP-2 induced bone formation. rhBMP-2 was found to cause significant alveolar ridge augmentation in surgically-created mandibular alveolar

ridge defects. This effect was seen across the animal models which included dogs and nonhuman primates. When endosseous dental implants were placed into alveolar ridge defects filled with rhBMP-2 induced bone, comparable bone-contact osseointegration was observed for rhBMP-2 treated sites. However, in histological studies where teeth were involved, periodontal ligaments (PDLs) observed in the alveolar bone defect studies were not functionally oriented. In more than one of these studies, functionally oriented PDL fibers were commonly observed in controls but they were rarely found among rhBMP-2 treated sites.

The effect of a barrier on rhBMP-2 induced bone was sometimes variable. One study investigating ePTFE showed that the barrier provided space for bone formation, however bone defects were only partially filled with bone. The majority of defect spaces were filled with dense connective tissue. Comparably denser bone with narrow marrow spaces, occupied by fibrovascular tissue, were observed in defects receiving the buffer only in contrast to rhBMP-2 in this study. Another study showed that rhBMP-2 plus the ePTFE barrier accounted for more bone formation (area) than with either rhBMP-2 alone or with buffer only.

Preclinical study results support the interpretation that GBR with rhBMP-2 can lead to a better designed outcome. Other studies investigating the ability of rhBMP-2 to form bone in a sinus floor elevation procedure in goats showed successful results. In a rabbit maxillary sinus defect model rhBMP-2 formed bone that was equivalent to autogenous-bone graft bone induction.

Some of the adverse events or findings that were seen in preclinical animal model evaluations and that can be anticipated in human clinical use are:

- Swelling,
- Wound dehiscence, and
- Radiolucent voids – in one study bone voids were observed in  defects

Seromas, fluid filled areas, as indicated by radiolucencies were also seen. The seromas generally resolved, however in one evaluation the seromas/radiolucencies had not resolved by the study's endpoint.

No inflammatory responses were seen in the presence of rhBMP-2.

The bone generated in these studies was determined to be equivalent to bone formed by autogenous bone grafts. Good bone to implant contact (BIC) is formed to dental implants in rhBMP-2 formed bone. The preclinical information demonstrated a proof of concept in animals that supports the following:

- Ridge preservation.
- Sinus augmentation.
- Vertical and horizontal augmentation.

## **CLINICAL STUDIES**

Autogenous bone graft is presently being used to repair oromaxillofacial bone defects with good success in a large percentage of cases. However, autogenous bone graft is often associated with risks due to the bone harvest procedure. The sponsor claims that InFuse® Bone Graft (rhBMP-2/ACS) is intended to treat such defects by inducing bone formation to replace both the function and structure of the tissue without requiring a bone harvest procedure.

InFuse® Bone Graft has been previously approved in two PMA applications for spinal fusion procedures (P000058) in July, 2002, and treating acute, open tibial fractures (P000054) in April, 2004.

The objective of this PMA is to obtain approval for additional indications for InFuse® Bone Graft as an alternative to autogenous bone graft for sinus augmentation and localized alveolar ridge augmentation for alveolar bone defects associated with extraction sockets.

To support these indications, this PMA contains:

- Data from 5 clinical studies
- Anecdotal case reports from off-label use of InFuse® Bone Graft.
- Supportive Documentation for Treatment Failures, Withdrawals and Death.
- Serious Adverse Events (SAE) and Death Narratives (none were reported).
- Data Listings, Raw Data Set [redacted] S Programs Death – in current submission.
- CT Scans for Study Subject [redacted] Death – in current submission. The death was not due to the device.

The sponsor proposed that the indications for use identify two specific oral maxillofacial sites for the use of InFuse® Bone Graft:

- Sinus augmentation procedures.
- Localized alveolar ridge augmentations for defects associated with extraction sockets.

These two oral maxillofacial implant sites are claimed by the sponsor to have several important features in common:

- Each site is located in the mandible or maxilla.
- Each site requires bone graft.
- Each site consists of a space or void which is large enough to allow placement of InFuse® Bone Graft and that the defect shape is maintained and minimal pressure is placed on the graft material.
- Grafting sites may have one or more bony walls from which the implanted InFuse® Bone Graft recruits cells for bone growth.
- Histological data demonstrates that bone grown by InFuse® Bone Graft is physiologically the same as the host bone and the same as that grown by autogenous bone graft.

studies performed by [redacted] under [redacted] [redacted] to support these new [redacted] or au [redacted] ies (sing and pivotal) and two extraction [redacted] ies (pilot and dosing). The first study subject was enrolled [redacted] The last follow-up in the last study was in 2004. A similar surgi [redacted] in each of the five studies with the treatment course consisting of study device implantation followed by an osteoinduction phase, dental implant placement, osseointegration phase, and functional loading of a dental prosthesis.

The PMA originally pooled the clinical study data from extraction socket augmentation and sinus lift procedures based on similarities in study protocol, dose administered (1.5 mg/ml BMP), and performance against a common endpoint (ability to grow bone in order to load dental implants). At FDA's request, the sponsor unpooled the data so that data from these studies could be evaluated separately. None of the studies were designed to be specifically compared to a control group for primary study endpoints and no statistical hypotheses to be tested were prospectively identified. Two of the s [redacted] es included active controls of allograft or autograft. Data in Studies [redacted] were used to support a secondary analysis.

#### Inclusion and Exclusion Criteria

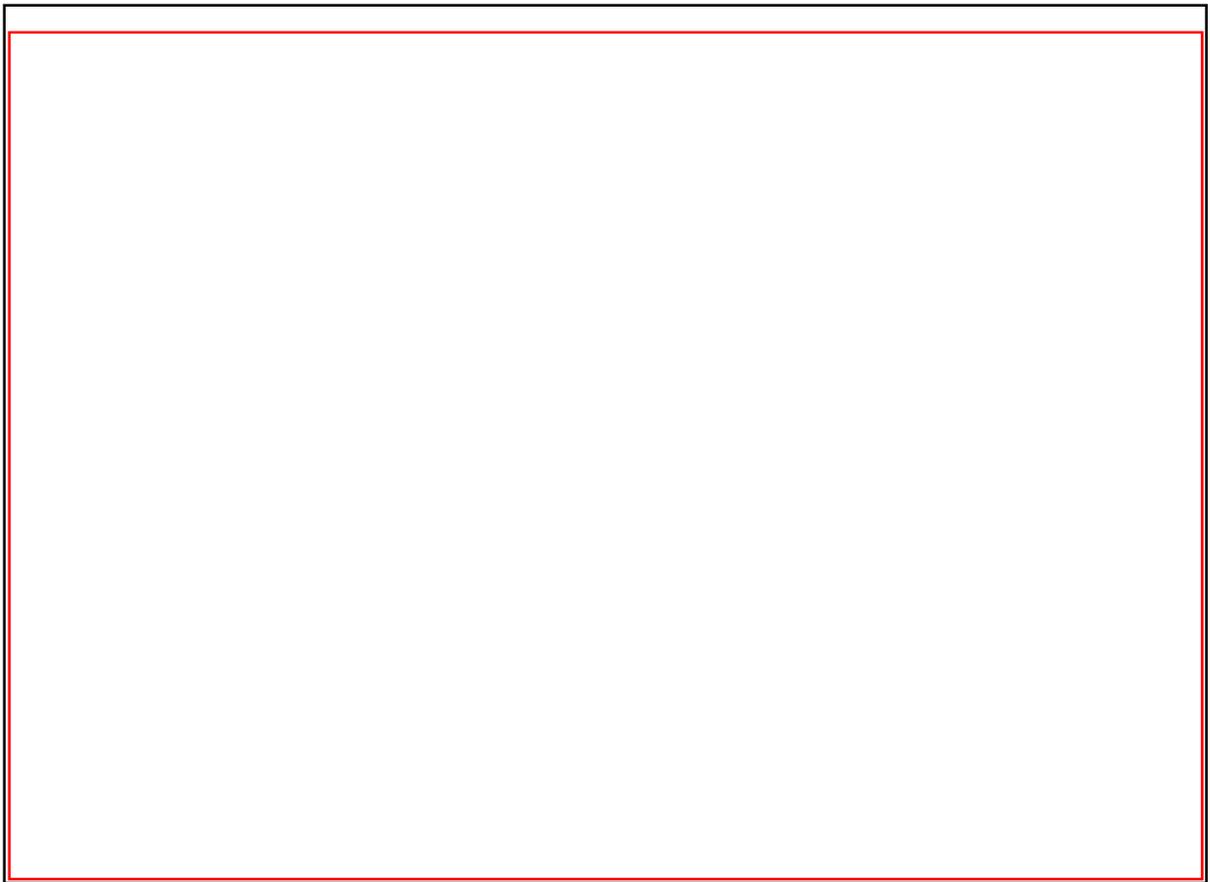
Subjects in all [redacted] studies were enrolled according to protocol-defined inclusion and exclusion criteria. Subjects were eligible if they met all inclusion criteria and none of the exclusion criteria. All studies used similar criteria for enrolling subjects.

#### Inclusion Criteria

[redacted]

E \_\_\_\_\_

[redacted]



**Clinical Studies Used to Support [redacted] tation at Extraction Sockets**



The following studies were submitted in this PMA to support the indication for use for InFuse® Bone Graft for ridge augmentation at extraction socket sites. There are two pilot studies that used smaller concentrations of rhBMP-2 than those used in the extraction site dosing study and the sinus augmentation study. Because of the differences in BMP concentration, combination of effectiveness data in these extraction socket studies may not be appropriate

In the dosing study, [redacted] patients received 1.5 mg/ml of rhBMP-2/ACS. Analysis of the combination of these results with the results from the sinus augmentation study may result in conclusions that may not be statistically valid.

Study Description	Pilot Studies		Do <input type="text"/> dy
	Short-Term <input type="text"/>	Long-Term <input type="text"/>	
Number of Subjects	n=12 rhBMP-2/ACS <input type="text"/> mg/ml	(same subjects as <input type="text"/> )	<input type="text"/>
Study Design	Open-label, non-randomized, two-center study	Long-term follow-up of sub-enrolled in <input type="text"/>	Randomized multi-center trial (8 centers) of two dosage levels, plus ACS alone and no treatment
Follow Up	16 weeks post-surgery	16 to 24 months post-surgery	24 months post-prosthesis

Primary endpoints:

1. The change (decrease or increase) in alveolar bone height and width at the treated sockets.
2. The rate of success in placing dental implants without additional augmentation.

Secondary endpoints:

1. The rate of success in fitting prostheses without additional augmentation
2. The rate of success
3. The rate of success
4. The rate of success
5. The rate of success

Bone dimensions were measured at baseline and four months after baseline.

These dimensions were:

- Bone height.
- Alveolar bone width at position measured in the coronal  $\frac{1}{4}$  of the tooth socket depth.
- Bone width at position measured at the middle ( $\frac{1}{2}$ ) of the tooth socket depth..
- Bone width at position measured in the apical  $\frac{1}{4}$  of the tooth socket depth.

These measures were analyzed using a one-way analysis of variance, followed up by the two-group contrast between the no-treatment control group and the 1.5 mg/ml active treatment group.

Results

In [redacted] only 0.43 mg/ml of rhBMP-2 was used. These data were not combined with data from studies using 1.5 mg/ml BMP. This PMA does not include clinical outcome data for these patients.

[redacted] was an [redacted] patient in a [redacted] ongoing study involving ridge preservation at [redacted] sites. This [redacted] duration. [redacted] patients received 0.75 mg/ml rhBMP-2 and [redacted] received 1.5 mg/ml concentrations of rhBMP-2. [redacted] received the carrier collagen sponge alone. Primary objectives were to determine optimal rhBMP-2 concentration and the ability to place dental implant in the grafted site. Secondary objectives were to estimate success in placing dental implants. There were no treatment controls.

The sponsor’s analysis indicated that with 1.5 mg/ml rhBMP-2/ACS bone height is maintained after a tooth is extracted. With no rhBMP-2, present, postextraction bone resorption leads to a 1.17 mm loss of bone, and with ACS alone, a 1.00 mm loss of bone is seen.

The second primary endpoint is the rate of success in placing dental implants without additional bone augmentation. The table below contains this data.

Dental Implant Placement without Augmentation [redacted]

	No treatment	rhBMP-2/ACS 0.00 mg/mL	1.5mg/ml rhBMP-2/ACS	Total
Needed augmentation				
Failed				
Withdrew				
Succeeded				
Total				

As indicated above, rhBMP-2/ACS was associated with greater success (18/21 = 85.7%) than no treatment (9/20 = 45%).

Six Months Functional Loading [redacted]

	No treatment	rhBMP-2/ACS 0.00	1.5mg/ml rhBMP-2/ACS	Total

		mg/mL		
Needed augmentation				
Failed				
Withdrew				
Missed visit				
Succeeded				
Total				

At six months after [redacted] dental implants [redacted] implants were successful while with no treatment [redacted] were classified [redacted] s.

**Clinical Studies Used [redacted] for Augmentation**

[redacted]

Study Description	Pilot Studies		Dose Study	Pivotal Study
	Short-	Long-		
Number of Subjects	n=[redacted] rhBM 2/ACS [redacted] mg/	n=[redacted] rhBMP- 2/ACS [redacted] mg/	[redacted]	[redacted]
Study Design	Open-label, non-randomized, four-center study	Follow-up study of subjects enrolled in [redacted]	Randomized multi-center trial (6 centers) of two dosage levels vs. auto/allograft. Biopsies of implant cores were evaluated	[redacted]
Follow-Up	16 weeks post-surgery	36 months post-prosthesis	36 months post-prosthesis	24 months post-prosthesis

The sponsor stated that based on the similarity between the study protocols, procedures, patient [redacted] tions and re [redacted] ey could combine the results from the sinus augmentation pivotal [redacted] and dosing [redacted] studies. Data from the dosing study patients are

combined with the rhBMP-2/ACS patients from the pivotal study, all of whom received the commercial concentration of rhBMP-2/ACS, 1.5 mg/ml. In addition, the autogenous bone graft patients from both studies were combined.

The primary endpoints are as follows:

1. To estimate the effectiveness of rhBMP-2/ACS (when used for [redacted]) [redacted] fully supports dental implant [redacted]
2. [redacted] us bone graft in [redacted]  
[redacted]

The initial IDE study endpoints indicate that implant success was the primary study endpoint.

The secondary endpoints are as follows:

1. To compare the effectiveness of rhBMP-2/ACS to autogenous bone graft [redacted]  
[redacted]
2. To evaluate the amount of new bone formation following treatment with either rhBMP-2/ACS or autogenous bone graft.
3. To evaluate the density of the newly induced and adjacent native bone [redacted] following treatment with rhBMP-2/ACS or autogenous bone graft, and [redacted] post dental implant placement.
4. To estimate the use of medical resources associated with [redacted]  
[redacted]

Success criteria for patients in the pivotal study [redacted] protocol include:

- Patients receive rhBMP-2/ACS.
- No additional sinus floor augmentation for dental i [redacted] ment is required.
- Patients receive endosseous dental implants within [redacted] of graft placement.
- Placement of loaded implant borne devices [redacted] ion with dental prostheses.
- Functional prosthesis maintained for at least [redacted]

Please note that the above success criteria for this study were present in the PMA but not present in the IDE study protocol.

## Results

Primary Effectiveness Augmentation (Intent to Treat Population)			
	Number of Patients (%)	Number of Patients (%)	Combined
	(88.2%)	(81.7%)	(82.8%)
	(82.4)	(79.3)	(79.8)
	(82.4)	(79.0)	(79.6)
		(68.5, 87.3)	(70.3, 87.1)
	(82.4)	(78.8)	77 (79.4)
	(56.6, 96.2)	(68.2, 87.1)	(70.0, 87.0)
	(82.4)	77.9	(78.7)
	(56.6, 96.2)	(67.0, 86.6)	(69.1, 86.5)
	(82.4)	76.0	(77.2)
	(56.6, 96.2)	(64.7, 85.1)	67.3, 85.3)

- a. Subjects who successfully received prosthesis but were lost to follow-up or withdrew anytime thereafter were excluded from the ITT analysis.
- 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. 2-sided 95% exact confidence interval.

From this PMA analysis, the sponsor states that the combined data from the two sinus augmentation studies resulted in 80% success with a lower confidence interval which exceeds the primary effectiveness criteria of at least 73% functional [redacted] interval of greater than [redacted]

Subjects Who Received Prosthesis and Maintained [redacted]  
(Intent to Treat Population)

Subjects	Combined Bone Graft Number of Patients (%)	rhBMP-2/ACS 1.50 mg/ml Number of Patients (%)	P-Value <sup>a,f</sup>
	[ ] (95.6%)	82 [ ]	
	[ ]	[ ]	
	[ ]	[ ]	
	[ ] (89.9)	[ ] (79.6)	[ ]
	[ ]	[ ]	[ ]
	[ ]	[ ]	
	[ ] (88.5)	[ ] (79.4)	[ ]
	[ ]	[ ]	[ ]
	[ ]	[ ]	
	76 [ ]	[ ] (78.7)	[ ]
	[ ]	[ ]	[ ]
	[ ]	[ ]	
	[ ]	[ ]	[ ]
	[ ]	[ ]	[ ]

st. \* Indicates the p-value is less than 0.05.

- b. Subjects who successfully received prosthesis but were lost to follow-up or withdrew anytime thereafter were excluded from the ITT analysis.
- c. 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.
- d. 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.
- e. 2-sided 95% exact confidence interval.
- f. 95% Confidence interval on logit estimate of the Odds Ratio.

Bone density, height, and width were measured using radiography and CT scans. The quality of bone generated was histologically similar to that of native bone taken from the same patients. The amount of bone generated was similar to that observed when bone grafts were used. The numbers of implants placed for all groups were similar. More prostheses were placed in bone graft sites than rhBMP-2 sites. At the 36 month time point, a slightly larger number of successfully loaded rhBMP-2 patients remained functionally loaded. The most frequent adverse event reported was edema. Only 2 patients demonstrated a transient antibody response to the rhBMP-2.

[redacted] discontinued treatment. [redacted] additional patients were lost to [redacted] these patients [redacted] were considered treatment failures. The other [redacted] drew for nonrhBMP-2 related reasons. [redacted] of these treatment failures ([redacted] were in the rhBMP-2 group.

Almost all patients in this study reported adverse events; mainly related to the surgical procedure itself. [redacted] of the adverse events reported, occurred during the first [redacted] [redacted] after surgery. The rhBMP-2 group reported greater facial edema.

Antibody reactions did not occur in the bone graft site, but did occur in 2% of the BMP-2 sites.

### Case Studies

[redacted] were submitted in the PMA in support of the sponsor's claim of being able to treat all maxillofacial defects with In Fuse. Because these [redacted] were incomplete and did not address the proposed indications for use, [redacted] support a general claim that InFuse is safe to use in the maxillofacial region, and indicate that InFuse has the potential to grow bone in the maxillofacial skeleton.

During the November 9, 2006 Dental Products Panel Meeting the Panel will be asked to discuss the safety and effectiveness data presented solely for the stated indications.

### Statistical Review

This statistical review will discuss the sinus augmentation studies followed by the ridge [redacted] tation at tooth extraction site study. It begins with a synopsis of the dosing study [redacted]. The pivota [redacted] will then be described in detail and the results analyzed. [redacted] tistical anal [redacted] rotocol for [redacted]. The statistical analysis will be based on data from [redacted]. For some [redacted] relevant information is also available from [redacted]. [redacted] alysis will be presented as well.

### [redacted] Dosing Study for Sinus Floor Augmentation

[redacted] was designed as a multi-center, randomized, active-controlled evaluation of [redacted] concentrations of rhBMP-2 delivered on an ACS for maxillary sinus floor augmentation. Specifically, two concentrations (0.75, 1.5 mg/ml) of rhBMP-2 were



The primary effectiveness endpoint was the proportion of [redacted] treated patients with successful dental implant borne restoration at [redacted]. No statistical hypotheses were formulated concerning the primary effectiveness endpoint. The secondary effectiveness endpoints were:

1. The proportion of [redacted] successful dental implant borne restoration at [redacted]
2. The proportion of [redacted] (per group) that once placed into the augmented maxillary sinus(es) achieve clinical osseointegration and maintain functional restoration at [redacted]
3. Bone height change over [redacted] after treatment,
4. [redacted] density change from baseline to [redacted] and from baseline to [redacted] post-dental implant placement
5. Cost drivers (harvest procedure, concomitant medications, adverse events, non study related surgical/dental procedures, and dental implant failures).

Safety was to be evaluated via oral examinations, vital signs, radiographs, adverse events, bone histology, serum chemistry, hematology, and antibody formation to rhBMP-2, bovine type 1 collagen, and human type 1 collagen (if necessary).

### **Patient Accountability in the Pivotal Study**

A total of [redacted] were enrolled and randomized; [redacted] to the bone graft group, and [redacted] to the rhBMP-2/ACS group. [redacted] did not successfully complete the study. These [redacted] in the [redacted] (in the rhBMP-2/ACS group) were determined to be technical failures at various sites including the last visit. [redacted] were withdrawn from the study for reasons not apparently related to treatment failure. Specifically, [redacted] in the bone graft group [redacted] had adverse events [redacted] (in the rhBMP-2/ACS group), and another [redacted] in the [redacted] were lost to follow-up. The remaining [redacted] in the rhBMP-2/ACS group) completed [redacted] visits at [redacted].

In the primary effectiveness analysis [redacted] (one in the bone graft group, one in the rhBMP-2/ACS group) who were discontinued from the study (withdrawn or lost to follow-up) before or at prosthesis placement will be considered failures, while those (two in the bone graft group, one in the rhBMP-2/ACS group) who successfully received prosthesis but were discontinued before the [redacted] visit will be excluded from the analysis, according to the protocol.

A total of [redacted] violations occurred during the study including conducting study-related procedures prior to obtaining informed consent [redacted], randomized treatment not received [redacted], eligibility criteria not met [redacted], use of bone graft substitutes in combination with autograft [redacted], and use of protocol-prohibited medications [redacted] (mostly prophylactic corticosteroids). In addition, there was one unspecified violation [redacted].

Patient Accountability of the Sinus Pivotal Study [redacted]

	Control	rhBMP2/ACS
n = number of patients	[redacted]	[redacted]
Failures	[redacted]	[redacted]
Lost to Follow-up	[redacted]	[redacted]
Withdrawn Total	[redacted]	[redacted]
Withdrawn Refused treatment	[redacted]	[redacted]
Withdrawn Adverse Event	[redacted]	[redacted]
Withdrawn Relocation	[redacted]	[redacted]
Total n at 24 months (all were successful)	[redacted]	[redacted]

**Patient Demographic and Baseline Characteristics in the Pivotal Study**

Table 2A-2 summarizes the demographic and baseline characteristics of the study subjects. Age is presented both as a continuous variable and as a categorical one, using [redacted] as a cutoff. Also categorized is the amount of alcohol consumption. There was a significantly higher proportion of subjects who were at least [redacted] of age in the rhBMP-2/ACS group than in the bone graft group (p = 0.024, Fisher's exact test). However, the distribution of age as a continuous variable did not appear to vary much across treatment groups, with means [redacted] for the bone graft and rhBMP-2/ACS groups, respectively. There was a significantly higher proportion of male subjects in the rhBMP-2/ACS group than in the bone graft group (p = 0.003, Fisher's exact test). No association was detected between treatment assignment and any of the other characteristics.

**Descriptive Findings of the Pivotal Study**

[redacted] present partial results pertaining to the success rates at various stages of the study. [redacted] patients in the bone graft group and [redacted] in the rhBMP-2/ACS group successfully received total implants into newly induced bone without additional augmentation. Of these, [redacted] in the bone graft group and [redacted] in the rhBMP-2/ACS group successfully received prostheses and became functionally loaded. Group-specific success rate estimates at different time points [redacted] [redacted] in the [redacted] were discontinued (withdrawn or lost to follow-up) from the study were handled in accordance with rules specified in the protocol. Specifically, patients who were discontinued without successful functional loading were counted as failures, while those

[redacted] were excluded from the analysis  
s, the observed success rate in  
the rhBMP-2/ACS group was consistently lower [redacted] oup. While  
the control rate remained constant throughout the [redacted] the rhBMP-  
2/ACS rate declined over time, increasing the observed difference between groups.

**Table 2A-2: Demographic and Baseline Characteristics**

--

**Table 2A-11: Number (%) of Subjects Who Received Prosthesis (Functionally Loaded) and Maintained Functional Loading (ITT Population)**

**Statistical analysis of the pivotal study**

Primary effectiveness analysis

Success endpoint pertains to the maintenance of [redacted] [redacted]. Within [redacted] in the bone graft group and one in the rhBMP-2 [redacted] and thus excluded from the analysis. Among those seen at [redacted] one in the bone graft group and none in the rhBMP-2/ACS group [redacted]. Thus the success rate at six [redacted] post-loading is estimated to be 90.8% [redacted] in the bone graft group and 79.0% [redacted] in the rhBMP-2/ACS group. The two [redacted] are significantly different (two-sided p = 0.03, Fisher's exact test). The study protocol did not specify a non-inferiority margin.

**Secondary Effectiveness Analysis of the Pivotal Study**

Group-specific success rate estimates at later time points [redacted] after functional loading are displayed in Table 2A-11, together [redacted] confidence intervals and two-sided p-values from Fisher's exact test. At each time point, the difference between groups is statistically significant, and the significance appears to strengthen over time (as suggested by decreasing p-values), despite patient withdrawals and losses to follow-up.

Another secondary endpoint is bone height, which was measured by CT scans at baseline and six months postoperative. Table 2A-16 presents the summary statistics concerning bone height. There was not a significant difference in baseline bone height between the two groups. Over the 6-month postoperative period, the mean change in bone height in the bone graft group was 9.46 mm with a standard deviation of 4.11 mm, and the mean change in bone height in the rhBMP-2/ACS group was 7.83 mm with a standard deviation of 3.52 mm. Their respective 95% confidence intervals are given in Table 2A-16. Both confidence intervals have lower boundaries well above 0, indicating a significant bone growth in both groups during the 6-month postoperative period. On the average, 1.64 mm more new bone was formed in the bone graft group than in the rhBMP-2/ACS group. A two-sided t-test comparing this difference with 0 yields a p-value of 0.0078. According to the sponsor, the nonparametric Mann-Whitney test gives a p-value close to 0.01. Both tests indicate that bone graft induces more new bone than does rhBMP-2/ACS. A 95% confidence interval for the difference is not provided in Table 2A-16 but can be calculated as (0.43, 2.85) using the summary statistics in Table 2A-16. Bone height data are also

**Table 2A-12: Number (%) of Dental Implants That Received Prosthesis (Functionally Loaded) and Maintained Functional Loading (ITT Population)**

Dental Implants Placed	Bone Graft (n=251)	rhBMP-2/ACS 1.50 mg/mL (n=241)	P-Value <sup>a</sup>

Source: table2\_implant\_ITT\_12, table2\_implant\_ITT\_13, table2\_implant\_ITT\_14, table2\_implant\_ITT\_15

- a. P-value is from Fisher's exact test. \* Indicates the p-value is less than 0.05.
- b. Dental implants from subjects who successfully received prosthesis but were lost to follow-up or withdrew anytime thereafter were excluded from the ITT analysis.
- c. Success is defined as a dental implant placed into newly induced bone that received prosthesis and maintained functional loading.
- d. For subjects who missed a functional loading visit but whose dental implant status at flanking visits was known, the known status at the last visit was imputed.

Another secondary endpoint is bone height, which was measured by CT scans at baseline and six months postoperative. Table 2A-16 presents the summary statistics concerning bone height. There was not a significant difference in baseline bone height between the two groups. Over the 6-month postoperative period, the mean change in bone height in the bone graft group was 9.46 mm with a standard deviation of 4.11 mm, and the mean change in bone height in the rhBMP-2/ACS group was 7.83 mm with a standard deviation of 3.52 mm. Their respective 95% confidence intervals are given in Table 2A-16. Both confidence intervals have lower boundaries well above 0, indicating a significant bone growth in both groups during the 6-month postoperative period. On the average, 1.64 mm more new bone was formed in the bone graft group than in the rhBMP-2/ACS group. A two-sided t-test comparing this difference with 0 yields a p-value of 0.0078. According to the sponsor, the nonparametric Mann-Whitney test gives a p-value close to 0.01. Both tests indicate that bone graft induces more new bone than does rhBMP-2/ACS. A 95% confidence interval for the difference is not provided in Table 2A-16 but can be calculated as (0.43, 2.85) using the summary statistics in Table 2A-16. Bone height data are also

available from the dosing study. Note, however, that CT scans were given at a different time, i.e., four months postoperative, in the dosing study. It is not clear that the two studies may be combined for this analysis.



An analysis for bone density or use of medical resources was not presented for the pivotal study.

### **Safety**

A total of 1884 adverse events occurred during the study. The frequent adverse events (experienced by at least 10% of patients) are summarized in Table 2A-19. A significantly higher proportion of patients in the bone graft group relative to the rhBMP-2/ACS group experienced edema ( $p < 0.0001$ ), pain ( $p = 0.0001$ ), arthralgia ( $p = 0.037$ ), abnormal gait ( $p < 0.0001$ ), and rash (erythema) ( $p < 0.0001$ ). A significantly higher proportion of patients in the rhBMP-2/ACS group relative to the bone graft group experienced facial edema ( $p = 0.048$ ). The number and percentage of subjects with adverse events by treatment group and severity for the entire study is summarized in Table 2A-20. Most adverse events were mild (34%) or moderate (50%) in severity. The severity of the events was comparable between the two treatment groups, with a p-value of 0.29 for Pearson's chi-square test.

The proportion of subjects that developed treatment-emergent elevation in anti-rhBMP-2/ACS antibodies was 0% (0/78) in the bone graft group and 2% (2/82) in the rhBMP-2/ACS group. The proportion of subjects that developed treatment-emergent elevation in antibodies to Type I bovine collagen was 32% (25/78) in the bone graft group and 29% (24/82) in the rhBMP-2/ACS group.

**Table 2A-19: Number (%) of Subjects With Frequent Adverse Events (≥10% of Subjects) by Treatment Group, Body System, and COSTART Term**

Body System COSTART Term	rhBMP-2/ACS		Total (n=160)	P-value <sup>a</sup> Overall
	Bone Graft (n=78)	1.50 mg/mL (n=82)		
Subjects with records	78 (100)	82 (100)	160 (100)	
Subjects with AEs	77 (99)	82 (100)	159 (99)	
Subjects without AEs	1 (1)	0	1 (1)	
<b>Body as a Whole</b>				
Edema	28 (36)	2 (2)	30 (19)	0.0000*
Face edema	44 (56)	59 (72)	103 (64)	0.0481*
Headache	7 (9)	11 (13)	18 (11)	0.4566
Infection	32 (41)	22 (27)	54 (34)	0.0669
Pain	40 (51)	20 (24)	60 (38)	0.0006*
<b>Digestive System</b>				
Mouth pain	66 (85)	71 (87)	137 (86)	0.8229
Oral edema	50 (64)	54 (66)	104 (65)	0.8690
Oral erythema	50 (64)	41 (50)	91 (57)	0.0807
<b>Hemic and Lymphatic System</b>				
Ecchymosis	18 (23)	14 (17)	32 (20)	0.4297
<b>Metabolic and Nutritional Disorders</b>				
Hyperglycemia	15 (19)	8 (10)	23 (14)	0.1148
<b>Musculo-Skeletal System</b>				
Arthralgia	19 (24)	9 (11)	28 (18)	0.0365*
Bone Disorder	9 (12)	9 (11)	18 (11)	1.0000
<b>Nervous System</b>				
Abnormal gait	34 (44)	0	34 (21)	0.0000*
<b>Respiratory System</b>				
Sinusitis	10 (13)	9 (11)	19 (12)	0.8089
<b>Skin and Appendages</b>				
Rash	28 (36)	8 (10)	36 (23)	0.0001*

Source: ae\_360d2

a. P-value is from 2-sided Fisher's exact test. \*Statistically significant at p<0.05.

Abbreviation: AE = Adverse event

**Table 2A-20: Number (%) of Subjects With Adverse Events by Treatment Group and Severity:**

Severity	rhBMP-2/ACS		Total (n=160)
	Bone Graft (n=78)	1.50 mg/mL (n=82)	
Subjects with records	78 (100)	82 (100)	160 (100)
Subjects with AEs	77 (99)	82 (100)	159 (99)
Subjects without AEs	1 (1)	0	1 (1)
Mild	29 (37)	26 (32)	55 (34)
Moderate	34 (44)	46 (56)	80 (50)
Severe	14 (18)	10 (12)	24 (15)
Life-threatening	0	0	0

Source: ae\_308z

Abbreviation: AEs = Adverse events

The interpretation of the primary effectiveness analysis may have been subtle due to the lack of pre-specified statistical hypotheses concerning the primary effectiveness endpoint. Additional information was needed to fully evaluate the secondary endpoints.

## **Pooling**

The dosing and pivotal studies are shown to be similar with respect to demographic characteristics as well as successful functional restoration. It is not clear, however, that from a statistical standpoint, bone height data from the two studies may be combined. In the pivotal study, bone height was measured at baseline and six months postoperative, while in dosing study measurements were taken at baseline and four months postoperative. Ironically, greater average gains in bone height were observed in dosing study than in

pivotal study (10.16 vs. 7.81 mm for rhBMP-2/ACS patients; 11.29 vs. 9.41 in the control group). The p-values for the differences between the two studies (0.07 for rhBMP-2/ACS; 0.13 for control) do not reach the usual significance level of 0.05. However, this does not provide evidence that the two studies are homogeneous with respect to bone height; it means only that there is not sufficient evidence that the studies are heterogeneous.

### **Implant-level success rates**

The pivotal study report contains a rough analysis (Table 2A-12, page 21), without adjusting for the within-subject correlation, of the implant-level data. No significant differences were found between the two arms. The sponsor submitted a refined analysis under the GEE approach, which finds no significant differences between the two treatment arms (Table IV.A-14). However, this does not provide evidence that the two arms are similar. To claim noninferiority, a noninferiority margin would need to be specified, and the test can be based on a confidence interval for the difference between the two arms.

The sponsor explains that “As functional loading at the six-month and subsequent milestones was not recorded in the pivotal study, the analyses of these endpoints were carried out for the dosing study data only”. This seems to contradict the existence of Table 2A-12 in the pivotal report.

### **Bone height**

Combining bone height data from the dosing and pivotal studies would result in average gains in bone height of [redacted] for autogenous bone graft and rhBMP-2/ACS, respectively. The p-value on between the two groups is 0.0113.

### **[redacted] Extraction socket augmentation**

The indication for use of ridge augmentation at tooth extraction socket sites is supported by a dosing study. No pivotal extraction site study was performed.

### **Study design**

[redacted] was a dosing study that was designed as a multi-center, randomized, placebo and no treatment controlled evaluation of escalating concentrations of rhBMP-2 delivered on an ACS for localized alveolar ridge augmentation of buccal wall defects in extraction sockets. Specifically, two concentrations (0.75, 1.5 mg/ml) of rhBMP-2 were compared to a placebo control (ACS only) and a no treatment control.

The study population consisted of candidates for a two-stage local alveolar ridge augmentation procedure for buccal wall defects in extraction sockets. A total of [redacted] were to be recruited at about eight sites. Two sequential cohorts of [redacted] each were to be randomized in a 2:1:1 ratio to receive either rhBMP-2/ACS (20), ACS only (10) or no treatment (10). Randomization was to be performed in a double-masked manner between the rhBMP-2/ACS and ACS-only groups. *Assignment to the no treatment arm would not*

*be masked.* The two cohorts differed in the concentration of rhBMP-2, with the lower concentration (0.75 mg/ml) followed by the higher concentration (1.5 mg/ml). Progression from the first cohort to the second was to take place upon ascertainment of acute safety. The sample size was chosen to detect a 31% difference in the proportion of patients with adequate bone formation for dental implant placement with 90% power, assuming a 15% loss to follow-up.

Following initial surgery, the patient's treatment course would depend on whether the patient received dental implants. Patients who did not receive dental implants or who required another bone regenerative procedure at the treatment site prior to dental implant placement would be followed for [redacted] received dental implants would be followed for [redacted] of the dental implants. Their treatment course consisted of a 4-month short-term safety and bone induction phase, a 4- to 8-month [redacted] se (initiated with dental implant placement), and a [redacted] (initiated with prosthesis placement) during wh [redacted] d every 6 months.

The primary endpoints of the study were to determine a safe and effective concentration for inducing bone formation and to estimate the proportion of patients within each treatment group that have adequate bone formation to support the placement of endosseous dental implants at four months. The secondary endpoints were:

1. To estimate the proportion of patients within each treatment group that receive endosseous dental implant(s) without the need for an additional bone augmentation procedure,
2. To estimate the proportion of endosseous dental implants placed into the study treatment area that achieve clinical osseointegration and allow functional loading,
3. To estimate the proportion of patients that have a prosthesis placed onto the dental implants in the study treatment area,
4. To estimate the proportion of patients that maintain a successful prosthesis a [redacted] [redacted]
5. [redacted] duced bone.

Patient safety would be monitored by oral examinations, radiographs, the occurrence of adverse events, and the collection of blood samples to measure serum chemistries, hematology and antibody formation to study treatment.

### **Patient accountability**

Patient disposition in the study is as follows:

## Patient disposition

Treatment Group	Enrolled, Randomized	Died	Discontinued <sup>a</sup>	Lost to Follow-Up	Completed <sup>b</sup>

Source: cpp\_307a

a Discontinued included (1) patients who were treatment failures and (2) patients who elected to withdraw from the study.

b Completed included patients who completed the final study visit.

[redacted] were enrolled and randomized to treatment: [redacted] patients (25%) received no treatment, [redacted] patients (21.3%) received 0.0 mg/ml rhBMP-2/ACS, [redacted] patients (27.5%) received 0.75 mg/ml rhBMP-2/ACS, and [redacted] patients (26.3%) received 1.50 mg/ml rhBMP-2/ACS. A total of [redacted] patients (37.5%) completed the study. Of the [redacted] patients who did not complete, [redacted] patients (50.0%) discontinued prematurely (failed or withdrew), [redacted] patients (11.3%) were lost to follow-up, and [redacted] patient (1.3%) died during the study.

A total of 14 protocol violations were reported for [redacted] patients. [redacted] patients did not receive the treatment to which they were randomized and [redacted] patient was administered 0.0 mg/ml rhBMP-2/ACS prior to randomization. [redacted] patients did not provide written informed consent before undergoing a study procedure that was not considered standard of care, and 1 patient did not provide informed consent before participating in the extended follow-up period. One patient used a disallowed medication (Didronel® for postmenopausal bone loss).

### **Demographic and baseline characteristics**

At study entry, no statistically significant differences among treatment groups were detected for any of the patients' demographic and baseline characteristics (see Table 3 below). The patients' mean age ranged between 45 years and 49 years, and their mean weight was between 76.7 kg and 84.9 kg. The majority of patients in all but the 1.5 mg/ml treatment group were Caucasian (65%-73%); in the 1.50 mg/ml group, the highest proportion of patients was Black (57%). There were approximately equal proportions of males and females in all but the 0.0 mg/ml group; males predominated in the 0.0 mg/ml group (76%). The concurrent use of alcohol ranged from 32% in the 0.75 mg/ml group to 71% in the 0.0 mg/ml group.

## Summary of demographic information by treatment group

No Treatment	rhBMP-2/ACS 0.00 mg/mL	rhBMP-2/ACS 0.75 mg/mL	rhBMP-2/ACS 1.50 mg/mL

Of the [ ] randomized patients, [ ] patients had at least one incisor treated, and [ ] patients had at least one non-incisor treated; [ ] patient had a molar treated, in violation of the protocol. No statistically significant differences were noted among the treatment groups in any of several dental characteristics (periodontitis history, plaque, periodontal disease).

### **Results Extraction Socket Study**

[ ] Patients in this study received the 1.5mg/ml rhBMP-2/ACS. [ ] of the [ ] patients had dental implants placed without additional augmentation and [ ] of the [ ] had a prosthesis placed without additional augmentation and [ ] had a functional loading of the prosthesis at six months. The study was powered as a pivotal study and not sufficiently powered as a pivotal study.

## **SAFETY DATA**

A total of [ ] subjects were enrolled across the 5 studies. [ ] subjects received one of the concentrations of rhBMP-2/ACS (0.43 mg/ml, 0.75 mg/ml, or 1.5 mg/ml) [ ] subjects received bone graft, either autogenous bone (autograft) or autogenous bone and allogeneic bone (autograft plus allograft). Two subgroups were also treated to evaluate no treatment ([ ] subjects) and a placebo consisting of Absorbable Collagen Sponge (ACS) alone, the carrier for rhBMP-2 ([ ] subjects).

A total of [ ] adverse events occurred during the study. Most adverse events were mild (34%) or moderate (50%) in severity. The severity of the events was comparable between the two treatment groups, with a p-value of 0.29 for Pearson's chi-square test.

The sponsor concluded that based on the data from [ ] the incidence of adverse events reported in [ ] subject randomized to bone graft was statistically significantly higher than that reported for [ ] rhBMP-2/ACS subjects. Adverse events included edema ( $p < 0.0001$ ), pain ( $p = 0.000$ ), arthralgia ( $p = 0.037$ ), abnormal gait ( $p < 0.0001$ ), and rash (erythema) ( $p < 0.0001$ ).

The sponsor also concluded that bone graft subjects reported significantly more edema, infection, pain, nausea, hyperglycemia, arthralgia (sensory loss), abnormal gait, hypesthesia, and rash, and that none of the rhBMP-2/ACS subjects reported abnormal gait or gait disturbance compared to 41% of bone graft subjects.

The proportion of subjects that developed treatment-emergent elevation in anti-rhBMP-2/ACS antibodies was 0% (0/78) in the bone graft group and 2% (2/82) in the rhBMP-2/ACS group. The proportion of subjects that developed treatment-emergent elevation in antibodies to Type I bovine collagen was 32% (25/78) in the bone graft group and 29% (24/82) in the rhBMP-2/ACS group.

## **Conclusions to be Drawn**

Conclusion related to the suitability of data submitted in this PMA to support the safety and effectiveness of InFuse® Bone Graft for its intended uses will be the subject of the Dental Products Panel Meeting on November 9, 2006.