

# SECTION XII – SUMMARY OF SAFETY AND EFFECTIVENESS

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## **XII. Summary of Safety and Effectiveness**

### **XII.A. General Information**

Device Generic Name: Recombinant human bone  
morphogenetic protein / absorbable  
collagen sponge

Device Trade Name: INFUSE<sup>®</sup> BONE GRAFT

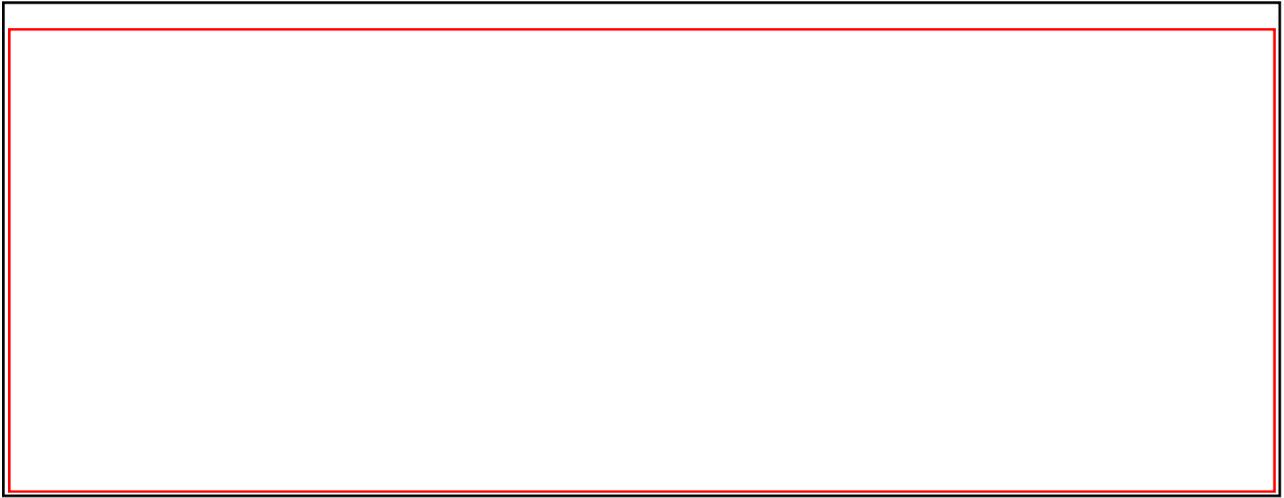
Applicant's Name and Address: Medtronic Sofamor Danek, Inc. USA  
1800 Pyramid Place  
Memphis, TN 38132

Premarket Approval Application

(PMA) Number: P050053

Date of Notice of Approval of Application: Pending

## **XII.B. Indications for Use**



## **XII.C. Contraindications**

INFUSE<sup>®</sup> 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 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.

## **XII.D. Warnings and Precautions**

### **XII.D.1. Warnings**

- Women of childbearing potential should be advised that the influence of rhBMP-2 on fetal development has not been assessed. In the clinical trials supporting the safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT for oral maxillofacial bone grafting procedures where space maintenance is present, [ ] (2.2%) patients treated with INFUSE<sup>®</sup> BONE GRAFT and [ ] (0.0%) patients treated with bone graft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus 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<sup>®</sup> 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<sup>®</sup> BONE GRAFT.

### **XII.D.2. Precautions**

#### **XII.D.2.a.1. General**

- The safety and effectiveness of repeat applications of INFUSE<sup>®</sup> BONE GRAFT has not been established.
- INFUSE<sup>®</sup> 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. Retain the packaging and vials and contact a Medtronic Sofamor Danek representative.
- Do not use after the printed expiration date on the label.

#### **XII.D.2.a.2. Hepatic and Renal Impairment**

- The safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT in patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

#### **XII.D.2.a.3. Bone formation**

- The safety and effectiveness of INFUSE<sup>®</sup> 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.

#### **XII.D.2.a.4. Antibody Formation/Allergic Reactions**

- The safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT has not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT has not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy or other treatments.

#### XII.D.2.a.5. Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to a component of INFUSE<sup>®</sup> BONE GRAFT. The immune response to INFUSE<sup>®</sup> BONE GRAFT components was evaluated in [ ] investigational patients and [ ] control patients during human clinical trials of INFUSE<sup>®</sup> BONE GRAFT for oral maxillofacial bone grafting procedures where space maintenance is present.
  - *Anti-rhBMP-2 antibodies:* 2.2% patients receiving INFUSE<sup>®</sup> BONE GRAFT component developed antibodies vs. 0.0% in the control group.
  - *Anti-bovine Type I collagen antibodies:* 20% of patients receiving INFUSE<sup>®</sup> 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. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to INFUSE<sup>®</sup> BONE GRAFT with the incidence of antibodies to other products may be misleading.

## **XII.E. Device Description**



### **XII.E.1. Device Overview and Properties Relevant to Indications for Use**

INFUSE<sup>®</sup> BONE GRAFT consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermis alfa) placed on an absorbable collagen sponge (ACS). The INFUSE<sup>®</sup> BONE GRAFT component induces new bone tissue at the site of implantation. Based on data from non-clinical studies, the bone formation process develops from the outside of the implant towards the center until the entire INFUSE<sup>®</sup> BONE GRAFT component is replaced by trabecular bone.

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

### **XII.E.2. INFUSE<sup>®</sup> Bone Graft Kit**

Each INFUSE<sup>®</sup> BONE GRAFT Kit (See **Figure XII.E-1**) contains vial(s) of rhBMP-2, absorbable collagen sponge(s) (ACS), and the necessary materials to

reconstitute the lyophilized rhBMP-2 and place the reconstituted rhBMP-2 on the ACS.

**Figure XII.E-1 INFUSE® BONE GRAFT Kit**



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.

ACS for use with rhBMP-2 is provided in packages containing two, four or six 1" x 2" pieces or a single 3" x 4" piece depending upon the size and configuration of the kit. The ACS is packaged in a polyvinyl chloride blister pack with a Tyvek lid. Prior to implantation, rhBMP-2 is reconstituted with Sterile Water for Injection and the solution is then uniformly applied to the ACS.

Two new kit sizes (XX Small and X Small) are currently being developed. These additional kits will be submitted to the FDA for approval as a PMA Supplement in a separate, future submission.

For this new indication, an additional package insert will be developed and included in the four currently available commercial INFUSE® BONE GRAFT kits.

After approval, for marketing purposes, an additional or secondary product name may be added; the only change will be on the outside of the kit.

### **XII.E.3. INFUSE<sup>®</sup> BONE GRAFT Components**

**Table XII.E-1** provides a description and photo of the components of the various kits of INFUSE<sup>®</sup> BONE GRAFT.

**Table XII.E-1 Small 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	
Absorbable Collagen Sponge (ACS)	1, 2, or 4 pieces per kit	Absorbable Collagen Sponge (ACS); sponge sizes are 1" x 2" or 3" X 4"	

**Table XII.E-1 Small INFUSE® BONE GRAFT Kit Contents and Description**

Part	Number	Brief Description	Photograph
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	See Appendix IV-2 of the original submission
Package Insert	1 per kit	Provides important medical information about INFUSE® BONE GRAFT	See Appendix IV-3 of the original submission
Patient Label	1 set per kit	Provides mechanism for recording device information on patient charts, reimbursement forms, hospital records, etc.	See Appendix IV-4 of the original submission
Packaging	1 set per kit	Styrene tray containing vials and syringes; Styrene tray containing ACS; SBS carton containing the two trays	See Appendix IV-5 of the original submission

#### XII.E.4. Previous FDA Market Clearances

INFUSE<sup>®</sup> BONE GRAFT kits which are the subject of this PMA have been approved through the PMA process. **Table XII.E-2** identifies the submissions associated with each of the parts.

**Table XII.E-2 Previous Market Approvals for INFUSE<sup>®</sup> BONE GRAFT**

Part	Description	Market Approval(s)
rhBMP-2 Vial	Vial containing lyophilized rhBMP-2	P000054: INFUSE <sup>®</sup> BONE GRAFT P000058: INFUSE <sup>®</sup> BONE GRAFT/LT Cage <sup>®</sup> Lumbar Tapered Fusion Device
Water for Injection Vial	Vial containing sterile water for injection	P000054: INFUSE <sup>®</sup> BONE GRAFT P000058: INFUSE <sup>®</sup> BONE GRAFT /LT Cage <sup>®</sup> Lumbar Tapered Fusion Device
Syringe	5 ml and 10 ml syringes with 20 G 1 ½" needles	P000054: INFUSE <sup>®</sup> BONE GRAFT P000058: INFUSE <sup>®</sup> BONE GRAFT /LT Cage <sup>®</sup> Lumbar Tapered Fusion Device
ACS	Absorbable Collagen Sponge	P850010: Helistat <sup>®</sup> Absorbable Collagen Hemostatic Sponge P000054: INFUSE <sup>®</sup> BONE GRAFT P000058: INFUSE <sup>®</sup> BONE GRAFT /LT Cage <sup>®</sup> Lumbar Tapered Fusion Device

### XII.E.5. Instructions for Preparation

INFUSE<sup>®</sup> BONE GRAFT is prepared at the time of surgery. With each of the different size kits, rhBMP-2 solution has a concentration of 1.5 mg/ml after reconstituting the lyophilized rhBMP-2 with the volume of Sterile Water for Injection specified in the instructions for preparation. Then the specified volume of rhBMP-2 solution is applied to each of the provided ACS pieces. After waiting for the prescribed amount of time (15 to 120 minutes), cut the wetted sponge as needed and carefully apply to the defect site.

**Figure XII.E-2 Instructions for Preparation**

	<p>Using one of the syringes, Sterile Water for Injection is withdrawn from the vial. (Depending on kit size, either 3.2 ml or 8.4 ml is used.)</p>
	<p>The rhBMP-2 is reconstituted with the Sterile Water for Injection.</p>

**Figure XII.E-2 Instructions for Preparation**

	<p>To ensure adequate mixing, the rhBMP-2 vial is gently swirled.</p>
	<p>A second syringe is used to withdraw reconstituted rhBMP-2 from the vial. (Depending on kit size, either 1.4 ml or 4.0 ml is used.)</p>
	<p>The reconstituted rhBMP-2 is then uniformly distributed on a sponge. The process is repeated using the other vial of rhBMP-2 as required, Sterile Water for Injection, syringes and sponges, depending on the kit size.</p>

## XII.F. Alternative Practices and Procedures

The non-surgical alternative to performing oral maxillofacial procedures with INFUSE<sup>®</sup> 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
- Demineralized Bone Matrix – (DBX<sup>®</sup>) paste or putty composed of human cortical and corticocancellous bone

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

40,000 to 50,000 second-site surgeries are performed for bone graft harvest each year. Risks associated with bone harvesting are well documented in the literature. These are summarized in Section IX.C.5 of the original PMA submission: *Human Clinical References Relevant to the Incidence of Bone Graft Morbidity*.

In the sinus floor augmentation pivotal clinical 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.

## Marketing History

The INFUSE<sup>®</sup> BONE GRAFT has not been marketed for the use described in this PMA in the United States or any foreign country. Medtronic Sofamor Danek is the manufacturer of record for the INFUSE<sup>®</sup> BONE GRAFT device.

The rhBMP-2 is marketed in the United States as a component of INFUSE<sup>®</sup> BONE GRAFT, for both spine and trauma indications. INFUSE<sup>®</sup> 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<sup>®</sup> BONE GRAFT alone is approved for treating acute, open tibial shaft fractures (P000054). INFUSE<sup>®</sup> BONE GRAFT has not been withdrawn from the market for any reason.

The specific marketing history for these products is summarized in **Table XII.G-1**.

**Table XII.G-1: Countries where INFUSE<sup>®</sup> Bone Graft is Currently Marketed**

Country	Spine Indication	Trauma Indication

## **XII.H. Potential Adverse Effects of the Device on Health**

The following is a list of potential adverse events which may occur with dental implant surgery with the INFUSE<sup>®</sup> BONE GRAFT device. Some of these adverse events may have been previously reported in the adverse events table or have been reported to the manufacturer:

- Bowel or bladder problems
- Damage to internal organs and connective tissue
- Death
- Development of respiratory problems
- Disassembly, bending, breakage, loosening, and/or migration of dental implant components
- Ectopic and/or exuberant bone formation
- Fetal development complications
- Incisional complications
- Infection
- Neurological system compromise
- Scar formation
- Tissue or nerve damage
- Edema (swelling)
- Inflammation
- Erythematous tissue
- Allergic reaction
- Itching
- Pain
- Hematoma

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

## **XII.I. Summary of Non-Clinical Studies**

### **XII.I.1. Safety Studies**

Extensive non-clinical testing has been conducted demonstrating that the INFUSE<sup>®</sup> BONE GRAFT performs as intended and is safe and effective for use in spinal fusion procedures as designed. Testing was conducted in the following categories:

- rhBMP-2 Protein and Absorbable Collagen Sponge (ACS) Characterization
- Preclinical Safety:



- Preclinical Effectiveness in Oral Maxillofacial Indications:



- Comparability of Bone Induction by rhBMP-2 and Autogenous Bone
- Pharmacokinetics and Dosing

- Previously Reported Studies
- Stability Testing

**XII.I.1.a. Intravenous Toxicity and Implant Toxicity**

rhBMP-2 has been studied in single- and multiple-dose general toxicology studies in the rat and canine with up to 28 days of daily dosing. rhBMP-2 was administered intravenously (IV), and doses were selected to constitute a range that varied from slightly lower to substantially higher than the total doses (weight-based) of rhBMP-2 used in human clinical trials and commercial applications (up to 1 mg/kg, total delivered dose). There were no treatment-related toxicities observed in these studies. **Table XII.I-1** summarizes the testing and relevant findings.

**Table XII.I-1: Safety of rhBMP-2/ACS in situ**

Study Type: Species/Strain (Study Number)	Relevant Findings

**Table XII.I-1: Safety of rhBMP-2/ACS in situ**

Study Type: Species/Strain (Study Number)	Relevant Findings

**XII.I.1.b. Biocompatibility Studies**

The safety of rhBMP-2/ACS was assessed in a series of standardized studies. Because the INFUSE® BONE GRAFT device is a unique combination product, the establishment of the appropriate biocompatibility testing was a combination of the USP- and device-appropriate tests. Under the conditions of these studies, there was no mortality or evidence of significant systemic toxicity in the mouse, no intracutaneous toxicity in the rabbit, no evidence of cell lysis or toxicity in the extract and overlay cytotoxicity tests, no evidence of hemolysis, and no evidence of cellular mutagenicity. **Table XII.I-2** below list the specific biocompatibility testing conducted.

**Table XII.I-2: Biocompatibility Testing of the rhBMP-2/ACS Device**

Study Type

**XII.I.1.c. Tumor Cell Activity**

rhBMP-2 has been examined *in vitro* for growth activity on human tumor cell lines and primary tumor cell isolates. It was found that rhBMP-2 did not show any growth potentiating activity and that it actually showed growth inhibition of several carcinoma-derived tumors. Three other tumor cell line studies were also completed. [REDACTED]

[REDACTED] of y

[REDACTED] Ten of the eleven cancer cell lines showed no additional mitogenic activity in response to the addition of rhBMP-2. The remaining cell line was growth inhibited by rhBMP-2 in a dose-dependent fashion. The third study examined the effects of rhBMP-2/ACS on the growth of subcutaneously implanted human tumor cell lines in athymic nude mice. rhBMP-2/ACS did not promote *in vivo* growth of any of the seven different human tumor cell lines tested.

#### **XII.I.1.d. Fertility, Reproduction and Teratology**

Because BMP-2 participates in embryological development, it was evaluated for any effect on reproduction or fetal development. Studies evaluated rhBMP-2 at total doses (weight based) that ranged from slightly lower to substantially higher than rhBMP-2 doses that will be used in commercial applications. The effects of rhBMP-2 on the reproduction and fertility of male and female Sprague-Dawley rats was studied. Maternal and paternal mating performance and reproductive parameters were not affected by treatment. Range-finding studies followed by definitive developmental toxicity studies were conducted in both Sprague-Dawley rats and New Zealand White rabbits. There was no evidence of maternal toxicity, embryolethality, fetotoxicity, or teratogenicity. **Table XII.I-3** summarizes relevant findings.

**Table XII.I-3: Safety of rhBMP-2 Administered Intravenously: Fertility, General Reproductive Performance and Teratology**

<b>Study Type: Species/Strain</b>	<b>Relevant Findings</b>
Fertility: Rat/Sprague-Dawley	Maternal and paternal mating performance and reproductive parameters were not affected by treatment.
Range-Finding Teratology: Rabbit/New Zealand White Administered on Days 6 to 18 gestation	No maternal toxicity, embryolethality or gross fetal abnormalities.
Teratology: Rabbit/New Zealand White Administered on Days 6 to 18 gestation	No maternal toxicity, embryolethality or gross fetal abnormalities.
Range-Finding Teratology: Rat/Sprague-Dawley Administered on Days 6 to 17 gestation	No maternal toxicity, embryolethality or gross fetal abnormalities.
Teratology: Rat/Sprague-Dawley Administered on Days 6 to 17 gestation	No maternal toxicity, embryolethality, fetotoxicity or teratogenicity and no difference in skeletal formation between the control and rhBMP-2 groups.

#### **XII.I.2. Preclinical Effectiveness in Oral Maxillofacial Indications**

Effectiveness of rhBMP-2 has been demonstrated in earlier submissions through many preclinical studies, published literature and also in human clinical trials.

These studies are summarized below in **Table XII.I-4**.

Preclinical effectiveness studies evaluating oral maxillofacial indications are grouped into five categories and summarized in the following section:

- Oral Maxillofacial indications including Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS
- 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
- Periodontal Defect and Dental Implant Studies

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
Preclinical Effectiveness in Oral Maxillofacial Indications		
Canine		Results indicate that rhBMP-2/ACS can induce healing of mandibular segmental defects in dogs as assessed radiographically, clinically, and functionally. These results also indicate that post-surgical swelling was related to rhBMP 2 concentration in this animal model.
		This study demonstrated that facial edema following implantation of rhBMP-2 in a critical-size mandibular defect was found to be within the clinically acceptable range. This study also demonstrated the powerful osteoinductive capability of rhBMP-2, with active bone formation occurring at the periphery of the implant at only 10 days postoperatively.
		At five days post-surgery, neovascularization, mesenchymal cell infiltration, and small amounts of osteoid produced by osteoblasts were evident. Ten days post-surgery, vascularization, mesenchymal cell infiltration, and bone formation extended into the deeper layers. Woven trabecular bone was observed in the outer layer. At the later time points (14, 21, and 28 days) a larger area of the implant was occupied by woven trabecular bone. No chondrocytes were observed at any time, suggesting that intramembranous (direct) bone formation occurred after implantation of rhBMP-2/ACS at this concentration and site. No apparent histologic evidence of inflammatory or other adverse effects were observed in the soft tissues adjacent to the rhBMP-2 implant at any time point.
		Results suggest that rhBMP-2/ACS has significant potential to reconstruct large alveolar ridge defects without a potential for wound failure observed following GBR. Induced bone appears of similar quality to the native bone. Combining rhBMP-2/ACS with GBR appears to have limited value due to the potential for wound failure and frequent, persistent bone voids.
		Recombinant human bone morphogenetic protein-2 in an absorbable collagen sponge (ACS) carrier has been shown to support significant bone formation for several indications in the craniofacial skeleton. When used as an onlay, however, rhBMP-2/ACS may become compressed with limited resulting bone formation. The bioglass and demineralized/mineralized bone matrix biomaterials utilized in this study in combination with rhBMP-2/ACS supported clinical and histological ridge augmentation.

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
		<p>Recombinant human bone morphogenetic protein-2 in an absorbable collagen sponge (ACS) carrier induces bone formation for reconstruction of a variety of skeletal defects. The results suggest that rhBMP-2/ACS has limited effect alone in this augmentation model of class III alveolar ridge defects.</p>
Non-Human Primates		<p>Study demonstrates the ability of rhBMP-2/ACS to reconstruct segmental mandibular defects in the nonhuman primate. The observed therapeutic rhBMP-2 concentration range in the nonhuman primate is substantially higher than in the dog.</p> <p>The histologic analysis of the five month samples indicated substantial new trabecular bone formation and remodeling across the defect margins in all implanted sites. However, more uniform bone formation was observed with the high rhBMP 2 concentration.</p>
		<p>The results of these three subhuman primate defect studies—(a) mandibular resection defects in the middle aged <i>Macaca fascicularis</i> animals (b) mandibular resection defects in <i>Macaca fascicularis</i> animals over 20 years of age, and (c) simulated bilateral clefts in <i>Macaca mulatta</i> animals 1 ½ years of age (comparable with a five-year-old child) were very encouraging.</p> <p>Histomorphometric analysis in all of these investigations indicated that the use of rhBMP-2 in bone repair without the use of bone grafting materials will offer a new method of osseous reconstruction in clinical facial bone defects.</p>
Extraction Socket Augmentation using rhBMP-2/ACS with Dental Implant Placement		
Non-Human Primates		<p>Boyne et al. (1999) demonstrated the ability of rhBMP-2/ACS to regenerate hemimandibulectomy defects in nonhuman primates, and to support installation and functional loading of dental implants. The results from this study suggest the ability of rhBMP-2/ACS-regenerated bone to support dental restoration is superior to that of autogenous bone graft.</p> <p>After the six months of functional loading, the rhBMP-2-induced bone was uniform throughout the defect and of similar density to the bone present at the time of biopsy harvest. In addition, high level of osseointegration (&gt;80%) of the dental implants into the induced bone was observed.</p>

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
Canine		Study investigated the ability of rhBMP-2/ACS-induced bone to support dental implant installation and functional loading. Six (6) 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. In conclusion, rhBMP-2-induced bone allows installation, osseointegration, and long-term functional loading of machined, threaded, titanium dental implants.
		This study concluded that rhBMP-2/ACS has a unique potential to induce alveolar bone formation. Combining rhBMP-2/ACS with space-providing, macro-porous GTR device provides advantages for alveolar bone augmentation in clinically challenging situations such as vertical augmentation of the alveolar ridge. Periodontal regeneration following application of rhBMP-2/ACS is compromised by ankylosis.
		The results of this study demonstrate the benefit of combining rhBMP-2/ACS with a space-providing, macro-porous GBR device for (vertical) alveolar ridge augmentation. The combined technology provides significant advantages over either GBR or rhBMP-2/ACS as stand-alone therapies.
Maxillary Sinus Floor Augmentation using rhBMP-2/ACS		
Caprine		These reports show that surgical implantation of rhBMP-2/ACS in a subantral space results in clinically significant bone augmentation for placement and osseointegration of titanium dental implants.
Rabbit		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 PCBM induces comparable histologic and histometric evidence of bone formation in rabbits.

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
Maxillary Sinus Floor Augmentation using rhBMP-2/ACS with Dental Implant Placement		
Non-Human Primate		<p>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.</p>
Periodontal Defect and Dental Implant Studies		
Canine		<p>At four weeks, rhBMP-2/ACS resulted in three to four times the amount of bone within the defect area than control (ACS or ACS with membrane) defects. In the presence of membranes, rhBMP-2/ACS defects had approximately twice the amount of bone regeneration than control defects; however, the amount of bone regeneration was substantially less than in rhBMP-2/ACS treated defects without membranes. At 12 weeks, the amount of bone defect fill in the rhBMP-2/ACS-treated defects was still greater than the corresponding control defects. The effect of membrane placement was less evident at this time point. Osseointegration was also superior in the rhBMP-2/ACS-treated defects. The amount of bone-to-implant contact was at least twice that of the control implants at both 4 and 12 weeks.</p>
		<p>In the current study, rhBMP-2 induced alveolar ridge augmentation, and dental implant osseointegration were evaluated in critical-size, supra-alveolar, mandibular peri-implant defects in five beagle dogs. The healing interval was 16 weeks. Radiographs were taken at treatment, and at two, four, eight, and 16 weeks. Histometric analysis was completed at sacrifice.</p>
		<p>In summary, surgical implantation of rhBMP-2/ACS resulted in partial bone regeneration of supraalveolar peri-implant defects. Collectively, the radiographic, histologic and histometric analysis suggests that there are no dramatic differences in bone regeneration and osseointegration within this dose interval.</p>

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
		<p>The objective of the study was to characterize, by ultrastructural techniques, tissue reactions following surgical implantation of rhBMP-2/ACS into periodontal defects.</p> <p>rhBMP-2/ACS elicits an osteoinductive process throughout the implant as well as along and onto the instrumented adjacent root surface. Lamellated trabecular bone was the predominant regenerated tissue</p>
		<p>Recombinant human bone morphogenetic protein-2 (rhBMP-2) in an absorbable collagen sponge (ACS) carrier was evaluated as a candidate therapy for periodontal regeneration. The objective of this study was to evaluate regeneration of alveolar bone and cementum, and associated root resorption and ankylosis following surgical implantation of rhBMP-2/ACS in a canine clinical model.</p> <p>Bilateral three-wall intrabony periodontal defects were surgically induced in the premolar teeth region in the maxilla and mandible in eight young adult Korean mongrel dogs</p> <p>Surgical implantation of rhBMP-2/ACS may be used safely to support regeneration of alveolar bone in intrabony periodontal defects without aberrant events such as root resorption or ankylosis complicating the regenerative procedure. rhBMP-2/ACS does not appear to have a significant effect on cementum regeneration and formation of a functional periodontal ligament in this model.</p>
Non-Human Primate		<p>Histometric analysis indicated that rhBMP 2/ACS resulted in 3-fold greater vertical bone gain than controls. Osseointegration between the fundus of the defect and the top surface of the implant was significantly greater in the rhBMP-2/ACS-treated defects. There were no significant differences between maxillary and mandibular defect sites for any histometric parameter.</p>
		<p>The objective of this study was to evaluate bone formation and osseointegration at alveolar dehiscence defects following augmentation of the defect with rhBMP-2/ACS at dental implant installation including transmucosal positioning of the dental implant.</p> <p>The observations in this study suggest that rhBMP-2/ACS may augment the establishment of bone-implant contact in large buccal dehiscence defects with non-submerged immediate dental implants.</p>

**Table XII.I-4: Preclinical Effectiveness in Oral Maxillofacial Indications**

Study Model	Study Title	Summary
		<p>The objective of this study was to evaluate the potential of recombinant human bone morphogenetic protein-2 (rhBMP-2) in an absorbable collagen sponge (ACS) carrier to enhance bone healing following endodontic surgery, and whether bone healing will progress without complications such as ankylosis or root resorption.</p> <p>This study concluded that surgical implantation of rhBMP-2/ACS may be used safely to support regeneration of alveolar bone in bone defects including partially resected root structures such as in endodontic surgery. Aberrant healing events including root resorption or ankylosis do not appear to complicate healing.</p>

### **XII.I.3. Comparability of Bone Induction by rhBMP-2 and Autogenous Bone in Oral Maxillofacial, Spine, and Trauma Indications**

This section summarizes relevant preclinical studies which directly compare the effectiveness of rhBMP-2/ACS to autogenous bone graft at inducing *de novo* bone formation which is similar in quality to native bone in oral maxillofacial, spine, and trauma indications. A summary of these studies is provided in **Table XII.I-5**.

**Table XII.I-5: Comparison of Effectiveness between INFUSE® BONE GRAFT and Autogenous Bone Graft**

Study	Species (n per group)	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. 9/9 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, both indicating favorable long-term response to function.
Maxillary Sinus Floor Augmentation (Wada et al. 2001)	Rabbit	At two weeks postoperative, the rhBMP-2/ACS group showed newly formed bone with no cartilage formation and remnants of ACS toward the center of the implant. In the autograft group, there was a mixture of grafted bone (no osteocytes) and newly formed bone. At four weeks, the rhBMP-2/ACS group bone continued to mature and trabeculae were observed throughout the augmented area. For the autograft group, remnants of old grafted bone was still observed interspersed with newly formed bone. At eight weeks, the healing stage of the grafts were the same between the rhBMP-2/ACS and autograft groups.
Bilateral intertransverse lumbar fusion (Schimandle et al. 1995)	Rabbit	Animal treated with rhBMP-2/ACS had 100% fusion rate while animals treated with autograft had a 42% fusion rate. rhBMP-2/ACS fusions were significantly stronger (p = 0.05) and stiffer (p = 0.03) than the autograft fusions. The histology demonstrated more mature fusions in the rhBMP-2/ACS animals with peripheral corticalization and more advanced remodeling marrow formation as compared to autograft fusions.
Bilateral intertransverse fusion (David et al. 1999)	Dog	All 4 groups treated with rhBMP-2 had 100% fusions as opposed to 33% for autograft-treated animals. All animals completed the study without adverse neurological abnormality.
Cervical Interbody Using Titanium Cage (Zdeblick et al. 1998)	Goat	95% of goats tested with rhBMP-2 fused at 12 weeks as assessed by histological evaluation. Only 45% of autografts fused.
Cervical interbody	Goat	67% of levels treated with rhBMP-2 fused at 12 weeks. 47% of autografts fused.
Cervical interbody with anterior plating	Goat	Radiographic scores higher for autograft than for rhBMP-2. Difference was not statistically significant
Lumbar interbody fusion (Sandhu et al. 2002)	Sheep	All groups had 100% fusion via manual palpation; no difference between groups for mechanical stiffness, interbody height. Histological analysis revealed 37% fusion rate with autograft and 100% fusion for rhBMP-2 group.
Interbody fusion (Hecht et al. 1999)	Non-human primate	At 6 months, all animals treated with rhBMP-2/ACS and one with autograft was fused. The rate of new bone formation and fusion with the use of rhBMP-2/ACS with cortical allograft dowel was far superior to that of autogenous cancellous iliac crest bone graft with cortical allograft bone dowel.

**Table XII.I-5: Comparison of Effectiveness between INFUSE® BONE GRAFT and Autogenous Bone Graft**

Study	Species (n per group)	Results
Interbody fusion with a carbon-composite device.	Sheep	There were no statistically significant differences in fusion rates between the groups; the fusion rate for the rhBMP-2 group was 86% compared to 83% for the animal treated with autograft. Also, there was no statistically significant difference in biomechanical stiffness between these groups, all 3 groups were stiffer than sham treated controls. Mean radiographic score for rhBMP-2/ACS group was slightly higher than those of the other groups, but not statistically different.
Interbody fusion with Titanium Mesh device	Sheep	Radiographic fusion showed no statistical differences between the 3 treatment groups. Biomechanical tests showed no difference between the 2 groups receiving rhBMP-2 but both rhBMP-2 groups had significant increases in extension and tensile loading compared to autograft group. All animals (8/8) treated with rhBMP-2/CRM achieved solid fusion, 5 of 6 animals treated with rhBMP-2/ACS achieved solid fusion while one achieved partial fusion. 3 of 6 animals treated with autograft achieved solid fusion, 2 achieved partial fusion and 1 demonstrated non-fusion.
Radial defect	Canine	Little or no bone formation was observed in defects treated with buffer/ACS alone, which went on to radiographic and histologic nonunion. Radiographic union was achieved in all limbs treated with rhBMP-2 and total energy to torsional failure was equal or superior to autologous bone graft.
Radial defect	Canine	All autograft- and rhBMP-2/ACS-treated radii achieved radiographic union. rhBMP-2/ACS-induced bone integrated more rapidly with the surrounding cortical bone than did autograft-induced bone. Biomechanical testing demonstrated that the rhBMP-2/ACS groups tended to be stronger than the ABG groups.

## XII.I.4. Pharmacokinetics

### XII.I.4.a. Intravenous Pharmacokinetic Studies

Although rhBMP-2 is intended to be delivered with a carrier as an implant, pharmacokinetic results obtained from intravenous (IV) dosing provide a means to evaluate the extent and duration of systemic exposure of rhBMP-2. Studies were conducted to characterize the pharmacokinetics of rhBMP-2 in the blood of rats and monkeys. A study conducted in juvenile and adult Sprague-Dawley rats revealed that juvenile rats, like adult rats, cleared rhBMP-2 rapidly. Results also showed a lower maximal concentration, higher clearance and a larger initial volume of distribution for rhBMP-2 in juvenile rats as compared to adult rats. As a result of these pharmacokinetic characteristics, systemic presence of rhBMP-2 in the circulation was found to be minimal after IV dosing. Relevant findings are summarized in **Table XII.I-6** below.

**Table XII.I-6: Pharmacokinetic Studies**

Study Type/ Species/ Strain	Relevant Findings
	Clearance of <sup>125</sup> I-rhBMP-2 was rapid and biexponential
	Clearance of <sup>125</sup> I-rhBMP-2 was rapid and biexponential
	Rapid localization to liver with metabolism and excretion into urine. Biphasic disposition was observed.
	<sup>125</sup> I-rhBMP-2 rapidly distributed to the highly perfused tissues
	Clearance of <sup>131</sup> I-rhBMP-2 was rapid and biexponential in both juvenile and adult rats as assessed by serum acid precipitable radioactivity and by ELISA.
	Clearance of <sup>125</sup> I rhBMP-2 was rapid and biexponential

#### **XII.I.4.b. Local Retention Kinetics Studies**

Local retention kinetics are well understood using the ACS sponge. Rat ectopic studies indicate that rhBMP-2 protein retention is a relevant factor for *in vivo* activity, and that local retention is not affected by most product and handling variables such as diluent formulation, collagenase sensitivity, the percent incorporation of rhBMP-2 in the carrier, or the amount of time the rhBMP-2 protein is allowed to soak onto the ACS prior to implantation. A rat femoral overlay study showed that systemic rhBMP-2 exposure was minimal. These studies demonstrate that the ACS carrier adequately retains rhBMP-2 protein at the desired site, facilitating bone formation in the models tested.

#### **XII.I.5. Previously Reported Studies**

There are additional published studies, not included in the PMA submission which indicate that rhBMP-2/ACS can heal calvarial defects, repair cleft palate defects, regenerate periodontal tissues, repair segmental long bone defects, promote integration and healing of femoral allografts, accelerate fracture repair, create successful inter-transverse process spinal fusions, result in inter-vertebral body fusion in conjunction with spinal fusion cages, and accelerate the bone consolidation phase in a distraction osteogenesis procedure. Thus, the ability of rhBMP-2/ACS to induce bone, and its clinical applicability, are not limited to preservation and augmentation of the alveolar ridge.

Other studies, which have been previously submitted to FDA, have shown rhBMP-2 to be osteoinductive regardless of the carrier matrix and model and that the bone induction activity of rhBMP-2 was not inhibited by agents which typically inhibit bone formation.

### **XII.I.6. Stability Testing**

Testing was performed to demonstrate the stability over time of the rhBMP-2 active drug substance (bulk rhBMP-2), the lyophilized vialled rhBMP-2 protein (4.2 mg and 12 mg dosage strengths), the ACS matrix, and the assembled kit. In addition, testing was done to show that the packaging adequately protects the product during shipping. INFUSE<sup>®</sup> BONE GRAFT components and the final product meet the requirements for stability.

### **XII.I.7. Preclinical Conclusions**

In summary, the safety (toxicology and pharmacokinetics) and bone-forming capacity (effectiveness) of INFUSE<sup>®</sup> BONE GRAFT have been extensively investigated and are well understood. The non-clinical safety of systemically delivered rhBMP-2 and locally delivered rhBMP-2 has been extensively studied and no toxicities have been identified in these studies. The disposition of rhBMP-2 and rhBMP-2/ACS is characterized by slow release of rhBMP-2 from the implantation site and rapid systemic clearance. This profile results in minimal systemic exposure to rhBMP-2. Application of rhBMP-2 results in the induction of normal bone locally at the site of implantation. This process includes the migration of mesenchymal cells into the site, their proliferation and apparent differentiation into bone-forming cells. The bone induced by rhBMP-2 remodels and assumes the structure appropriate to its location and function, as would be expected from host bone.

Safety studies resulted in the following findings. There were no treatment-related toxicities observed. There was no mortality or evidence of systemic toxicity, cell lysis or toxicity, hemolysis, or cellular mutagenicity. rhBMP-2 did not show any growth potentiating activity and that it actually showed growth

inhibition of several carcinoma-derived tumors. Maternal and paternal mating performance and reproductive parameters were not affected by treatment. There was no evidence of maternal toxicity, embryolethality, fetotoxicity, or teratogenicity.

Efficacy studies have demonstrated the ability of rhBMP-2/ACS to grow clinically relevant bone across a wide range of animal models and oral maxillofacial implant locations. Studies show that INFUSE<sup>®</sup> BONE GRAFT grows bone that is structurally and biologically the same as native bone. In studies comparing the effectiveness of INFUSE<sup>®</sup> BONE GRAFT with autogenous bone graft, INFUSE<sup>®</sup> BONE GRAFT meets or exceeds the performance of autograft.

## **XII.J. Clinical Studies**

### **XII.J.1. Overview**

A clear clinical need exists to provide an alternative to the current standard of treatment for oral maxillofacial defects. At present, autogenous bone graft is used to repair these defects with good success in a large percentage of cases. However, autogenous bone graft is associated with multiple risks largely due to the bone harvest procedure. INFUSE<sup>®</sup> 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<sup>®</sup> Bone Graft has been previously approved in two PMA applications for 1) spinal fusion procedures (P000058) in July, 2002 and 2) treating acute, open tibial fractures (P000054) in April, 2004. The current PMA is seeking another indication for this currently approved product:

This PMA requests a new indication for this currently approved product:

- 
- 
- 
- 

IDE clinical studies to support these new indications consist of three sinus floor augmentation studies (pilot, dosing and pivotal) and two extraction socket augmentation studies (pilot and dosing). The oral maxillofacial study series spanned nearly 10 years from the first study subject enrolled [REDACTED]

[REDACTED] to the last follow-up in the last study [REDACTED]

[REDACTED] 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. The five studies are summarized in Table III.A-1, Sinus Floor Augmentation Studies and III.A-2, Extraction Socket Augmentation Studies below.

Table III.A-1: Sinus Floor Augmentation Study Summaries [redacted]

Study Description	Pilot Study [redacted]		Dosing Study [redacted]	Pivotal Study [redacted]
	S [redacted]	Long-Term [redacted]		
Number of Subjects	[redacted] rhBMP 2/ACS [redacted] mg/ml	(same subjects [redacted])	[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, plus bone graft	Multi-center trial (21 centers) with subjects randomized to rhBMP-2/ACS and bone graft
Follow-Up	16 weeks post-surgery	36 months post-prosthesis	36 months post-prosthesis	24 months post-prosthesis

Table III.A-2: Extraction Socket Augmentation Study Summaries [redacted]

Study Description	Pilot Study [redacted]		Dosing Study [redacted]
	Short-Term [redacted]	Long-Term [redacted]	
Number of Subjects	rhBM [redacted] mg/ml [redacted]	(same subjects as [redacted])	[redacted]
Study Design	Open-label, non-randomized, two-center study	Long-term follow-up [redacted] subjects enrolled in [redacted]	Randomized multi-center trial (8 centers) of two dosage levels, plus ACS alone and no treatment
Follow-Up	16 weeks post-surgery	24 months post-surgery	24 months post-prosthesis

Due to similarities, IDE clinical evidence from the oral maxillofacial bone grafting in sinus augmentation and extraction socket augmentation implant location and procedures apply to the cystic defect repair and vertical and horizontal alveolar

augmentation implant location and procedures. The clinical effectiveness of these latter procedures is further demonstrated by case studies.

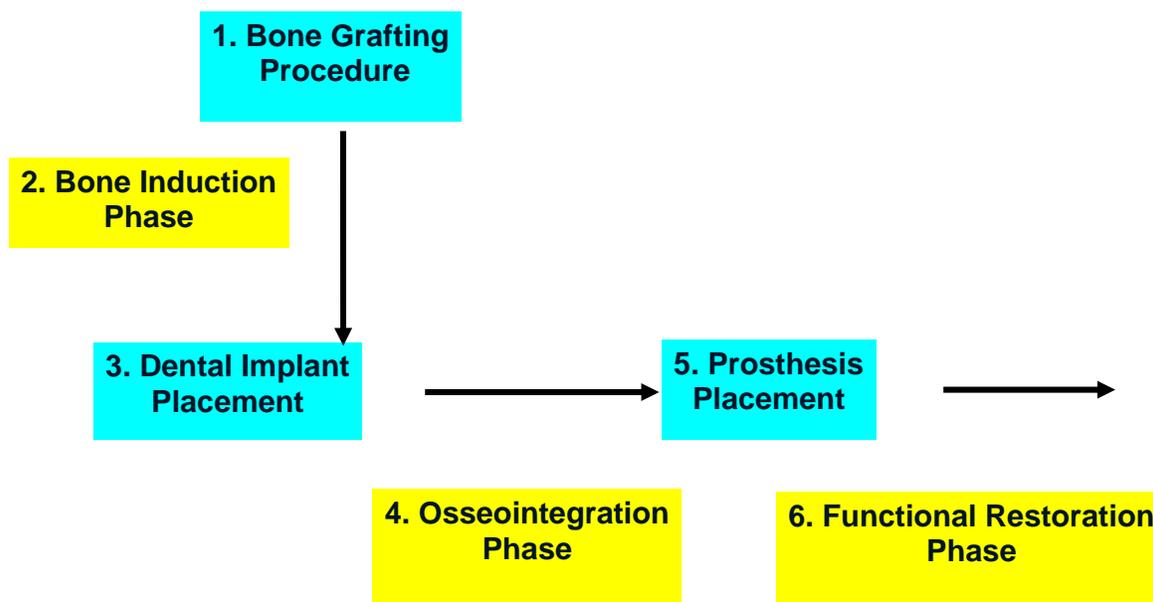
### Safety

Based on the data from five studies, the incidence of adverse events reported in [redacted] subjects randomized to bone graft was statistically significantly higher than that reported for [redacted] rhBMP-2/ACS subjects. This remained true when the adverse event rate for bone graft subjects were compared to adverse events for either the entire rhBMP-2/ACS cohort [redacted] or the 1.5 mg/ml commercial concentration cohort [redacted]. Bone graft subjects experienced significantly more edema, infection, pain, nausea, hyperglycemia, arthralgia (sensory loss), abnormal gait, hypesthesia, and rash than rhBMP-2/ACS subjects. None of the rhBMP-2/ACS subjects reported abnormal gait or gait disturbance compared to 41% of bone graft subjects reporting this adverse event.

### **XII.J.2. Study Design/Methods**

The [redacted] 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 [redacted] as shown in the Figure below.

Figure XII.J-1: Subject Treatment Course Across all [redacted] Studies



In all studies, safety was monitored by oral examinations, radiographs, recording of adverse events, collection of core bone biopsy specimens from the treatment site to evaluate the histology of the newly induced bone, and collection of blood samples to measure serum chemistries, hematology, and antibody formation to the study treatment.

#### **XII.J.2.a. Surgery and Evaluation Procedures**

Subjects enrolled across the [redacted] 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.

### **XII.J.2.b. Combined Demographics – All Studies**

A variety of study treatments were applied during the conduct of the five studies. This section describes the subject population for all study treatments across all studies. All subjects who received rhBMP-2/ACS treatment, regardless of the concentration of rhBMP-2, along with subjects who received bone graft provide data for the safety analysis.

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, race, and alcohol use were categorized for all study subjects.

**Table XII.J-1: Demographics**

<b>Characteristic</b>	<b>AV Ridge Pilot 1.5 mg/ml</b>	<b>Sinus [redacted] 1.5 mg/ml</b>	<b>Sinus Pivotal 1.5 mg/ml</b>	<b>Total rhBMP-2/ACS 1.5 mg/ml</b>
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%

### **XII.J.2.c. Subject Disposition**

Among subjects across all treatment groups, [redacted] withdrew or were lost to follow-up. All of the studies included in support of this PMA application had more than 85% study compliance.

One death was reported during the conduct of the Extraction Socket Augmentation Dosing study. The death was judged not to be related to the study treatment. Subject withdrawals were both voluntary and withdrawn based on missed follow-ups. Per protocol, subjects who failed to complete their scheduled follow-up were withdrawn. Across the three studies, nine subjects withdrew. Statistical analyses in this PMA are performed on an intent-to-treat basis. Therefore, subjects were analyzed in the groups to which they were assigned, not the groups in which they were treated.

#### **XII.J.2.c.1. Treatments Administered**

For the subjects analyzed for effectiveness (1.5 mg/ml concentration), subjects received treatments; subjects 54% were treated at one anatomic site and 46% were treated at multiple anatomic sites.

### **XII.J.3. Results**

#### **XII.J.4. Sinus Augmentation**

##### **XII.J.4.a. Overview**

Demonstration of the effectiveness for the sinus floor augmentation indication is based on the combined data from the sinus floor pivotal study [redacted] and the sinus floor dosing study [redacted]. These data are evaluated in accordance with the endpoints and methodology from the sinus floor pivotal study protocol.

##### **XII.J.4.b. Pivotal Study Endpoints**

The endpoints, as defined in the pivotal study [redacted] protocol, are:

Primary endpoints:

1. To estimate the effectiveness of rhBMP-2/ACS [redacted]  
[redacted]

supports dental implant borne restoration after [redacted]  
[redacted]

2. [redacted] us bone graft in [redacted]  
[redacted]

Secondary endpoints:

1. To compare the effectiveness of rhBMP-2/ACS to autogenous bone graft

[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]  
[redacted] following treatment with rhBMP-2/ACS or autogenous bone graft,  
and [redacted]

4. To estimate the use of medical resources associated with maxillary sinus floor augmentation procedures.

**XII.J.4.c. Results of Primary Endpoints**

Primary Objective #1:

To estimate the effectiveness of rhBMP-2/ACS [redacted]

[redacted]

**Table III [redacted] Effectiveness Endpoint Results Sinus Augmentation Studies [redacted] with [redacted] rhBMP-2/ACS (ITT Populati**

Subjects	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] (88.2)	[redacted] (81.7)	[redacted] (82.8)
[redacted]	[redacted]	[redacted] (79.3)	[redacted] (79.8)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] (82.4)	[redacted] (79.0)	[redacted] (79.6)
[redacted]	[redacted] (56.6, 96.2)	[redacted] (5, 87.3)	[redacted] (70.3, 87.1)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] (82.4)	[redacted] (78.8)	[redacted] (79.4)
[redacted]	[redacted] (56.6, 96.2)	[redacted] (68.2, 87.1)	[redacted] (70.0, 87.0)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] (82.4)	[redacted] (77.9)	[redacted] (78.7)
[redacted]	[redacted] (.6, 96.2)	[redacted] (67.0, 86.6)	[redacted] (9.1, 86.5)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] (82.4)	[redacted] (76.0)	[redacted] (77.2)
[redacted]	[redacted]	[redacted] (.7, 85.1)	[redacted] (.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.

The combined data from the [redacted] sinus augmentation studies resulted in 80% success with a lower confidence interval of 70% which exceeds the primary effectiveness criteria of at least 73% [redacted] prosthesis placement with a lower confidence interval of greater than 60%.

**Primary Objective #2:**

To evaluate the safety of rhBMP-2/ACS and autogenous bone graft in [redacted]  
 [redacted]

Safety Results are summarized below.

**XII.J.4.d. Results of Secondary Endpoints**

Secondary Objective #1:

*To compare the effectiveness of rhBMP-2/ACS to autogenous bone graft* [redacted]

[redacted]

[redacted]

The analysis is presented below by patient. All analyses used the rules for patient accounting as identified in the pivotal study [redacted] protocol.

Table III.A-5 [redacted] Number (%) of Subjects Who Received Prosthesis (Functionally Loaded) and Maintained Functional Loading (ITT Population)

Subjects	Combined aft	rhBMP-	P-Value <sup>a,f</sup>
	[red box] (95.6)	[red box] (82.8)	
	[red box] 93.4)	[red box] (79.8)	
	[red box] (89.9) [red box] .7, 95.3)	[red box] (79.6) [red box] .3, 87.1)	[red box]
	[red box] (88.5) [red box] .9, 94.4)	[red box] 79.4) [red box] (70.0, 87.0)	[red box]
	[red box] (87.4) [red box] .5, 93.5)	[red box] (78.7) [red box] (69.1, 86.5)	[red box]
	[red box] 87.4) [red box] .5, 93.5)	[red box] (77.2) [red box] .3, 85.3)	[red box]

Source: pe\_endpoint\_analysis.sas

- a. P-value is from Fisher's exact test. \* 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.

#### XII.J.4.e. Results of Other Analyses

The connection between growing bone and success in implantation was assessed. The sinus study gave a breakdown into the subjects in whom the DIP was successful, and those in whom it was not. Summary statistics of these two groups are as follows. Also shown is the *t* value testing for difference between the two groups, and its P value.

Table III.A-6 Bone Height in Successful and Unsuccessful Sinus Patients

	Success	
N		
mean		
s.d.		
t		
P		

Source: defic\_bone\_height.sas

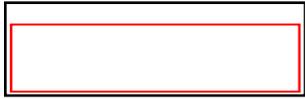
The difference between the two groups is highly significant. The subjects whose implants were successful had an average bone height gain of [redacted] those who were not implanted successfully averaged a bone height gain of only [redacted]

Based on this analysis, it is concluded that the ability to grow bone is predictive of the ability of the new bone to support dental implants and to support dental prostheses which remain functionally loaded as well.

**XII.J.4.f. Summary**

Based on the clinical evidence, INFUSE® Bone Graft is concluded to be effective in growing bone in the sinus cavity which allows placement of dental implants and subsequent prosthesis placement and functional restoration. Specifically:

- The combined data from the two sinus augmentation studies resulted in 80% success with a lower confidence interval of 70% which exceeds the primary effectiveness criteria which required at [redacted] with a lower confidence interval of greater than 60%.
- The combined data from the two sinus augmentation studies shows no statistical difference from that of autogenous bone graft in the ability to place dental implants, [redacted]



- Analysis of the clinical data shows a statistical relationship between the ability to grow bone in the sinus and the ability to place dental implants.

#### **XII.J.5. Extraction Socket**

The effectiveness of the extraction socket augm [redacted] procedure is demonstrated by the results of the dosing study [redacted] which was conducted to study the extraction socket augmentation procedure. This clinical evidence is enhanced through clinical similarity between the extraction socket augmentation and sinus augmentation implant location and procedures

##### **XII.J.5.a. Endpoints**

For the purpose of this analysis, the applicable endpoint from the [redacted] trial was the demonstration that treatment with rhBMP-2/ACS leads to bone growth, and that the bone resulting from the treatment allows the successful insertion of dental implants without additional augmentation. Secondary endpoints were assessed by the success in subsequent placement of prosthesis, and in functional loading of the prosthesis.

Primary endpoints:

1. The increase or loss in 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 in
- 3. The rate of success in
- 4. The rate of success in
- 5. The rate of success in

**XII.J.5.b. Results of Primary Endpoints**

Change in Bone Height and Width

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

- Bone height
- Bone width at position  $\frac{1}{4}$  (the crest of the extraction socket)
- Bone width at position  $\frac{1}{2}$  (the midpoint of the extraction socket)
- Bone width at position  $\frac{3}{4}$  (the base of the extraction socket)

The summary tables show the statistics of each group. Also shown is the 'treatment effect': the difference in response between the control group and the 1.5 mg/ml group, and its standard error. Finally, the tables show the P value testing this difference.

Table XII.J-8 Change in Bone Height

	No Treatment	rhBMP-2/ACS 0.00 mg/mL	rhBMP-2/ACS 0.75 mg/mL	rhBMP-2/ACS 1.50 mg/mL
N				
Mean	-1.17	-1.00	62	02
Standard deviation	1.23	1.4	1.39	1.20
Treatment effect				
Standard error		0.437		
95% CI for difference	(-2.08, -0.23)	(-1.95, -0.01)		
P value				

Source:

Table XII.J-9 Change in Bone Width: ¼ Position

	No Treatment	rhBMP-2/ACS	rhBMP-2/ACS	rhBMP-2/ACS g/mL
N				
Mean				
Standard deviation				
Treatment effect				
Standard error	0.689	0.712		
95% CI for difference	(-4.38, -1.02)	(-4.18, -0.71)		
P value				

Source:

Table XII.J-10 Change in Bone Width: ½ Position

	No Treatment	rhBMP-2/ACS 00 mg/mL	rhBMP-2/ACS 5 mg/mL	rhBMP-2/ACS 1.50 mg/mL
N				
Mean				
Standard deviation			1.38	2.48
Treatment effect				
Standard error	0.675	0.697		
95% CI for difference	(-4.04, -0.66)	(-3.92, -0.43)		
P value				

Source:

Table XII.J-11 Change in Bone Width: ¾ Position

	No Treatment	rhBMP-2/ACS .00 mg/mL	rhBMP-2/ACS .75 mg/mL	rhBMP-2/ACS 1.50 mg/mL
N				
Mean				
Standard deviation				
Treatment effect				
Standard error	0.505	0.521		
95% CI for difference	(-2.12, 0.40)	(-1.99, 0.60)		
P value				

Source: [redacted]

In all four measurements, the No treatment and ACS only groups yield similar changes in bone dimension from visit 1 to visit 8. Both No Treatment and ACS only are significantly less effective than 1.5 mg/mL BMP in terms of the change in bone height, and in both width at ½ and ¾ measurement points.

Successful Dental Implant Placement

The other primary endpoint is success in dental implant placement without further augmentation. Cross-tabulation of the patients at this point gave the results in Table III.A-12:

Table XII.J-12 Dental Implant Placement without Augmentation

	No	rhBMP-2/ACS	1.5mg/ml	
Needed augmentation				
Failed				
Withdrew				
Succeeded				

[redacted]

**XII.J.5.c. Results of Secondary Endpoints**

Table XII.J-15 Prosthesis Placement without Augmentation

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

Table XII.J-16

[Redacted]

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

Table XII.J-17

[Redacted]

		rhBMP-2/ACS	1.5 mg/ml	
Needed augmentation				
Failed				
Missed Visit				
Withdrew				
Succeeded				
Total				

Source

[Redacted]

Table III.A-18 shows the results at [redacted]

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

Source: [redacted]

Table III.A-19 shows the results at [redacted]

	No treatment	rhBMP-2/ACS 0.00 mg/mL	1.5 mg/m rhBMP-2/A [redacted]	Total
Needed augmentation				
Failed				
Missed Visit				
Withdrew				
Succeeded				
Total				

Source: [redacted]

**XII.J.5.d. Results of Other Analyses**

Bone Growth as a Predictor of Successful Dental Implant

The accepted mode of action leading to successful implants is that rhBMP-2/ACS leads to bone growth, and that greater bone growth leads to more successful implants. The data clearly demonstrate the first part of this connection; it is of interest to examine the second part.

This assessment was made by categorizing all patients in the [redacted] trial by their success or failure in DIP, and then studying the changes in bone dimensions between baseline and the four-month follow up observation. The success and failures were then compared by unequal-variance two-sample *t* tests. This gave the following results in Table IV.B-13.

**Table IV.B-13 Success Predicted by Bone Growth**

Change in		DIP		t	P
		Failure	Success		
Bone height					
width ¼					
width ½					
width ¾					

Source:

These tests show strong relationships between success in dental implant placement in bone height and width. Calculations are provided

Improved bone height and improved bone width at the extraction socket crest were strongly associated with successful placement of the implant. The gain in bone at the midpoint of the extraction socket was modestly significant. There was no perceptible association between implant success and bone growth at the base of the extraction socket.

*Prosthesis placement*

The successful patients showed significantly more growth in bone width at the crest and midpoint than was seen in the failures. There were no significant differences in width at the base of the extraction socket. The Success and Missing groups were indistinguishable on all measures, but

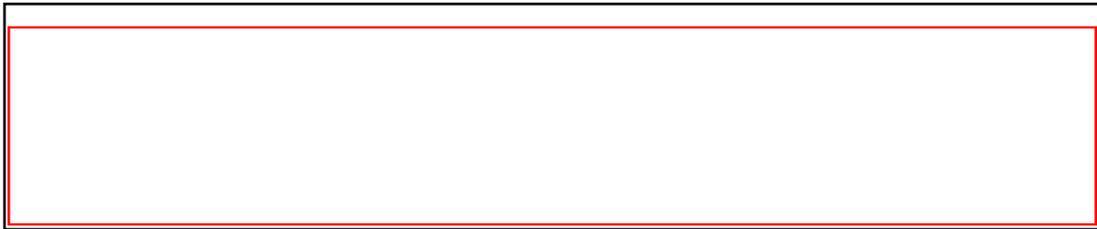
the Missing had significantly more gain in bone height than did the Failures.

*Functional loading*

The

showed the same results:

- The Successes and Missing were statistically indistinguishable on all measures
- The Successes were significantly higher than the Failures in bone width at the crest and midpoint of the extraction socket
- No differences were seen at the base of the extraction socket
- The difference between Success and Failure in bone height was just short of statistical significance at all the secondary endpoints



**XII.J.5.e. Comparability with Sinus Augmentation Procedure**

The extraction socket is similar to the sinus augmentation procedure in that both require augmentation through bone grafting. In addition, both sites are in the oral maxillofacial area. Although the extraction site represents a bony defect and the maxillary sinus site is a natural defect, both sites afford protection of the graft from excessive peripheral soft tissue pressures and both sites only include augmentation by the osseoinductive rhBMP-2/ACS material; thus, the results from the sinus augmentation can be used to support the indication at the extraction site.

Although both sites are similar with regard to the requirements for bone augmentation, they are different in that the sinus augmentation site has no bone (a sinus cavity) while in the extraction socket there is some bone that was appointed with the tooth root. The amount of required bone augmentation is also less for the extraction socket augmentation. However, in order to support dental implants, it is critical that bone height and width are preserved.

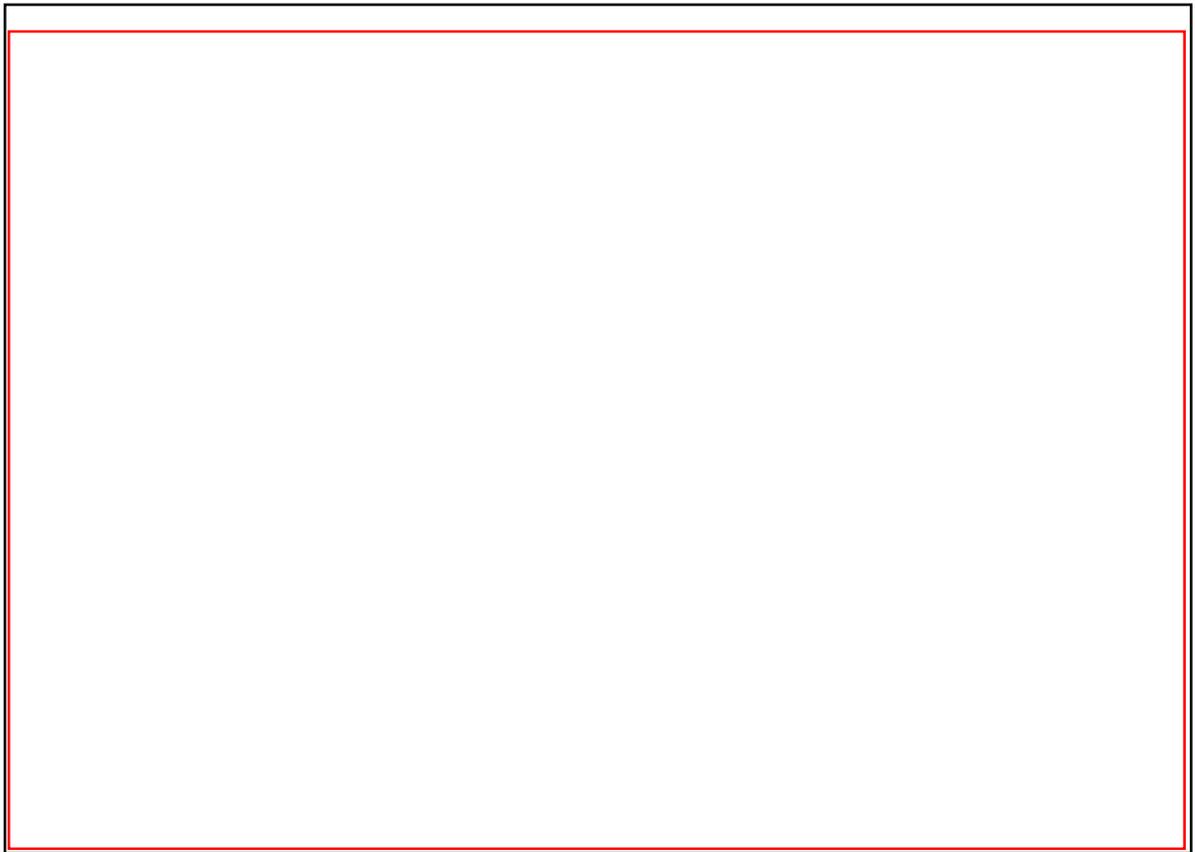
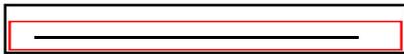
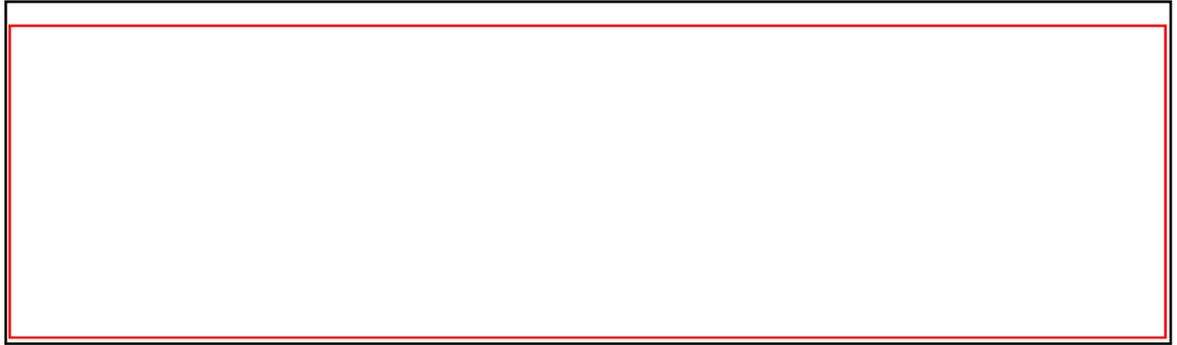
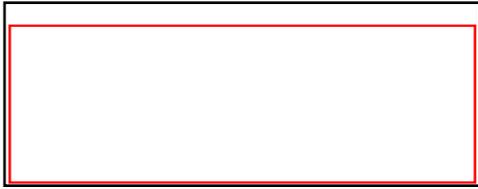
Based on the comparability of the extraction socket augmentation procedure to the sinus augmentation procedure, the results of the sinus augmentation clinical trial can be used to support the clinical effectiveness of INFUSE<sup>®</sup> Bone Graft in the extraction socket augmentation procedure.

**XII.J.5.f.** Conclusion

Based on the clinical evidence, INFUSE<sup>®</sup> Bone Graft is effective in growing bone in an extraction socket which allows placement of dental restoration and particularly implants and subsequent prosthesis placement and functional restoration.

**XII.J.6.**

**XII.J.6.a.**



**XII.J.6.b.**

[Redacted]

[Redacted]

[Redacted]

**XII.J.6.c.**

[Redacted]

[Redacted]

[Redacted]

**XII.J.7.**

○

[Redacted]

**XII.J.8.**

[Redacted]

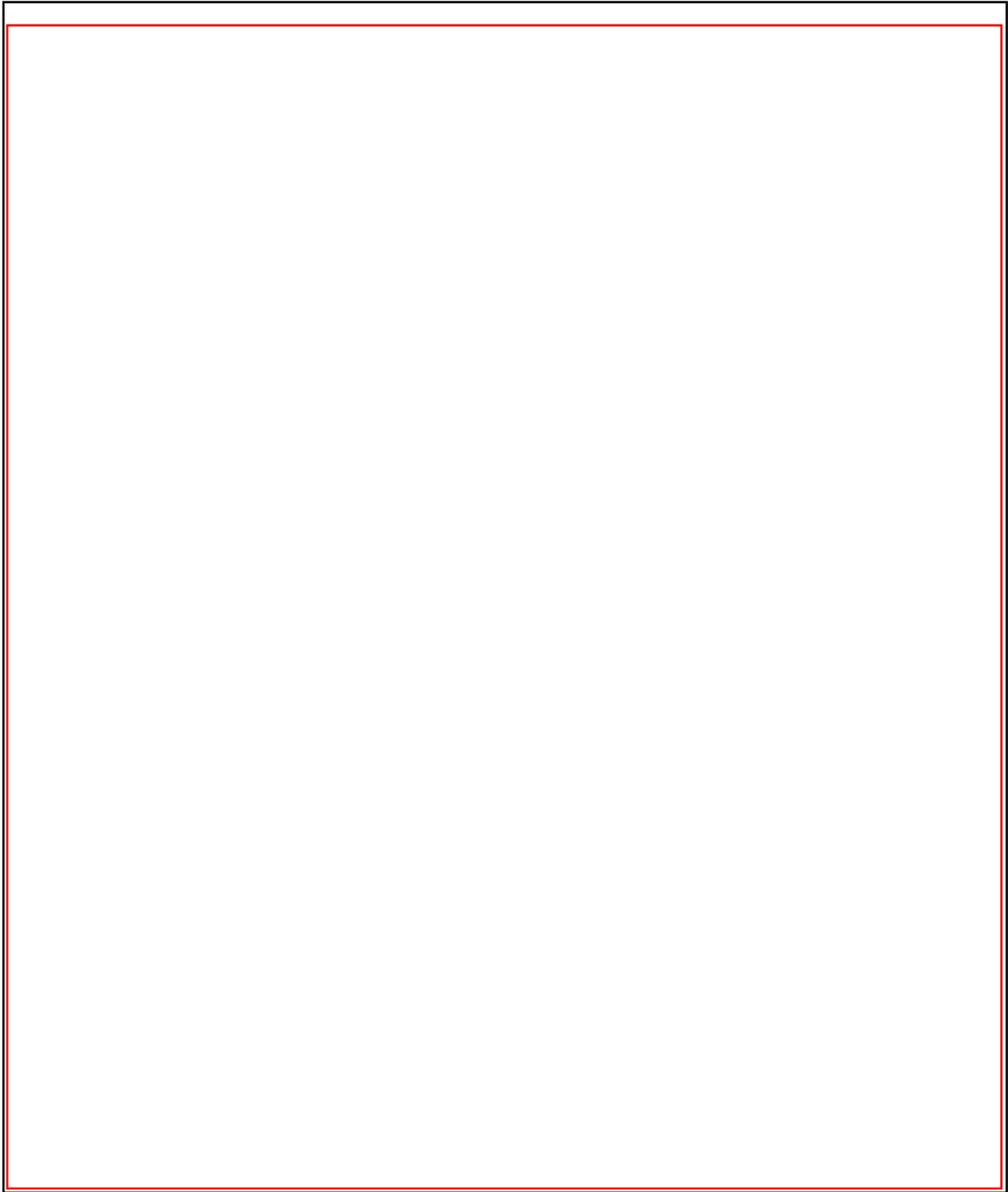
**XII.J.8.a.**

[Redacted]

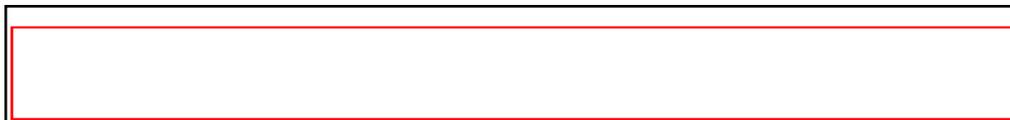
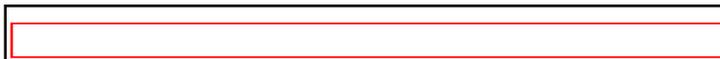
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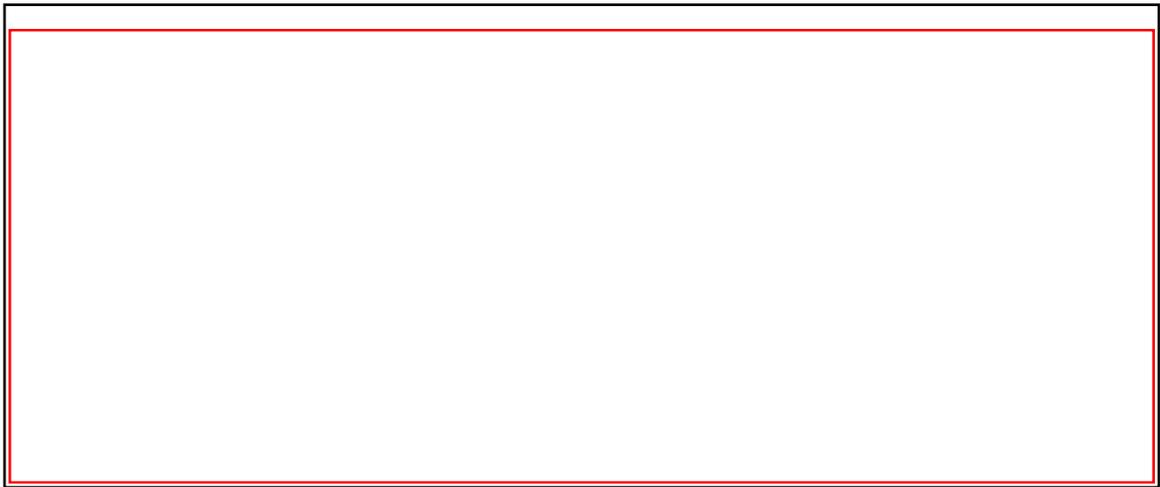
[Redacted]

[Redacted]

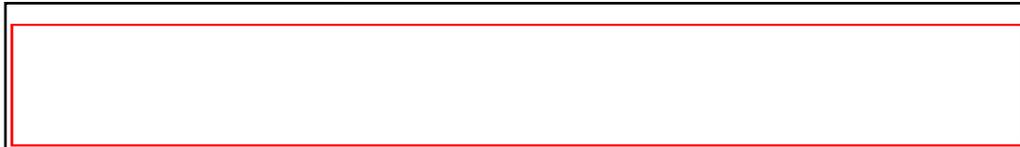


**XII.J.8.b.**





**XII.J.9.**



**XII.J.9.a.1. Secondary Effectiveness Results**

The following secondary endpoint was also used to assess the effectiveness of rhBMP-2/ACS for use in oral maxillofacial bone grafting procedures:

- Following treatment with rhBMP-2/ACS in oral maxillofacial bone, evidence of viable bone is observed via histology, bone density and CT scan

Across three studies in the 1.5 mg/ml treatment group, all but one subject developed measurable bone observable on CT scan. Histology and bone density data demonstrated the bone induced by rhBMP-2/ACS is biologically and structurally normal and is equivalent to the adjacent native bone density by six months post-prosthesis. In addition, 90% of subjects remained functionally loaded through 24-months post-prosthesis placement. This demonstrates that not only was the rhBMP-2/ACS effective in inducing bone formation sufficient for dental implant, it also

demonstrated clinical utility in that the dental implant remained functionally loaded.

**XII.J.9.b. Safety Results**

All subjects who were treated with any concentration of rhBMP-2 were included in the analysis. IDEs included Maxillary Sinus Floor Augmentation Studies [redacted] and Alveolar Ridge Augmentation/Preservation Studies [redacted]. The data were analyzed to provide a meaningful safety profile. Results were evaluated by study indication, concentration of rhBMP-2/ACS and comparison of the adverse events associated with the rhBMP-2/ACS procedure to the similar procedure using bone graft. This comparison provides a clear assessment of the risk profile of rhBMP-2/ACS.

A total of [redacted] subjects were enrolled across the [redacted] studies. [redacted] subjects received one of three concentrations of rhBMP-2/ACS. [redacted] 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 ([redacted] subjects) and a placebo consisting of Absorbable Collagen Sponge (ACS) alone, the carrier for rhBMP-2 ([redacted] subjects).

The analysis was performed three different ways: 1) for all rhBMP-2/ACS subjects [redacted] compared to the group of subjects from [redacted] [redacted] who received bone graft as a control [redacted] [redacted]

[redacted]

Based on the data from [ ] studies, the incidence of adverse events reported in [ ] subjects randomized to bone graft was statistically significantly higher than that reported for [ ] rhBMP-2/ACS subjects. This remained true whether the adverse event rate for bone graft subjects were compared to adverse events for the entire rhBMP-2/ACS cohort [ ] or the [ ] commercial concentration cohort [ ] alone.

At the commercial concentration, among frequently reported AEs, bone graft subjects reported significantly more edema, infection, pain, nausea, hyperglycemia, arthralgia (sensory loss), abnormal gait, hypesthesia, and rash. None of the rhBMP-2/ACS subjects reported abnormal gait or gait disturbance compared to 41% of bone graft subjects.

For the combined studies, the number and percentage of subjects with frequent adverse events (occurring in  $\geq 10\%$  of the subjects) by body system, COSTART terms and combined concentrations throughout the study period are presented in below.

Table XII.J-2: Frequent Adverse Event System, and COSTART Term - [REDACTED] Body			
Body System COSTART Term	Sinus Studies	AV Ridge	All rhBMP-2/ ACS
	n (%)	n (%)	n (%)
Subjects with an adverse event	[REDACTED]	[REDACTED]	[REDACTED]
<b>BODY AS A WHOLE</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HEADACHE	18 (14.0)	[REDACTED]	[REDACTED]
INFECTION	36 (27.9)	[REDACTED]	[REDACTED]
PAIN	28 (21.7)	2 (3.6)	30 (16.3)
<b>DIGESTIVE SYSTEM</b>			
[REDACTED]	76 (58.9)	37 (67.3)	[REDACTED]
ORAL ERYTHEMA	[REDACTED]	29 (52.7)	[REDACTED]
MOUTH PAIN	115 (89.1)	44 (80.0)	[REDACTED]
<b>HEMIC AND LYMPHATIC SYSTEM</b>			
ECCHYMOSIS	25 (19.4)	4 (7.3)	29 (15.8)
<b>MUSCULO-SKELETAL SYSTEM</b>			
SORDER	[REDACTED]	2 (3.6)	21 (11.4)

Source [REDACTED]

For the combined sinus and AV ridge studies, the most frequently reported adverse events in subjects treated with rhBMP-2/ACS were mouth pain

[REDACTED] oral erythema [REDACTED] and general infection [REDACTED]. These adverse events are not unusual for this type of surgical procedure.

Overall, the concentration of rhBMP-2/ACS received resulted in little difference in the adverse events experienced by subjects; the majority of subjects experienced mouth pain, facial and/or oral edema, and oral erythema. These adverse events are consistent with the type of surgical procedure performed, e.g., maxillary sinus floor augmentation, dental implant, abutment placement, and are not considered unusual.

### **XII.J.9.b.1.1. Comparison to Bone Graft**

#### **XII.J.9.b.2. All Concentrations of rhBMP-2/ACS Compared to 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

The number and percentage of subjects with frequent adverse events (occurring in at least  $\geq 10\%$  of subjects) by treatment group, body system

The number and percentage of subjects with frequent adverse events (occurring in at least  $\geq 10\%$  of the study subjects) by treatment group, body system and COSTART term for the entire study period are presented in .

**Table XII.J-3: Number of Subjects with Frequent Adverse Events (>10% of Body System, and COSTART Term – Comparing**

Body System COSTART Term	All 1.5 mg/ml rhBMP-2/ACS Subjects	Bone Graft	P Value <sup>a</sup> rhBMP-2/ACS vs Bone Graft
	n (%)	n (%)	
<b>BODY AS A WHOLE</b>			
EDEMA	[redacted]	[redacted]	[redacted]
HEADACHE	[redacted]	[redacted]	[redacted]
INFECTION	[redacted]	[redacted]	[redacted]
PAIN	30 (16.3)	[redacted]	[redacted]
<b>DIGESTIVE SYSTEM</b>			
ORAL ERYTHEMA	[redacted]	[redacted]	[redacted]
MOUTH PAIN	[redacted]	[redacted]	[redacted]
<b>HEMIC AND LYMPHATIC SYSTEM</b>			
ECCHYMOSIS	[redacted]	21 (23.1)	[redacted]
<b>MUSCULO-SKELETAL SYSTEM</b>			
ARTHRALGIA	16 (8.7)	24 (26.4)	[redacted]
BONE DISORDER	21 (11.4)	11 (12.1)	[redacted]
<b>NERVOUS SYSTEM</b>			
ABNORMAL GAIT	0 (0.0)	[redacted]	[redacted]
<b>RESPIRATORY SYSTEM</b>			
SINUSITIS	[redacted]	15 (16.5)	[redacted]
<b>SKIN AND APPENDAGES</b>			
RASH	11 (6.0)	34 (37.4)	[redacted]

Source: [redacted]

Overall, the most frequent adverse events reported for both the rhBMP-2/ACS treatment group and the bone graft treatment group were: mouth pain [redacted] and [redacted], respectively. [redacted] and oral erythema [redacted], respectively.

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%); edema (37.4% vs. 6.5%); rash (erythema)

(37.4% vs. 6%) and arthralgia (26.4 vs. 8.7%) compared to those in the rhBMP-2/ACS 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 rhBMP-2/ACS treatment group experienced significantly fewer adverse events than the bone graft treatment group.

#### **XII.J.9.b.2.1. 1.5 mg/ml Concentration of rhBMP-2/ACS Compared to Bone Graft**

Of subjects who received rhBMP-2/ACS, subjects from the sinus studies and AV ridge 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 .

**Table XII.J-4: Frequent Adverse Events (≥10% of Subjects) by Body System and COSTART Term – Comparing 1.5 mg/ml rhBMP-2/ACS to Bone Graft Subjects**

Body System COSTART Term	All 1.5 mg/ml rhBMP-2/ACS Subjects	Bone Graft	P Value <sup>a</sup> rhBMP-2/ACS vs Bone Graft
	n (%)	n (%)	
<b>BODY AS A WHOLE</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
INFECTION	30 (25.0)	39 (42.9)	[REDACTED]
PAIN	26 (21.7)	46 (50.5)	[REDACTED]
<b>DIG</b>			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ORAL ERYTHEMA	57 (47.5)	56 (61.5)	[REDACTED]
MOUTH PAIN	102 (85.0)	76 (83.5)	[REDACTED]
<b>HEMIC AND LYMPHATIC SYSTEM</b>			
ECCHYMOSIS	19 (15.8)	21 (23.1)	[REDACTED]
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>			
HYPERGLYCEMIA	8 (6.7)	15 (16.5)	[REDACTED]
<b>MUSCULO-SKELETAL SYSTEM</b>			
ARTHRALGIA	14 (11.7)	24 (26.4)	[REDACTED]
BONE DISORDER	14 (11.7)	11 (12.1)	[REDACTED]
<b>NERVOUS SYSTEM</b>			
ABNORMAL GAIT	0 (0.0)	37 (40.7)	[REDACTED]
HYPESTHESIA	5 (4.2)	15 (16.5)	[REDACTED]
SINUSITIS	11 (9.2)	15 (16.5)	[REDACTED]
<b>SKIN AND APPENDAGES</b>			
RASH	9 (7.5)	34 (37.4)	[REDACTED]

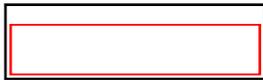
Source: [REDACTED]

The most frequent adverse events reported for both the 1.5 mg/ml rhBMP-2/ACS group and the bone graft group were: mouth pain [REDACTED]

[REDACTED]

and oral erythema [REDACTED], respectively. Although, not statistically significant, [REDACTED]

[REDACTED]



These adverse events were consistent with the surgical procedure performed.

Subjects in the bone graft treatment group showed a significantly greater amount of adverse events versus the 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); edema (37.4% vs. 1.7%); rash (erythema) (37.4% vs. 7.5%); arthralgia (26.4% vs. 11.7%); and hypesthesia (decreased sensation) (16.5% vs. 9.2%). 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 rhBMP-2/ACS treatment.

#### **XII.J.9.b.2.2. Morbidity by Harvest Location**

Subjects were randomized to the bone graft treatment group in two of the studies: sinus pivotal and sinus dosing.

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. Table XII.J-5 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.

Table XII.J-5 Adverse Events Reported by Harvest Site in 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%

### XII.J.9.b.2.3. Severity of 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 or 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.

Among the total subjects who received rhBMP-2/ACS in any concentration [redacted] adverse events were reported by the study Sponsor [redacted]. 80% [redacted] of the adverse events were mild, 17% [redacted] were moderate, 2% [redacted] were reported as severe, and 0.06% [redacted] was considered life-threatening in severity (though unrelated to rhBMP-2/ACS). Among the commercial concentration treatment group (1.5 mg/ml rhBMP-2/ACS), [redacted] adverse events were reported. 79.1% [redacted] were mild; 18.3% [redacted] were moderate; and 2.4% [redacted] were severe.

Of the [redacted] sinus augmentation subjects who received 1.5 mg/ml rhBMP-2/ACS, 17% [redacted] experienced adverse events that were reported as related (definitely, probably, possibly or associated) to the rhBMP-2/ACS treatment. Investigators were not asked to distinguish adverse events that could be procedure related from those thought to be related to the study device. In the extraction socket study, 23.8% [redacted] who received who received 1.5 mg/ml rhBMP-2/ACS had related adverse events. Among the reports of associated adverse events were: mouth pain, oral edema, face edema, oral erythema; hematoma, and ecchymosis. This result is unexpected; none of the clinical trials conducted subsequently have reported adverse events that were considered related to rhBMP-2/ACS.

Among the [redacted] subjects who received a bone graft, [redacted] adverse events were reported. 82.8% [redacted] were mild, 14.7% [redacted] were moderate and 2.16% [redacted] were severe. 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. As would be expected, none of the [redacted] adverse events reported for the [redacted] bone graft subjects was considered related (definitely, probably or possibly or associated) to rhBMP-2/ACS.

When the data from the [redacted] subjects treated with bone graft was compared to the group who received 1.5 mg/ml rhBMP-2/ACS, the severity of the events was comparable between treatment groups.

In the sinus augmentation studies, serious adverse events were reported in 14% [redacted] of patients who received the 1.5 mg/ml rhBMP-2/ACS and 13% [redacted] of the bone graft group. None of the SAEs reported for rhBMP-2/ACS were considered by the investigator to be related to the treatment. The majority of the serious adverse events and the only reported death were previously reported to FDA in the study specific reports submitted to the respective IDE.

#### **XII.J.10. Conclusions**

INFUSE<sup>®</sup> BONE GRAFT results in sufficient bone growth for dental implant placement and functional restoration with significantly fewer adverse events and a better overall safety profile than bone graft (autograft alone or in combination with allograft) which is the standard of care for oral maxillofacial procedures.

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