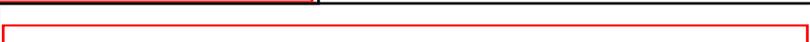
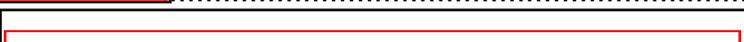


SECTION III – EXECUTIVE SUMMARY

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III. Executive Summary

INFUSE[®] BONE GRAFT, the subject of this Premarket Approval application 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). In this application, INFUSE[®] BONE GRAFT is being presented for oral maxillofacial bone grafting procedures.

This Executive Summary provides an overview of the information presented in support of the PMA submission. The information is organized in a manner similar to the structure of the original PMA application.



III.B. Device Description

III.B.1. Device Overview and Properties Relevant to Indications for Use

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

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

III.B.2. INFUSE[®] Bone Graft Kit

Each INFUSE[®] BONE GRAFT Kit (See Figure III.B-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 III.B-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.

For the new oral maxillofacial bone grafting indications, an additional package insert will be developed and included in the four currently available commercial INFUSE[®] BONE GRAFT kits.

III.B.3. INFUSE[®] BONE GRAFT Components

Table III.B-1 provides a description and photo of the components of the various kits of INFUSE[®] BONE GRAFT.

Table III.B-1 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"	
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	

Table III.B-1 INFUSE® BONE GRAFT Kit Contents and Description

Part	Number	Brief Description	Photograph
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 PMA submission
Package Insert	1 per kit	Provides important medical information about INFUSE® BONE GRAFT	See Appendix IV-3 of the original PMA 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 PMA 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 PMA submission

Note that 12 mg of the 12.7 mg of rhBMP-2 in the larger vial is applied to the ACS following reconstitution. Likewise, 4.2 mg of the 4.9 mg of rhBMP-2 in the smaller vial is applied to its ACS following reconstitution. As a result, the larger vial is sometimes referred to as the 12 mg vial and the smaller vial is sometimes referred to as the 4.2 mg vial.

III.B.4. INFUSE® BONE GRAFT Component Sources and Key Processes

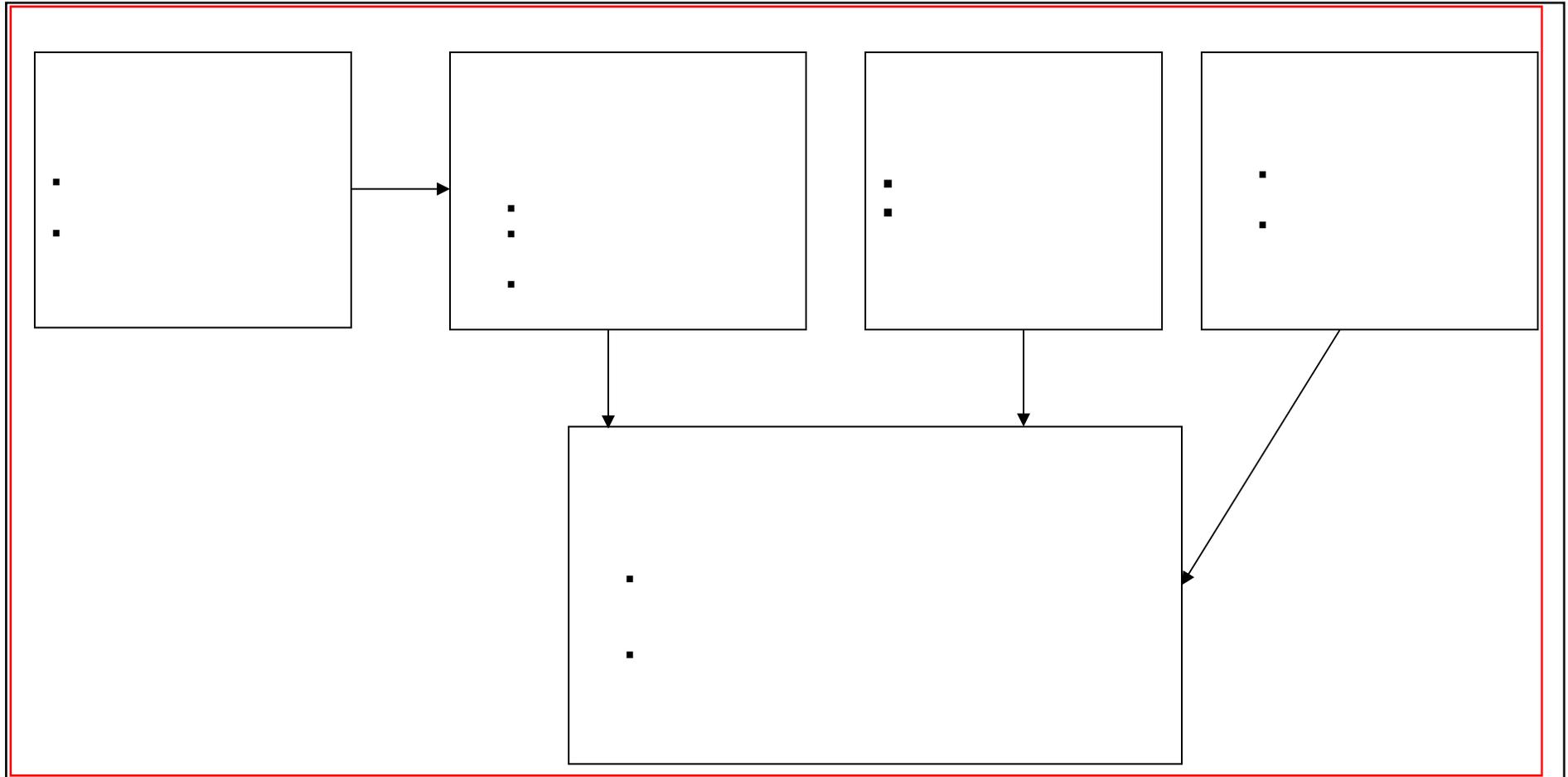
Table III.B-2 identifies the source and key processes for INFUSE® BONE GRAFT components.

Table III.B-2 Source for INFUSE® BONE GRAFT Parts

Part	Source/Process
Instructions for Preparation	Provided by Medtronic Sofamor Danek
Package Insert	Provided by Medtronic Sofamor Danek

Figure III.B-2 provides an overview of the parts manufacturing flow for INFUSE® BONE GRAFT.

Figure III.B-2 Overview of the Parts Manufacturing Flow for INFUSE® BONE GRAFT



III.B.5. Previous FDA Market Clearances

INFUSE[®] BONE GRAFT kits which are the subject of this PMA have been approved through the PMA process. Table III.B-3 identifies the submissions associated with each of the parts.

Table III.B-3 Previous Market Approvals for INFUSE[®] BONE GRAFT

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

III.B.6. Right of Reference Letters and Strategy

Some of the information used to support this PMA application is accessed through “right of reference.” Typically, this information includes confidential and/or proprietary information of major suppliers to Medtronic Sofamor Danek for INFUSE[®] BONE GRAFT program. These “right of reference” letters are provided in Appendix

IV-6 of the original PMA submission. The documents, which are resident at the agency, include:

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-
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-

III.B.7. Differences between Clinical Trial and Commercial Devices

[Redacted] are used to support the proposed indications for use. These studies are identified in Table III.B-4 below. Detailed results of these studies are provided in Section VIII of the original PMA as well as in Amendments 5 and 6 .

Table III.B-4 Clinical Studies Supporting the Proposed Indications for Use

			Use in this PMA
			Safety
			Safety and Effectiveness
			Safety
			Safety and Effectiveness
			Safety and Effectiveness

¹ Referred to as “Alveolar Ridge Preservation” in original PMA

² Referred to as “Alveolar Ridge Preservation” in original PMA

There is no difference in the composition (i.e., exact same rhBMP-2 formulation, concentration of rhBMP-2, type of excipients, concentration of excipients, ACS formulation) between the commercial and clinical products. This application includes four INFUSE[®] BONE GRAFT kit sizes which have a difference in the reconstitution process, and storage temperature requirements than the clinical product. Table III.B-5 compares the sizes and storage requirements of the clinical and commercial products.

Testing results which demonstrated the equivalency of the commercial and clinical products were provided in PMA Amendment 2.

Table III.B-5 Clinical and Commercial Device Comparison Table

Study	Kit Contents					Storage Requirements
	Lyophilized rhBMP-2	Diluent for Reconstituting rhBMP-2	Sterile water for Injection	Absorbable collagen sponge	Syringes	
Commercial Small	1 vial containing 4.9 mg	n/a	1 vial containing 5 ml	2 pieces 1" X 2"	(2) 5 ml	Store at room temperature (15–30 degrees Centigrade (59 to 86° F).
Commercial Medium	2 vials containing 4.9 mg	n/a	2 vials containing 5 ml	4 pieces 1" X 2"	(4) 5 ml	Store at room temperature (15 – 30 degrees Centigrade (59 to 86 ° F).
Commercial Large	1 vial containing 12.7 mg	n/a	(1) 10 ml vial	6 pieces 1" X 2"	(2) 10 ml	Store at room temperature (15 – 30 degrees Centigrade (59 to 86 ° F).
Commercial Large II	1 vial containing 12.7 mg	n/a	(1) 10 ml vial	1 piece 3" X 4"	(2) 10 ml	Store at room temperature (15 – 30 degrees Centigrade (59 to 86 ° F).

III.B.8. Instructions for Preparation

INFUSE[®] 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. The specified volume of rhBMP-2 solution is applied to each of the pieces of ACS provided. After waiting for the prescribed amount of time (15 to 120 minutes) the wetted sponge is cut as needed and carefully apply to the defect site. For complete instructions on preparation of INFUSE[®] BONE GRAFT, see Appendix IV-2 of the original PMA submission. When INFUSE[®] BONE GRAFT is prepared as described above, the volume and composition of rhBMP-2 solution applied to the matrix is as shown in Table III.B-6.

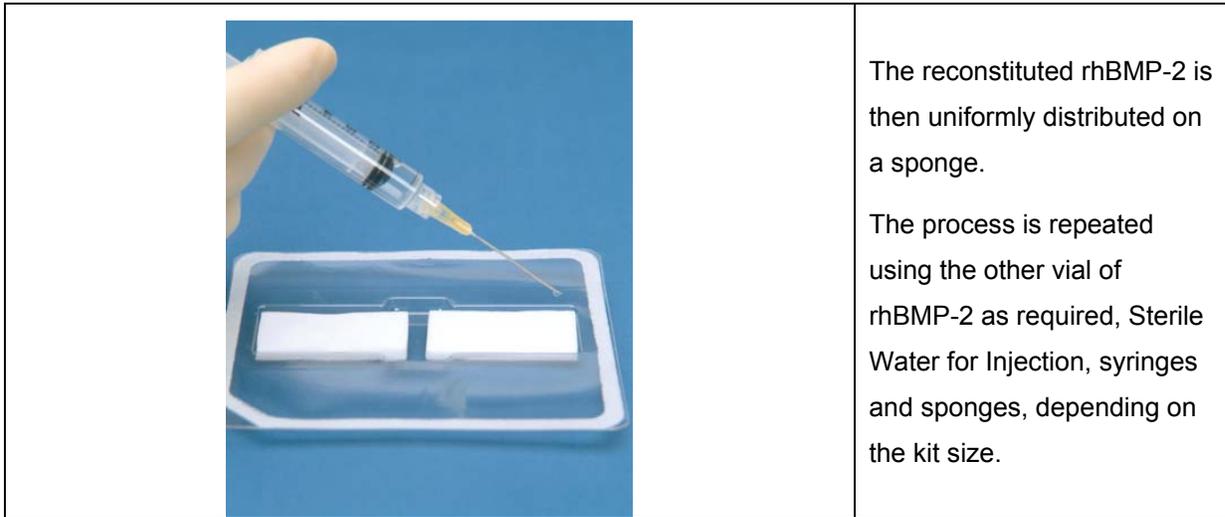
Table III.B-6 Preparation for Implant

	12 mg Vial	4.2 mg Vial
rhBMP-2 in vial	12.7 mg	4.9 mg
Sterile Water for Injection	8.4 ml	3.2 ml
rhBMP-2 placed on ACS	12 mg	4.2 mg
Reconstituted liquid rhBMP-2 applied to ACS	8.0 ml	1.4 ml
Final Concentration	1.50 mg/ml	1.50 mg/ml

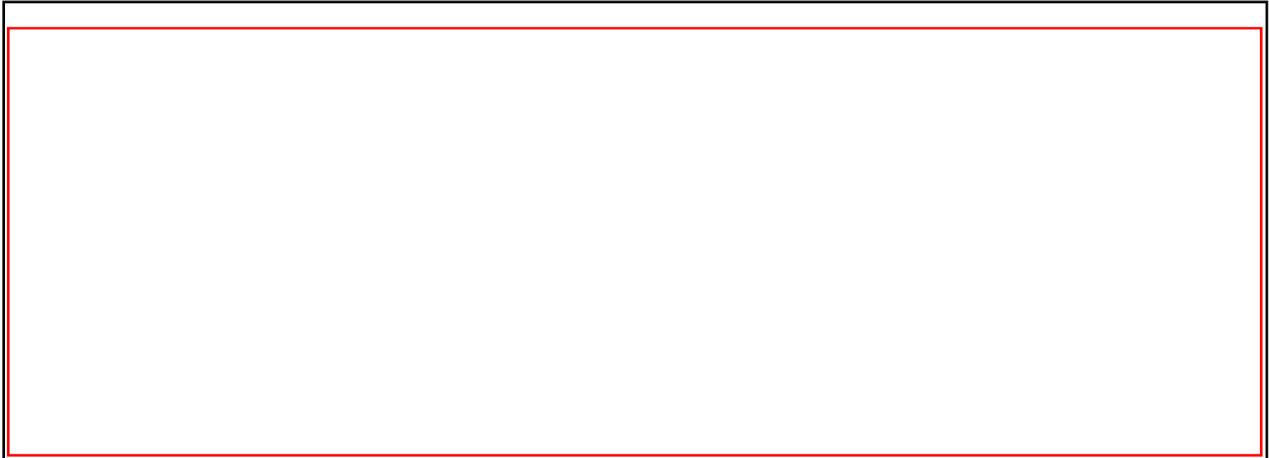
Figure III.B-3 Instructions for Preparation

	<p>Using one of the syringes, Sterile Water for Injection is withdrawn from the vial.</p> <p>(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>
	<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.</p> <p>(Depending on kit size, either 1.4 ml or 4.0 ml is used.)</p>

Figure III.B-3 Instructions for Preparation

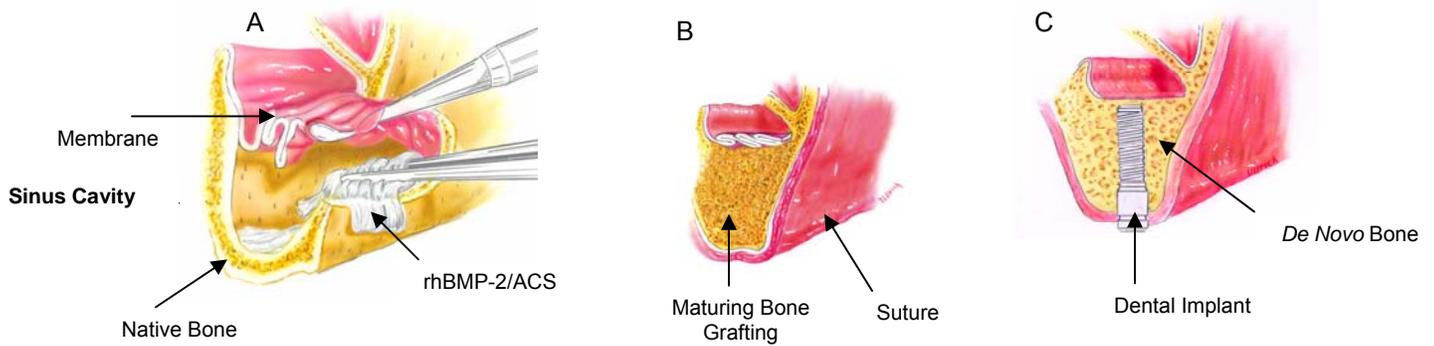


III.C. Clinical Utility



In application, the two device components, rhBMP-2 and absorbable collagen sponge, are combined to form a cohesive implant. The surgeon implants INFUSE[®] BONE GRAFT in a defect site.

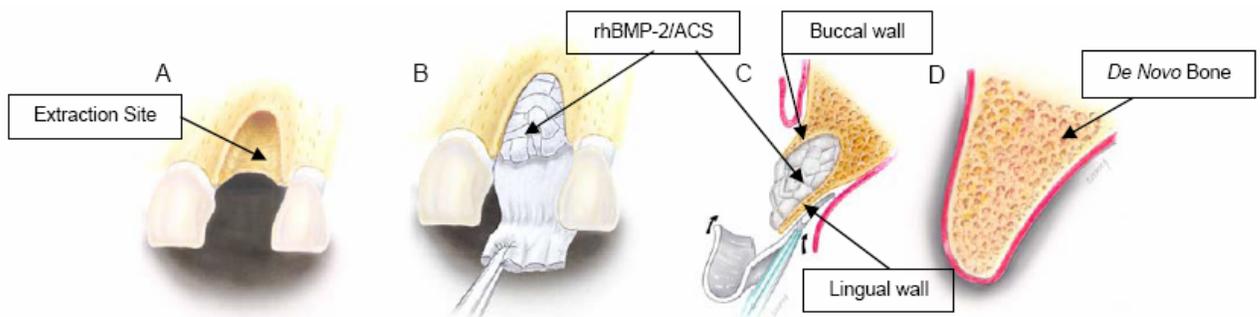
Figure III.C-1 and Figure III.C-2 show two oral maxillofacial applications of the INFUSE[®] BONE GRAFT product. Figure III.C-1 demonstrates the application of rhBMP-2/ACS in a maxillary sinus floor augmentation procedure. The goal in this procedure is to form bone in the sinus for dental implant restoration.



A) The membrane is peeled back revealing the sinus cavity. The rhBMP-2 loaded ACS is implanted into the cavity. B) Osseogenesis is occurring. C) Complete *De Novo* bone. All rhBMP-2/ACS has been resorbed and the site is ready for the endosseous implant.

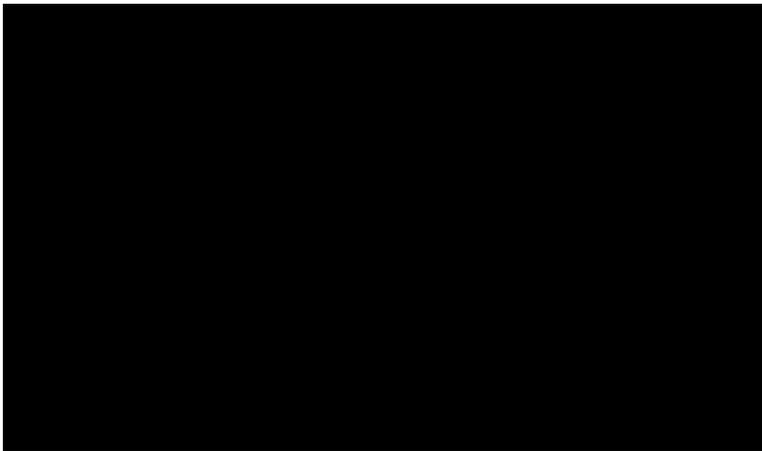
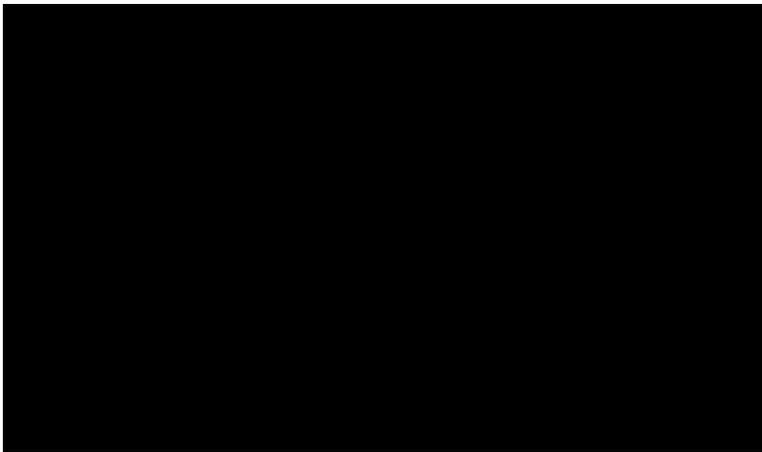
Figure III.C-1 INFUSE® BONE GRAFT Implanted in Sinus Cavity

Figure III.C-2 illustrates an extraction socket augmentation model using rhBMP-2/ACS. The goal in this procedure is to preserve height and grown bone to support dental restoration.



A) The extraction site where native bone has resorbed due to loss of the tooth. B) rhBMP-2 loaded ACS is implanted into the open area. C) A flap is created to hold the implant in place D) *De novo* bone formation with resorption of rhBMP-2/ACS.

Figure III.C-2 INFUSE® BONE GRAFT Implanted for Extraction Socket Augmentation





III.C.1. Principals of Operation

INFUSE[®] BONE GRAFT achieves its principal intended action by a pharmacologic mechanism of action attributable to rhBMP-2. rhBMP-2 binds to receptors on the surface of mesenchymal cells and signals undifferentiated cells to become cartilage- and bone-forming cells. These differentiated cells form trabecular bone as the ACS is resorbed, with vascular invasion evident at the same time. While application of rhBMP-2 alone is sufficient for osseointegration, rhBMP-2 is combined with a matrix (ACS) to form a cohesive implant and to facilitate surgical implantation and rhBMP-2 retention at the treatment site. Pre-clinical studies have demonstrated that rhBMP-2 induces both

endochondral and intramembranous ossification. In endochondral ossification the following events occur: osteogenic and chondrogenic precursor cells accumulate, cartilage forms and matures, vascularization occurs as bone formation proceeds, while the cartilage and collagen carrier are resorbed. In intramembranous ossification, bone is created without the intermediate cartilage forming step. Thus, the following events occur: osteogenic precursor cells accumulate, vascularization occurs as bone formation proceeds, and the collagen carrier is resorbed. The final result for both endochondral and intramembranous ossification is the production of bone and bone marrow in the site. Clinical testing has demonstrated that the bone formation process occurs safely and effectively for the target patient population.

III.C.2. Indications for Use



III.C.3. Surgical Procedure Overview

The Surgical Technique instructions are included in Appendix IV-11 of the original PMA submission. The procedure will require at least one INFUSE[®] BONE GRAFT kit.

1. Prepare the implant site utilizing the standard surgical techniques.
2. Select the proper size INFUSE[®] BONE GRAFT kit depending on volume requirement of implant site.
3. Prepare the implant material according to the instructions included in the kit.
4. If required, cut the implant to the desired size.
5. Implant using forceps to avoid excessive loss of fluid.

6. Note: Do not irrigate or suction in proximity to an implanted rhBMP-2/ACS device.

III.C.4. Contraindications

INFUSE[®] BONE GRAFT is contraindicated in the following:

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

III.C.5. Alternative Practices and Procedures

The non-surgical alternative to performing oral maxillofacial procedures with INFUSE[®] BONE GRAFT includes, but may not be limited to, watchful waiting with no intervention.

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

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

- Demineralized Bone Matrix – (DBX[®]) paste or putty composed of human cortical and corticocancellous bone

The above surgical alternative 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 [redacted] one or more harvest site may have been utilized to gather bone. In [redacted] 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.

III.C.6. Warnings and Precautions

III.C.6.a. Warnings

Note that Medtronic Sofamor Danek has recently completed testing required as a condition of approval for INFUSE[®] BONE GRAFT PMAs P000054 and P000058 which address the following fetal development warning.

- 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[®] BONE GRAFT for oral maxillofacial bone grafting procedures where space maintenance is present, (2.2%) patients treated with INFUSE[®] 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[®] 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.

III.C.6.b. Precautions

III.C.6.b.1. General

- 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. Retain the packaging and vials and contact a Medtronic Sofamor Danek representative.
- Do not use after the printed expiration date on the label.

III.C.6.b.2. Hepatic and Renal Impairment

- The safety and effectiveness of INFUSE[®] 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.

III.C.6.b.3. Bone formation

- 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.

III.C.6.b.4. Antibody Formation/Allergic Reactions

- The safety and effectiveness of INFUSE[®] BONE GRAFT has not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of INFUSE[®] 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.

III.C.6.b.5. Immunogenicity

- 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 for oral maxillofacial bone grafting procedures where space maintenance is present.
 - *Anti-rhBMP-2 antibodies:* 2.2% patients receiving INFUSE[®] BONE GRAFT component developed antibodies vs. 0.0% in the control group.
 - *Anti-bovine Type I collagen antibodies:* 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. 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[®] BONE GRAFT with the incidence of antibodies to other products may be misleading.

III.D. Non-Clinical Test Summary

III.D.1. Introduction

This section summarizes the non-clinical information supporting the conclusion that the INFUSE[®] BONE GRAFT is safe and effective for use in oral maxillofacial bone grafting procedures. INFUSE[®] BONE GRAFT has previously been approved for spinal fusion (P000058) and for the treatment of acute, open fractures of the tibial shaft (P000054). This PMA application is for an additional indication for the INFUSE[®] BONE GRAFT product.

The non-clinical studies are grouped into the following categories; unless otherwise noted, the corresponding reference to the Non-Clinical Section of the original PMA is included in parentheses. All testing demonstrates that the INFUSE[®] BONE GRAFT meets or exceeds the requirements for its intended use.

- rhBMP-2 Protein Characterization (VII.B.1)
- Absorbable Collagen Sponge (ACS) Characterization (VII.B.2)
- Preclinical Safety (VII.C):
 - Intravenous Toxicity and Implant Toxicity (VII.C.1)
 - Biocompatibility Studies (VII.C.2)
 - Tumor Cell Activity (VII.C.3)
 - Fertility, Reproduction and Teratology (VII.C.4)
- Preclinical Effectiveness in Oral Maxillofacial Indications (VII.D):
 - Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS (VII.D.1)
 - Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS with Dental Implant Placement (VII.D.2)
 - Maxillary Sinus Floor Augmentation using rhBMP-2/ACS (VII.D.3)

- Maxillary Sinus Floor Augmentation using rhBMP-2/ACS with Dental Implant Placement (VII.D.4)
- Periodontal Defect and Dental Implant Studies (VII.D.5)
- Comparability of Bone Induction by rhBMP-2 and Autogenous Bone (VII.E)
- Pharmacokinetics and Dosing (VII.F)
- Previously Reported Studies (VII.G)
- Stability Testing (VII.H)

This submission references or contains studies which were included in prior PMA submissions of the INFUSE[®] BONE GRAFT/LT- CAGE[®] Lumbar Tapered Fusion Device, P000058 and INFUSE[®] BONE GRAFT, P000054 and IDE submissions for:



III.D.2. Characterization

III.D.2.a. rhBMP-2 Protein Characterization

Bone Morphogenetic proteins were initially isolated from bovine bone based upon their ability to induce cartilage in a rat ectopic assay system. The activity of bone extracts was used to identify and clone a family of genes known as the BMPs (or GDFs, growth and differentiation factors), members of the multigene TGF- β superfamily of growth and differentiation factors. Proteins in this superfamily share seven conserved cysteines and have varying sequence homology with each other.

rhBMP-2 is well characterized with respect to its structure, function and stability. This fundamental knowledge underlies routine release testing of both active substance and

vial protein, and the corresponding formal stability programs, described in this filing. Testing was conducted to confirm the chemical composition and physical form of the rhBMP-2 and excipients.

III.D.2.b. Absorbable Collagen Sponge (ACS) Characterization

The absorbable collagen sponge is used to deliver the rhBMP-2; that is, it retains the rhBMP-2 at the site on implantation, helps to prevent soft tissue prolapse into the defect area, and enables bony vascular ingrowth to occur during the rhBMP-2-induced bone formation. This device format provides a cohesive and tissue-adherent implant material that can be folded and shaped to serve surgical needs. The quantity of implant material can be varied by cutting of the wet device to a smaller size or by utilizing multiple device kits. After implantation, the absorbable collagen sponge material is resorbed in a physiologic process while bone is being formed.

Several *in vitro* studies have been performed to optimize the device format. (See summaries in sections VII.B.2a and VII.B.2b of the original PMA). When wetted, with a small volume of liquid, the absorbable collagen sponge collapses in height but retains other dimensions. Addition of more liquid causes the sponge to swell back to its original height or to greater height. The volume of rhBMP-2 liquid to be added to the sponge (soak-load volume) has been set at 30% of the original sponge volume. This soak-load volume helps to ensure retention of the liquid by the sponge upon implantation and provides superior handling qualities to the device. In addition, it allows the device to absorb some blood or fluid at the implant site, which aids in adherence of the device to the surrounding tissues.

An advantage of using the absorbable collagen sponge as a delivery system for rhBMP-2 is its ability to bind rhBMP-2. *In vitro* studies have shown that rhBMP-2 rapidly binds to the sponge (>93% in 5 minutes) when the device is prepared; thus, even if liquid is intentionally expressed from the device, most of the

rhBMP-2 remains bound to the collagenous material. Studies conducted at [REDACTED] indicate that rhBMP-2 is released *in vitro* with biphasic kinetics; less than 50% of the rhBMP-2 is released within 24 hours, followed by approximately 10% release each day. This is consistent with the slow release of rhBMP-2 from the implanted device *in vivo*. Local retention kinetics studies are discussed in further detail in Section VII.F.2 of the original PMA submission.

III.D.3. Preclinical Safety

The safety of rhBMP-2/ACS (INFUSE[®] BONE GRAFT) has been evaluated in a series of studies of rhBMP-2/ACS and rhBMP-2 alone. rhBMP-2 protein has been studied in single- and multiple-dose toxicity studies in the rat and canine. Safety testing addresses biocompatibility, tumor cell activity, and potential for affecting reproductive cells. Additionally, immunological response and antibody formation have been studied. Neurological Safety was also evaluated in canines which showed no negative neurological effects when rhBMP-2 contacted the spinal cord via a breach in the dura. Table III.D-1 lists the studies that support the safety of INFUSE[®] BONE GRAFT.

INFUSE[®] BONE GRAFT met or exceeded all the requirements for preclinical safety as demonstrated by the testing reported in the original PMA.

Table III.D-1: Preclinical Safety Testing³

	Study Number	Summary Location	Full Report Location
Intravenous Toxicity and Implant			
		VII.C.1.a	Appendix VII-42
		VII.C.1.a	Appendix VII-43
		VII.C.1.c	Appendix VII-45
		VII.C.1.g	Appendix VII-49
		VII.C.1.b	Appendix VII-44
		VII.C.1.d	Appendix VII-46
		VII.C.1.f	Appendix VII-48
		VII.C.1.e	Appendix VII-47
		VII.C.1.h	Appendix VII-3
VII.C.2			
		VII.C.2.g	Appendix VII-56
		VII.C.2.c	Appendix VII-52
		VII.C.2.d	Appendix VII-53
		VII.C.2.f	Appendix VII-55
		VII.C.2.h	Appendix VII-57
		VII.C.2.a	Appendix VII-50
		VII.C.2.e	Appendix VII-54
		VII.C.2.b	Appendix VII-51
		VII.C.2.i	Appendix VII-58
VII.C.3			
		VII.C.3.e	Appendix VII-61
		VII.C.3.a	Appendix VII-59
		VII.C.3.c	Appendix VII-63
		VII.C.3.d	Appendix VII-62
		VII.C.3.b	Appendix VII-60
VII.C.4			
		VII.C.4.a	Appendix VII-64
		VII.C.4.c	Appendix VII-67
		VII.C.4.c	Appendix VII-68
		VII.C.4.c	Appendix VII-69
		VII.C.4.b	Appendix VII-65
		VII.C.4.b	Appendix VII-66

³ Location references are in the original PMA submission

III.D.4. 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. Many of the preclinical studies summarized in this section have been presented to FDA in IDE or PMA submissions [REDACTED] P000058, P000054, [REDACTED] PMA P000054

[REDACTED] These studies are summarized below for the convenience of the reviewer and full reports are included in appendices of the original PMA submission. Table III.D-2 lists the studies that support the preclinical effectiveness of INFUSE[®] BONE GRAFT.

Preclinical effectiveness studies evaluating oral maxillofacial indications are grouped into six categories and summarized in the following sections (unless otherwise noted) of the original PMA submission:

- Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS (VII.D.1)
- Extraction Socket Augmentation (referred to as Alveolar Ridge Preservation and Augmentation in the original PMA) using rhBMP-2/ACS with Dental Implant Placement (VII.D.2)
- Maxillary Sinus Floor Augmentation using rhBMP-2/ACS (VII.D.3)
- Maxillary Sinus Floor Augmentation using rhBMP-2/ACS with Dental Implant Placement (VII.D.4)
- Periodontal Defect and Dental Implant Studies (VII.E)

INFUSE[®] BONE GRAFT met or exceeded all requirements for pre-clinical effectiveness as demonstrated by this testing.

Table III.D-2: Preclinical Effectiveness in Oral Maxillofacial Indications⁴

Study Model	Study Number or Title	Summary Location	Full Report Location
Preclinical Effectiveness in Oral Maxillofacial Indications			
		VII.D.1.a	Appendix VII-70
		VII.D.1.b	Appendix VII-4
		VII.D.1.c	Appendix VII-5
		VII.D.1.d	Appendix VII-6
		VII.D.1.e	Appendix VII-7
		VII.D.1.f	Appendix VII-8
		VII.D.1.g	Appendix VII-9
		VII.D.1.h	Appendix VII-10
		VII.D.2.d	Appendix VII-13
		VII.D.2.a	Appendix VII-11
		VII.D.2.b	Appendix VII-12
		VII.D.2.c	Appendix VII-12
		VII.D.3.a	Appendix VII-14
		VII.D.3.a	Appendix VII-15
		VII.D.3.b	Appendix VII-16
		VII.C.4.a	Appendix VII-17
		VII.D.5.a	Appendix VII-18
		VII.D.5.b	Appendix VII-19
		VII.D.5.d	Appendix VII-21
		VII.D.5.g	Appendix VII-24
		VII.D.5.h	Appendix VII-25
		VII.D.5.c	Appendix VII-20
		VII.D.5.e	Appendix VII-22
		VII.D.5.f	Appendix VII-23
		VII.D.5.b	Appendix VII-19
		VII.D.2.b	Appendix VII-12
		VII.D.1.b	Appendix VII-4
		VII.D.1.g	Appendix VII-9
		VII.E & Table VII.E-2	Appendix VII-26
			Appendix VII-27
			Appendix VII-28

⁴ Location references are in the original PMA submission

Table III.D-2: Preclinical Effectiveness in Oral Maxillofacial Indications⁴

Study Model	Study Number or Title	Summary Location	Full Report Location
			Appendix VII-29
			Appendix VII-30
			Appendix VII-38
			Appendix VII-31
			Appendix VII-32
			Appendix VII-29
			Appendix VII-38
			Appendix VII-33
			Appendix VII-34
			Appendix VII-35
			Appendix VII-37

III.D.5. Comparability of Bone Induction by rhBMP-2 and Autogenous Bone in Oral Maxillofacial, Spine, and Trauma Indications

Preclinical studies allow us to examine the safety and effectiveness of various materials or devices. In these studies the material under investigation is usually compared to a predicate material or device. For bone grafting procedures, bone graft substitutes (e.g. rhBMP-2/ACS) under investigation are most often compared to autograft bone, the “gold standard” for bone grafting procedures. A number of testing methods are used to compare the effectiveness and quality of bone created by various bone graft substitutes to autograft bone. Testing methods include radiographic analyses, biomechanical testing, and histological analyses. 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 listing of these studies is provided in Table III.D-3 and copies of the study reports are included in their entirety in the designated appendices of the original PMA submission.

Table III.D-3: Comparison of Bone Induction by rhBMP-2 and Autograft⁵

Study Model	Study Number or Title	Summary Location	Full Report Location
Oral Maxillofacial			
Non-Human Primate	Boyne et al. 1999	Section VII.E & Table VII.E-2	Appendix VII-13
Rabbit	Wada et al. 2001		Appendix VII-46
Spine			
Non-Human Primate	Hecht et al. 1999	Section VII.E & Table VII.E-2	Appendix VII-30
	Martin et al. 1999		Appendix VII-29
Caprine	[redacted] 1998		Appendix VII-26
	[redacted]		Appendix VII-27
	[redacted]	Appendix VII-28	
Ovine	[redacted] 2002	Section VII.E & Table VII.E-2	Appendix VII-38
	[redacted]		Appendix VII-31
	[redacted]		Appendix VII-32
Rabbit	[redacted] et al. 1995		Appendix VII-36
Canine	David et al. 1999		Appendix VII-37
Trauma			
Canine	[redacted]	Section VII.E & Table VII.E-2	Appendix VII-33
	[redacted]		Appendix VII-35
	[redacted]		Appendix VII-34

III.D.6. Pharmacokinetics and Dosing

Both the concentration of rhBMP-2 and the length of time that rhBMP-2 is present at the implant site are positively correlated with the rate of bone formation, the amount of bone formed, and the density of the resulting bone. Both the concentration of rhBMP-2 administered and the nature of the carrier material can affect these outcome parameters.

Pharmacokinetic studies following IV dosing showed minimal systemic exposure of rhBMP-2 due to the high clearance rate of rhBMP-2. Although the uptake of rhBMP-2 by highly perfused tissues and organs is rapid, residence of the protein in these tissues is short. Catabolism of the protein is extensive and renal excretion of trichloroacetic acid (TCA)-soluble radioactivity is rapid (radioactivity not related to intact rhBMP-2). As a result of these pharmacokinetic characteristics, systemic presence of rhBMP-2 in the circulation is minimal after IV dosing. Following implantation of rhBMP-2/ACS,

⁵ Location references are in the original PMA submission

exposure of rhBMP-2 in the systemic circulation is even less because of the high clearance of rhBMP-2 and the slow release of the protein from ACS.

Pharmacokinetic studies using rat and nonhuman primates have shown that rhBMP-2 is rapidly eliminated from the systemic circulation following intravenous injection ($t_{1/2}$ – 16 minutes in the rat and 6.7 minutes in the nonhuman primate). When rhBMP-2 was implanted with ACS in the rat, a mean residence time (MRT) of four to eight days was demonstrated and low levels of rhBMP-2 were detected in systemic circulation. This showed that the use of an effective carrier increases the retention time of rhBMP-2 at the implant site. rhBMP-2 retention at the implant site along with rapid clearance of rhBMP-2 for systemic circulation resulted in low systemic exposure to rhBMP-2. Pharmacokinetic and dosing studies that are discussed in Section VII.F of the original PMA are listed in Table III.D-4.

Table III.D-4: Pharmacokinetic and Dosing Studies Discussed in Section VII.F⁶

	Study Number	Summary Location	Full Report Location
		VII.F.1.c	Appendix VII-75
		VII.F.1.b & VII.F.1.d	Appendix VII-74
		VII.F.1.e	Appendix VII-76
		VII.F.1.a & VII.F.1.b	Appendix VII-71
		VII.F.1.b	Appendix VII-72
		VII.F.1.b	Appendix VII-73
		VII.F.2.a	Appendix VII-77
		VII.F.2.b & VII.F.2.d	Appendix VII-78
		VII.F.2.b	Appendix VII-79
		VII.F.2.c	Appendix VII-80
		VII.F.2.d	Appendix VII-81

III.D.7. Previously Reported Studies

A large number of non-clinical studies have demonstrated that rhBMP-2/ACS induces bone formation, heals bony defects, and augments fracture repair. These studies are included in this PMA as those most applicable to the proposed use of rhBMP-2/ACS in oral maxillofacial indications. These studies demonstrate that rhBMP-2/ACS induces bone and heals critical sized defects in the craniofacial area, and induces bone of

⁶ Location references are in the original PMA submission

appropriate quantity and quality for successful dental reconstructive procedures and implant placement. As identified in Section VII.G of the original PMA there are additional published studies, not included in the original 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 (See Section VII.G of the original PMA submission), 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.

III.D.8. Stability Testing

Testing was performed to demonstrate the stability over time of the rhBMP-2 active substance (bulk rhBMP-2), the lyophilized vial 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[®] BONE GRAFT components and the final product meet the requirements for stability. The referenced sections are in the original PMA.

- Descriptions of Assays used for Stability Testing (VII.H.1)
- Stability Testing of the Active Drug Substance (Bulk rhBMP-2) (VII.H.2)
- Stability Testing of Lyophilized rhBMP-2 (VII.H.3 and VII.H.4)
- Stability Testing of ACS Carrier (VII.H.7)
- Stability Testing of the Assembled Kit (VII.H.5 and VII.H.6)

- Packaging testing of final product configuration(s) (VII.H.8)

III.D.9. Preclinical Conclusions



III.E. Clinical Studies

III.E.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[®] 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 1) spinal fusion procedures (P000058) in July, 2002 and 2) treating acute, open tibial fractures (P000054) in April, 2004.

The objective of this PMA is to obtain approval for and additional indication for the INFUSE[®] Bone Graft, specifically:

-
-
-
-

IDE clinical studies to support these new indications consist of [redacted] sinus floor augmentation studies [redacted] and [redacted] extraction socket

augmentation studies [redacted]. The oral maxillofacial study series spanned nearly [redacted] years from the first study subject enrolled [redacted]

[redacted] to the last follow-up in the last study [redacted]. A similar study protocol was followed in each of the [redacted] 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 [redacted] 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]
	Short-Term [redacted]	Long-Term [redacted]		
Number of Subjects	[redacted] rhBMP 2/ACS [redacted] mg/ml	[redacted] subjects	[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	[redacted] rhBMP [redacted] mg/ml	(same as [redacted])	[redacted]
Study Design	Open-label, non-randomized, two-center study	Long-term follow-up of [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

The IDE clinical data were previously submitted by [redacted] in IDE Submissions [redacted] IDE Annual Reports and IDE Final Study Reports.⁷ Throughout the Clinical Section, [redacted] is used to refer to either [redacted] [redacted] describe the original clinical study sponsor and responsible entity. [redacted]

[redacted]

Note that [redacted] directly supports the extraction socket indication. The formal title of this IDE was “Randomized, Dose Escalation Study Evaluating rhBMP-2/ACS for Localized Alveolar Ridge Augmentation of Buccal Wall Defects.” We refer to it here as “extraction socket augmentation” to match the proposed indication for use statement.

In the original submissions, the study numbers for each of the studies providing data for this PMA were configured per [redacted] For this PMA application, the study number designations have been simplified as indicated in Table III.A-1 below.

Table III.A-1: Study Nomenclature

IDE Number	Original Study Identifier	Study Identifier for PMA	Abbreviated Description for PMA

⁷ Medtronic Sofamor Danek has rights to use all data in support of this Premarket Approval application; a Right of Reference letter is provided in Appendix IV-6 of the Device Description (Section IV) in the original PMA submission.

Comparability Among Implant Locations and Procedures

The proposed indication for use identifies [] specific oral maxillofacial procedures/sites for the use of INFUSE[®] Bone Graft. The [] oral maxillofacial implant sites have several important features in common:

- Each is located in the mandible or maxilla.
- Each is a bony defect / space that requires bone graft
- Each site consists of a space or void which is large enough to allow placement of INFUSE[®] Bone Graft. This enables INFUSE[®] Bone Graft to grow sufficient bone in the site to achieve a clinically meaningful result.
- In each, the space maintains its shape after INFUSE[®] Bone Graft placement either through native structures or use of approved dental materials.

In addition, the comparability among the implant locations is demonstrated through:

- The implant sites may have one or more bony walls from which the implanted INFUSE[®] Bone Graft recruits stem cells for bone growth.
- The ability of INFUSE[®] Bone Graft has been demonstrated to grow clinically meaningful bone in each of the [] implant sites
- 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.

Because no difference in bone promulgated by INFUSE[®] Bone Graft and the host bone is evident, use of INFUSE[®] Bone Graft in all oral maxillofacial procedures is supported by these studies. All of the implant sites identified in the proposed indications for use

have common physiological structure (stable, empty space); allow INFUSE® Bone Graft to perform its function (grow clinically meaningful quantity and quality of bone); are proven successful in a reproducible, challenging procedure (sinus augmentation procedure; one to two walls); and result in growth of bone with bone histology comparable to that of the host site as well as bone grown by autogenous bone graft. In addition, the ability to grow bone is statistically related to the ability to place dental implants which allow functional restoration. Therefore, the clinical conclusions at one of these oral maxillofacial implant sites can be applied to the other oral maxillofacial sites as well.

III.E.2. Sinus Augmentation

III.E.2.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.

III.E.2.b. Combined Data from Study [REDACTED]

Based on the similarity between the study protocols, procedures, patient populations and results, Medtronic Sofamor Danek is combining the results from the sinus augmentation pivotal [REDACTED] and [REDACTED] studies. Specifically, data from the [REDACTED] 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 are combined. The clinical and statistical justification for combining the data from these two studies is presented below.

III.E.2.c. 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 (when used for two-stage maxillary sinus floor augmentation) to induce bone [redacted]

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

Secondary endpoints:

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

[redacted] to induce bone that successfully supports dental implant borne restoration after [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 maxillary sinus floor augmentation procedures.

In order for a patient to be counted as a success per the pivotal study [redacted] protocol, all of the following had to be true:

- Receive treatment with rhBMP-2/ACS
- Require no additional sinus floor augmentation for dental implant placement
- Receive endosseous dental implants within 12 months postoperative

- Achieve osseointegration of a sufficient number of dental implants to allow placement of implant borne device⁸
- Loaded with prosthesis
- Prosthesis maintains functional restoration for 6 months

III.E.2.d. Results of Primary Endpoints

Combined results of the dosing [] and pivotal [] sinus augmentation studies when evaluated against the endpoints and criteria as stated in the pivotal [] study protocol are presented below.

Primary Objective #1:

To estimate the effectiveness of rhBMP-2/ACS (when used for []

[]

Table III.A-2 Primary Effectiveness Endpoint Results Sinus Augmentation Studies [] and [] with [] rhBMP-2/ACS (ITT Population)

Subjects			
	[] (88.2)	[] 81.7	[]
	[]	[] 79.3	[] (79.8)
	[] (82.4)	[] 79.0	[] (79.6)
	(56.6, 96.2)	5, 87.3	.3, 87.1
	[]	[] 78.8	[] (79.4)
	(56.6, 96.2)	(68.2, 87.1)	.0, 87.0

⁸ Sufficient means that the patient was functionally restored with a dental implant borne prosthesis without the placement of additional dental implants in the grafted sinus. For bilateral cases sufficient osseointegration must occur in both sinuses.

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

Subjects	Combined aft	rhBMP-2/ACS	P-Value ^{a,f}
	[redacted] (95.6)	[redacted] (82.8)	
	[redacted] (93.4)	[redacted] (79.8)	
	[redacted] (89.9)	[redacted] (79.6)	
	[redacted] (7, 95.3)	[redacted] (70.3, 87.1)	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted] (87.4)	[redacted] (78.7)	
	[redacted] (.5, 93.5)	[redacted] (69.1, 86.5)	
	[redacted]	[redacted]	
	[redacted] (87.4)	[redacted] (77.2)	
	[redacted] (78.5, 93.5)	[redacted] (.3, 85.3)	

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.

III.E.2.f. 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

	ss	Failure
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.

III.E.2.g. 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 least 73% functional

[redacted]

- 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, functionally load a prosthesis placed on the dental implants and maintain that [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.

III.E.3. Extraction Socket

The effectiveness of the extraction socket augmentation 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

III.E.3.a. Treatment Groups

The primary purpose of the [REDACTED] trial was to determine the most suitable dosage of rhBMP-2/ACS to use. For this purpose, [REDACTED] treatment groups were studied:

- No-treatment control group
- A group receiving the absorbable collagen sponge (ACS) impregnated with diluent but no rhBMP-2/ACS
- A group receiving the ACS impregnated with [REDACTED] mg/ml rhBMP-2/ACS
- A group receiving the ACS impregnated with [REDACTED] mg/ml rhBMP-2/ACS

The first, second and fourth of these groups are relevant to this submission. The [REDACTED] was treated with the dosage of rhBMP-2/ACS now used for routine clinical use, and the first group demonstrates the consequences of attempting the insertion of a dental implant and a subsequent prosthesis without any supplemental material to promote bone growth (control).

III.E.3.b. 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:



III.E.3.c. 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)

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. These detailed analyses are included in Appendix IV.B-7. 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 III.E-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				
Standard deviation	1.23	1.4	1.39	1.20
Treatment effect				
Standard error	0.417	0.437		
95% CI for difference	(-2.08, -0.23)	(-1.95, -0.01)		
P value				

Source: [redacted]

These differences confirm that rhBMP-2/ACS leads to a highly significant improvement in bone height. With 1.50 mg/ml rhBMP-2/ACS bone height is maintained, whereas without treatment resorption leads to a [redacted] mm loss of bone and with ACS without 1.50 mg/mL rhBMP-2/ACS a [redacted] loss of bone is seen.

Table III.E-9 Change in Bone Width: ¼ Position

	No Treatment	rhBMP-2/ACS 0.00 mg/mL	rhBMP-2/ACS 5 mg/mL	rhBMP-2/ACS 0 mg/mL
N				
Mean				
Standard deviation	2.56	1.40	1.67	2.53
Treatment effect				
Standard error		0.712		
95% CI for difference	(-4.38, -1.02)	(-4.18, -0.71)		
P value				

Source: [redacted]

Here one sees another significant gain in bone dimension with 1.50 mg/mL rhBMP-2/ACS. Bone width growth at the socket crest is significantly greater for 1.50 mg/mL rhBMP-2/ACS than with either No Treatment patients or patients treated with ACS only. Patients with 1.50 mg/mL rhBMP-2/ACS experience an average of [redacted] mm additional width gain compared to subjects with no treatment, and an average of [redacted] mm additional width gain compared to subjects treated with ACS.

Table III.E-10 Change in Bone Width: 1/2 Position

	No Treatment	rhBMP-2/ACS	rhBMP-2/ACS	rhBMP-2/ACS 50 mg/mL
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect	[redacted]	[redacted]	[redacted]	[redacted]
Standard error	0.675	[redacted]	[redacted]	[redacted]
95% CI for difference	(-4.04, -0.66)	(-3.92, -0.43)	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

Source: [redacted]

Similarly, one sees a significant gain in bone width at the midpoint of the extraction socket with 1.50 mg/mL rhBMP-2/ACS compared to both No Treatment and ACS Only. Patients with 1.50 mg/mL rhBMP-2/ACS experience an average of 2.353 mm additional width gain compared to subjects with No Treatment, and an average of [redacted] mm additional width gain compared to subjects treated with ACS compared to both rhBMP leads to an additional [redacted] mm increase.

Table III.E-11 Change in Bone Width: 3/4 Position

	No Treatment	rhBMP-2/ACS 00 mg/mL	rhBMP-2/ACS 0.75 mg/mL	rhBMP-2/ACS 1.50 mg/mL
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	2.06	[redacted]	1.07	1.37
Treatment effect	[redacted]	[redacted]	[redacted]	[redacted]
Standard error	0.505	[redacted]	[redacted]	[redacted]
95% CI for difference	(-2.12, 0.40)	(-1.99, 0.60)	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

Source: [redacted]

Finally, treatment with 1.50 mg/mL rhBMP-2/ACS leads to a non-significant [] gain in bone width at the base of the extraction sockets beyond the gain seen in the No Treatment group and a [] mm gain in bone width beyond that seen in the ACS Only group.

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 1/2 and 1/4 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 III.E-12 Dental Implant 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				

Source: []

This table shows:

- A total of [] patients required additional augmentation and so, for purposes of this endpoint are regarded as failures
- A net additional [] patients whose alveolar ridge formation was considered inadequate for implantation are also failures for this endpoint
- []

III.E.3.d. Results of Secondary Endpoints

The secondary endpoints reflect the further progression from dental implant placement to positioning of the prosthesis so success in functional loading of the prosthesis.

The statistical assessment of the numbers, however, is affected by the attrition in the number of patient seen at the subsequent assessments. At the earlier stages, where the attrition was low, the statistically significant benefits of rhBMP-2/ACS treatment continue to be seen. At the longer time intervals, the statistical significance weakens, and becomes more dependent on assumptions about the reasons for patients' missed visits and withdrawal.

Table III.E-15 Prosthesis Placement without Augmentation

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

As with DIP success, different analyses result from making different assumptions about withdrawals. Regarding the withdrawals as “failures” gives a Fisher exact P-value [redacted] in the comparison of 1.5 mg/mL rhBMP-2/ACS to No Treatment. Regarding them as “censored observations” gives a Fisher Exact P value of [redacted]

In the comparison of 1.5 mg/mL rhBMP-2/ACS to ACS only, regarding the withdrawals as “failures” gives a Fisher exact P-value of [redacted] regarding them as “censored observations” gives a Fisher Exact P value of [redacted]

[redacted]

[Redacted]

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

The analysis at [Redacted] adds an element not seen in the two earlier endpoints: [Redacted]

[Redacted] This gives rise to three reasonable approaches:

1. To regard all patients without documented success as failures.
2. To regard all missing cases as “missing completely at random,” and remove them from the calculations, while counting the withdrawals as failures.
3. To regard both missing cases and withdrawals as “missing completely at random” and remove them from the calculations.

The P values for these analyses are included in table IV.B-9.a.

[Redacted]

Treatment	P-value	
	ment	ly
1	[Redacted]	[Redacted]
2	[Redacted]	[Redacted]
3	[Redacted]	[Redacted]

Source: [Redacted]

All three of these approaches, concur that there is a significantly higher success rate in the rhBMP group than in the No Treatment group.

Further comparisons show that the ACS Only group appears to be not statistically different from the No Treatment group. The [Redacted] only and No Treatment groups provided a [Redacted] This is in line with the effects of treatment on bone growth, and on association of bone growth with implant

success. The difference between ACS and 1.5 mg/mL rhBMP-2/ACS points in the right direction, as implied in these underlying relationships, but does not reach the statistical significance.

Table III.A-17 shows the results at [redacted]

Table III.E-17 [redacted]

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

Source: [redacted]

[redacted]

Treatment		ACS Only
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

Source: [redacted]

The approach that allow removal of patients missing show significantly better results for the rhBMP-2/ACS treatment compared to No Treatment; regarding all missing values as failures or regarding them as censored or failures gives a non-significant difference. Comparing rhBMP-2/ACS to ACS Only shows no statistically significant difference.

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	[redacted]	[redacted]	[redacted]	[redacted]
Failed	[redacted]	[redacted]	[redacted]	[redacted]
Missed Visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew	[redacted]	[redacted]	[redacted]	[redacted]
Succeeded	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Source: [redacted]

--	--

	P-value	
Treatment		
1		
2		
3		

Source:

This table continues the pattern of the preceding ones; the dilution of the treatment effect by withdrawals and missing data reduces the statistical significance of the treatment benefit.

Table III.A-19 shows the results at

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

Source:

--	--

	P-value	
Treatment		
1		
2		
3		

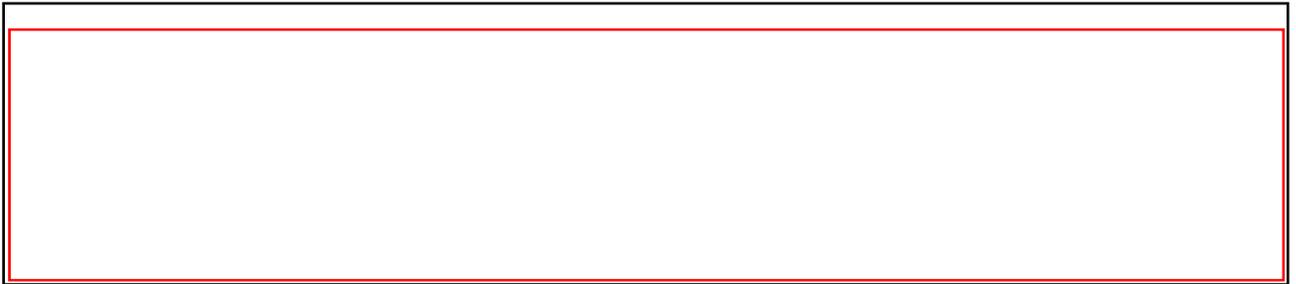
Source:

In this analysis, none of the three methods of analysis gives demonstrable treatment benefit compared to No Treatment or ACS Only. As no additional failures have accrued, this lack of statistical significance is seen as a result of sample size attrition.

III.E.3.e. 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.



Change in	DIP		t	P
	Failure	Success		
Bone height				
width 1/4				
width 1/2				
width 3/4				

Source: [Redacted]

These tests show strong relationships between success in dental implant placement and improvement in bone height and width. Calculations are provided in PMA Amendment 6).

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.

Bone Growth and Secondary Endpoints

The strong association between bone growth and success in DIP heightens interest in whether the subsequent success endpoints are also associated with bone growth.

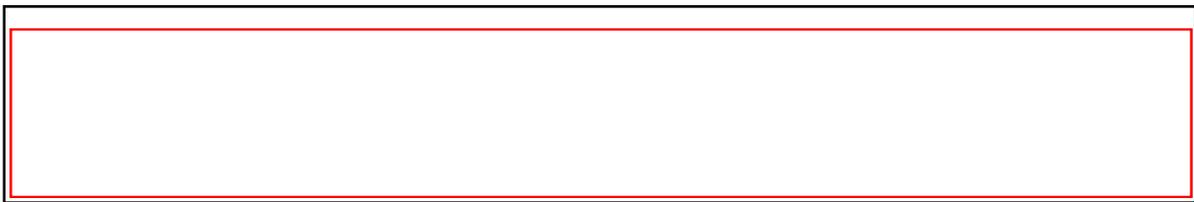
When these endpoints are considered, closer attention to withdrawals and missing information is required, as it is not clear to what extent these might be hidden failures. A three-way categorization was used for these later endpoints to reflect this concern – patients were divided into the groups: Success, where success in that endpoint was observed; Failure, where failure in that endpoint was observed; and, Missing, where valid data for the endpoint were not obtained. Analysis was by a one-way analysis of variance, with pairwise contrasts between these three groups. To allow for the multiple testing, [REDACTED]

[REDACTED] The results of this analysis are given in [REDACTED]

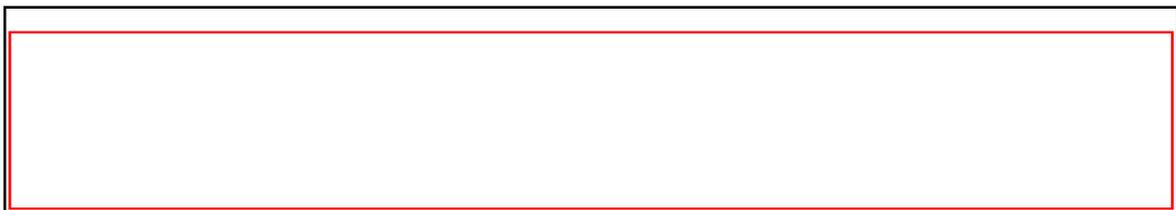
[REDACTED]

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.



- 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



III.E.3.f. 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 apposed with the tooth root. The amount of required bone augmentation is

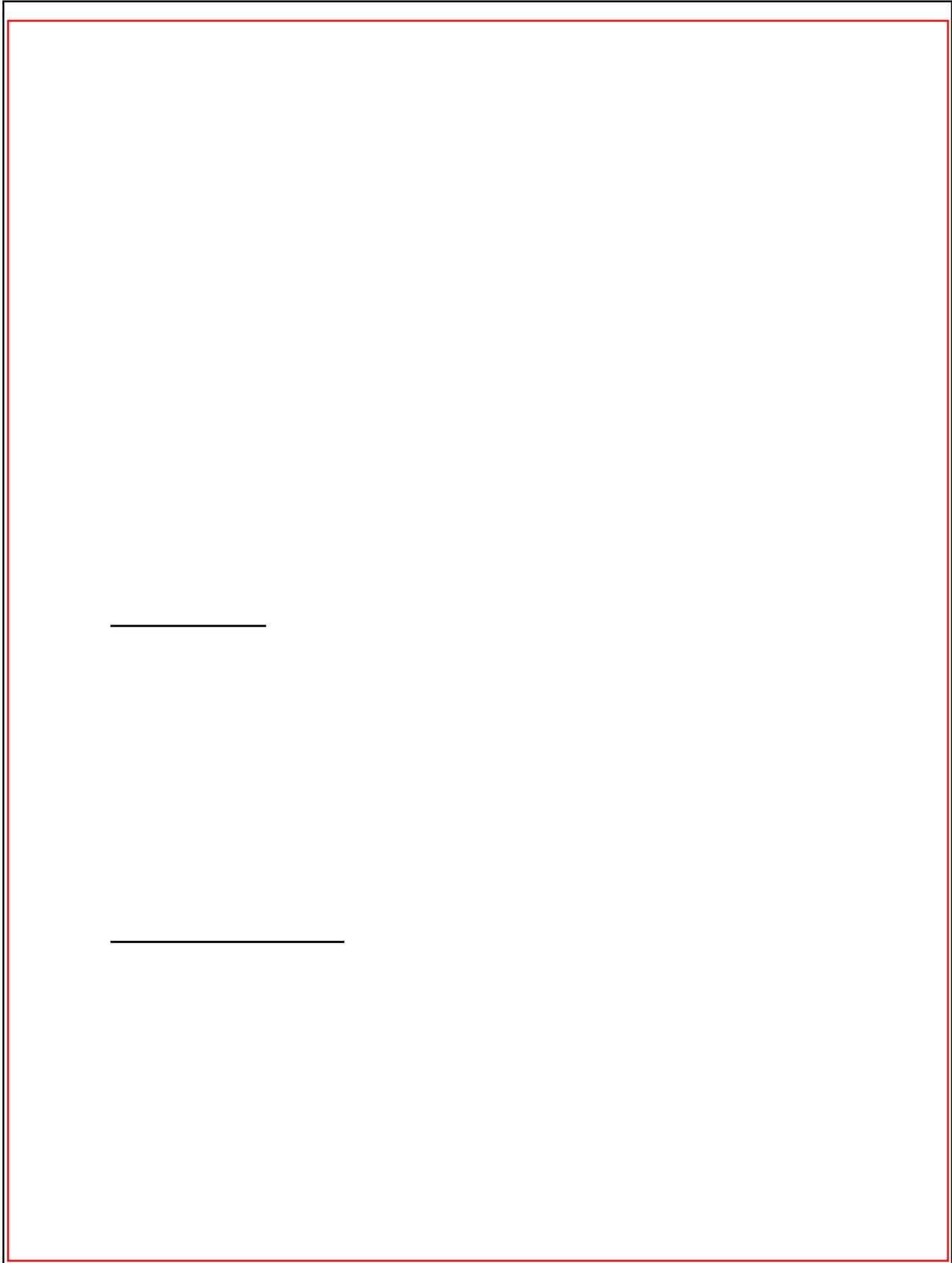
also less for the extraction socket augmentation. However, in order to support dental implants, it is critical that bone height and width are preserved.

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[®] Bone Graft in the extraction socket augmentation procedure.

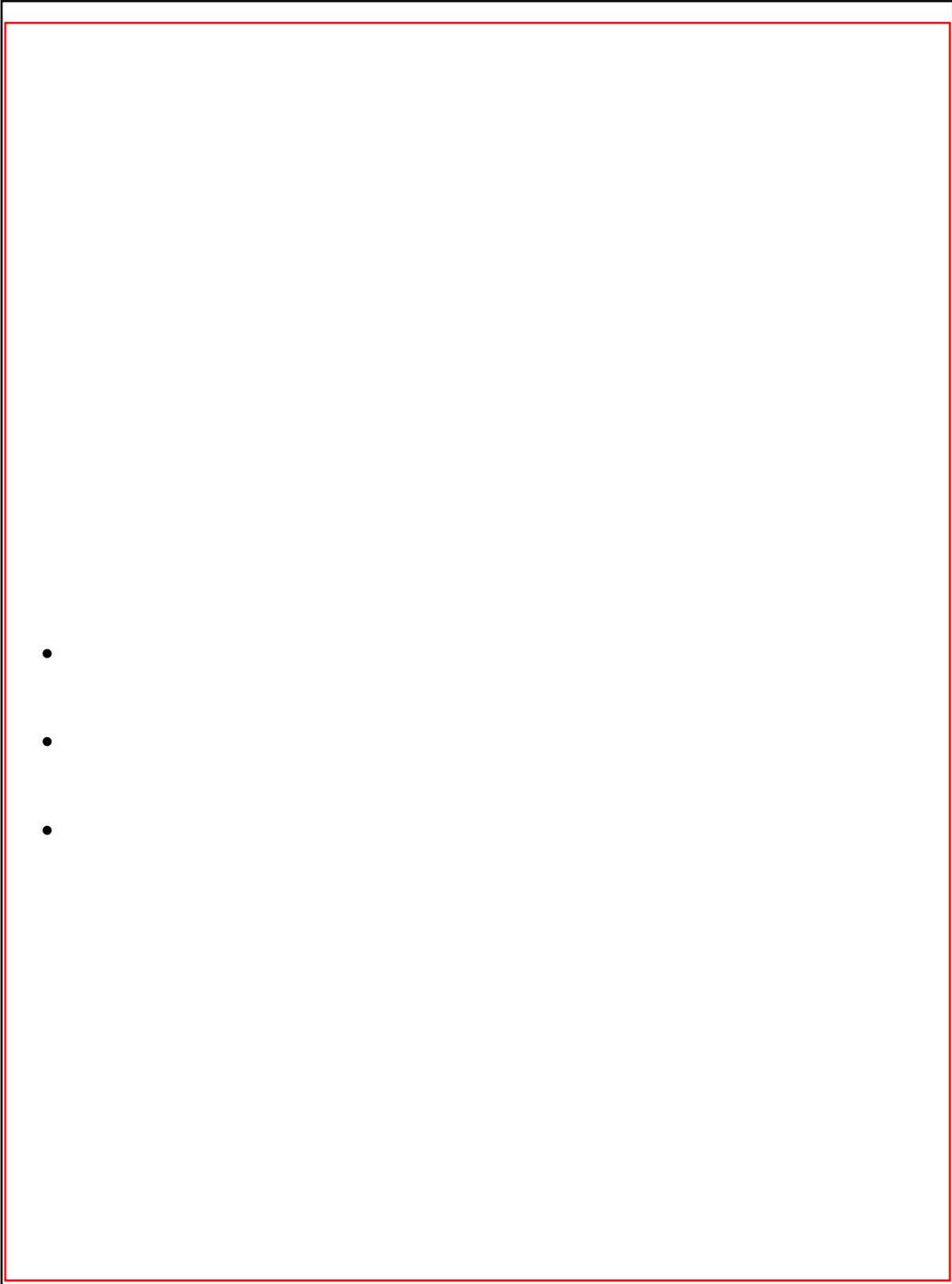
III.E.3.g. Conclusion

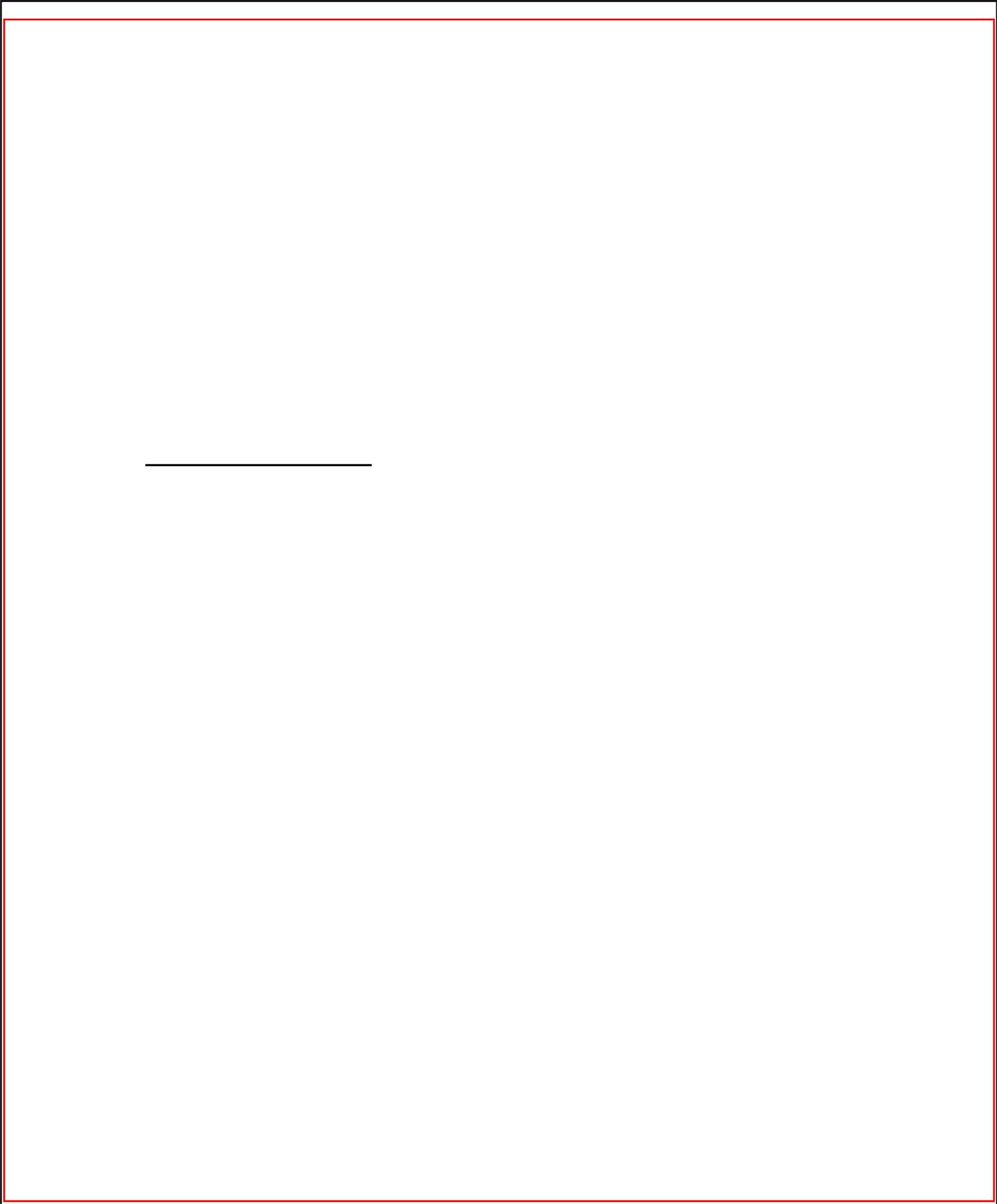
Based on the clinical evidence, INFUSE[®] Bone Graft is effective in growing bone in an extraction socket which allows placement of dental restoration and particularly implants and subsequent prosthesis placement and functional restoration. Specifically:

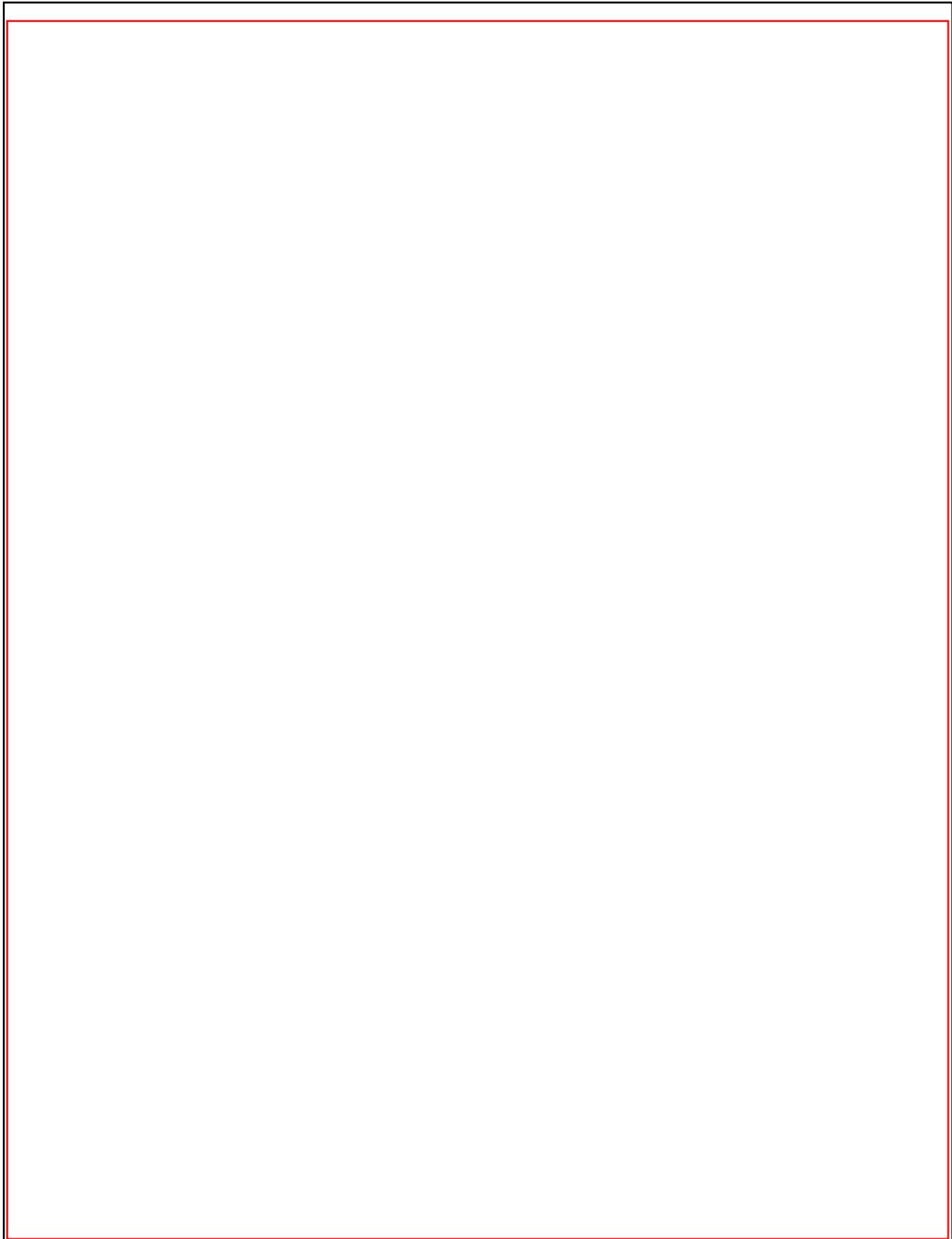
- Analysis of the clinical data demonstrates a statistical improvement in the ability to place dental implants, prostheses, and to maintain functional loading as compared to the no treatment control.
- Analysis of the clinical data shows a statistical relationship between the ability to grow bone in the extraction socket and the ability to place dental implants.
- 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[®] Bone Graft in the extraction socket augmentation procedure.
- Peer reviewed, published literature supports the use of INFUSE[®] Bone Graft for the extraction socket augmentation procedure
- Pre-clinical animal studies supports the use of INFUSE[®] Bone Graft for the extraction socket augmentation procedure.

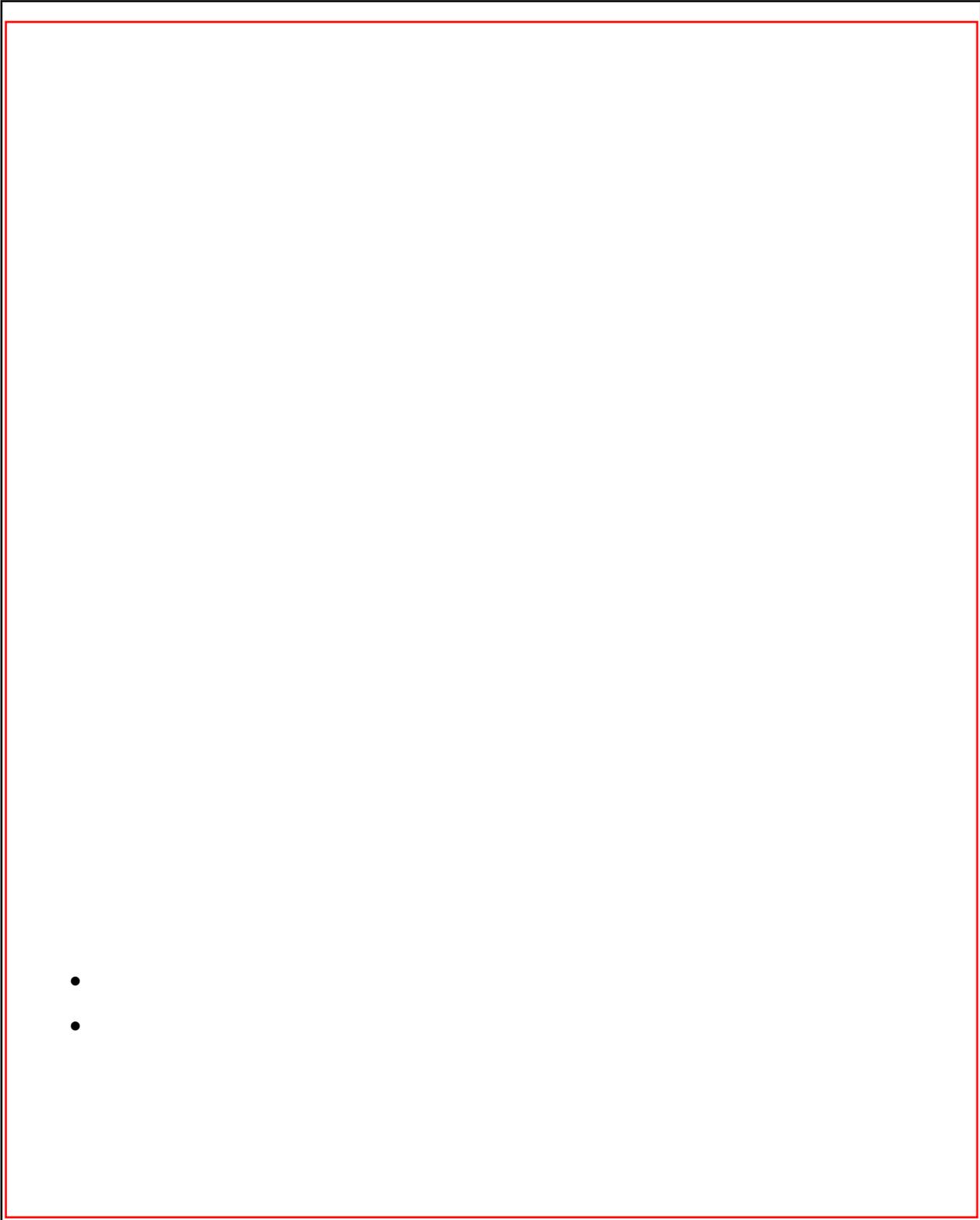












o [Redacted]

III.E.8. Safety

All subjects who were treated with any concentration of rhBMP-2 were included in the analysis of safety. The 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] [Redacted] [Redacted] subjects received one of three concentrations of rhBMP-2/ACS [Redacted] mg/ml, [Redacted] mg/ml, or [Redacted] mg/ml); [Redacted] subjects received bone graft, either autogenous bone (aut [Redacted] allograft). [Redacted]

[Redacted]

The analysis [Redacted]

[Redacted]

Based on the data from [Redacted] the incidence of adverse events reported in [Redacted] to bone graft was statistically significantly higher than

that reported for [redacted] 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 [redacted] or the [redacted] commercial concentration cohort [redacted] 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.

III.E.8.a. Combined Safety

To present a full evaluation of the safety of rhBMP-2/ACS in oral maxillofacial procedures, all subjects treated with rhBMP-2/ACS [redacted] regardless of the concentration of rhBMP-2/ACS used, were combined [redacted]. The cohort for assessing safety thus consists of [redacted] subjects in the sinus studies and [redacted] subjects in the AV ridge studies.

For the combined studies, the number and percentage of subjects with frequent adverse events (occurring in >10% of the subjects) by body system, COSTART terms and combined concentrations throughout the study period are presented in Table III.E-22 below.

Table III.E-22: Frequent Adverse Events (>10% of Subjects) by Indication, Body System, and COSTART Term [redacted]

Body System COSTART Term	Sinus Stu (n= [redacted])	AV Ridge Stu (n= [redacted])	All rhBMP-2/ ACS Subjects (n= [redacted])
	n (%)	n (%)	n (%)
Subjects with an adverse event	[redacted]	[redacted]	[redacted]
BODY AS A WHOLE			
[redacted]	[redacted]	[redacted]	[redacted]
HEADACHE	[redacted]	[redacted]	[redacted]
INFECTION	36 (27.9)	[redacted]	[redacted]
PAIN	28 (21.7)	2 (3.6)	[redacted]
DIGESTIVE SYSTEM			
[redacted]	[redacted]	[redacted]	[redacted]
ORAL ERYTHEMA	[redacted]	29 (52.7)	80 (43.5)
MOUTH PAIN	115 (89.1)	44 (80.0)	[redacted]
HEMIC AND LYMPHATIC SYSTEM			
ECCHYMOSIS	25 (19.4)	4 (7.3)	29 (15.8)
MUSCULO-SKELETAL SYSTEM			
BONE DISORDER	[redacted]	2 (3.6)	21 (11.4)

Source: ae3.sas

For a complete listing of all adverse events by body system and COSTART term reported [redacted] refer to Appendix VIII-24 or the original PMA submission.

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 (80/184=43%); and general infection [redacted]. These adverse events are not unusual for this type of surgical procedure.

III.E.8.b. Comparison to Bone Graft

III.E.8.b.1. 1.5 mg/ml Concentration of rhBMP-2/ACS Compared to Bone graft

Of [redacted] subjects who received rhBMP-2/ACS, [redacted] 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 [redacted] versus bone graft [redacted] adverse events for the two treatment groups were compared. The results are presented in Table III.E-23.

Table III.E-23: 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 ^a rhBMP-2/ACS vs Bone Graft
	n (%)	n (%)	
BODY AS A WHOLE			
EDEMA	2 (1.7)	34 (37.4)	
[redacted]			
PAIN	26 (21.7)	46 (50.5)	
DIG			
[redacted]			
ORAL ERYTHEMA	57 (47.5)	56 (61.5)	
MOUTH PAIN	102 (85.0)	76 (83.5)	
HEMIC AND LYMPHATIC SYSTEM			
ECCHYMOSIS	19 (15.8)	21 (23.1)	
METABOLIC AND NUTRITIONAL DISORDERS			
HYPERGLYCEMIA	8 (6.7)	15 (16.5)	
MUSCULO-SKELETAL SYSTEM			
ARTHRALGIA	14 (11.7)	24 (26.4)	
BONE DISORDER	14 (11.7)	11 (12.1)	
NERVOUS SYSTEM			
ABNORMAL GAIT	0 (0.0)	37 (40.7)	
HYPESTHESIA	5 (4.2)	15 (16.5)	
SINUSITIS	11 (9.2)	15 (16.5)	
SKIN AND APPENDAGES			
	9 (7.5)	34 (37.4)	

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 (85.0% vs. 83.5%), [redacted] and oral erythema [redacted]

[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.

Morbidity by Harvest Location

[REDACTED] subjects were randomized to the bone graft treatment group in [REDACTED]. Studies [REDACTED] collected data on a Harvest Site case report form for evaluation of the morbidities associated with bone graft harvest. The data are reported from [REDACTED] subjects randomized to bone graft in the [REDACTED] pivotal and [REDACTED] sinus dosing studies.

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 [REDACTED] [REDACTED] 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. These results are actually somewhat surprising compared to the literature on the morbidity of bone graft harvest and may reflect a smaller

amount of bone harvested. Another factor may have been that allograft was used in more than a third of bone graft subjects [redacted] to augment the autograft harvested. Table III.A-24 shows the adverse events reported on the Harvest Site form over the first six months post-surgery.

Table III.E-24: Harvest Site Adverse Events Reported at Each Time Period – Study [redacted] and [redacted] Bone Graft Subjects [redacted]

Variable	2 days post-op	10 days post-op	1 month post-op	2 months post-op	4 months post-op	6 months post-op
Pain	69.6% (55/79)	41.8% (33/79)	12.5% (10/80)	5.0% (4/80)	2.5% (2/79)	2.6% (2/78)
Hematoma	8.9% (7/79)	5.1% (4/79)	0.0% (0/80)	0.0% (0/80)	0.0% (0/79)	0.0% (0/78)
Edema	62.0% (49/79)	41.8% (33/79)	5.0% (4/80)	0.0% (0/80)	0.0% (0/79)	0.0% (0/78)
Erythema	48.1% (38/79)	32.9% (26/79)	3.8% (3/80)	1.3% (1/80)	0.0% (0/79)	0.0% (0/78)
Exudate	3.8% (3/79)	0.0% (0/79)	0.0% (0/80)	0.0% (0/80)	0.0% (0/79)	0.0% (0/78)
Infection	0.0% (0/79)	0.0% (0/79)	0.0% (0/80)	0.0% (0/80)	0.0% (0/79)	0.0% (0/78)
Sensory Loss	10.1% (8/79)	13.9% (11/79)	12.5% (10/80)	10.0% (8/80)	8.9% (7/79)	9.0% (7/78)
Wound Dehiscence	0.0% (0/79)	0.0% (0/79)	0.0% (0/80)	0.0% (0/80)	0.0% (0/79)	0.0% (0/78)
Gait Disturbance	43.0% (34/79)	29.1% (23/79)	11.3% (9/80)	2.5% (2/80)	2.5% (2/79)	2.6% (2/78)
Other	11.4% (9/79)	12.7% (10/79)	3.8% (3/80)	1.3% (1/80)	1.3% (1/79)	3.8% (3/78)

Source: hse.sas

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. Twelve subjects underwent harvest procedures from other locations; nine of these were harvests of intra-oral bone near the surgical site. Table III.E- 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 III.E-25 Adverse Events Reported by Harvest Site in Bone Graft Subjects from [REDACTED]

Variable	Harvest Site	2 days	10 days	1 month	2 months	4 months	6 months
Pain	Iliac Crest (n=14)	88.9%	44.4%	5.6%	5.6%	0.0%	0.0%
	Tibial Plateau (n=27)	66.7%	51.5%	24.2%	9.1%	6.1%	6.3%
	Intra-Oral Bone (n=14)	73.3%	46.7%	6.7%	0.0%	0.0%	0.0%
	Other (n=12)	46.2%	7.7%	0.0%	0.0%	0.0%	0.0%
Sensory Loss	Iliac Crest (n=14)	0.0%	0.0%	11.1%	11.1%	11.1%	11.1%
	Tibial Plateau (n=27)	0.0%	3.0%	3.0%	3.0%	0.0%	0.0%
	Intra-Oral Bone (n=14)	40.0%	60.0%	46.7%	33.3%	33.3%	33.3%
	Other (n=12)	15.4%	7.7%	0.0%	0.0%	0.0%	0.0%
Gait Disturbance	Iliac Crest (n=14)	55.6%	44.4%	16.7%	0.0%	5.6%	5.6%
	Tibial Plateau (n=27)	72.7%	45.5%	18.2%	6.1%	3.0%	3.1%

III.E.8.c. Risk/Benefit Analysis – INFUSE® Bone Graft versus Autogenous Bone Graft

The purpose of this section is to compare the risks and benefits of the proposed rhBMP-2/ACS (INFUSE BONE® GRAFT) to that of bone graft which is the current standard of care for oral maxillofacial bone grafting procedures. In this analysis, "bone graft" refers to the control device used in [REDACTED] [REDACTED] to evaluate the safety and effectiveness of rhBMP-2/ACS for its intended use. Bone graft in these studies consisted of autogenous bone (autograft) harvested from the iliac crest, tibia or intra-oral cavity used alone or in combination with allogeneic bone (allograft).

The benefits of INFUSE® Bone Graft are:

- Effective Bone Formation
- No second-site surgery
- Native Bone Formation
- Lower instances of adverse events
- Lower incidence of complications
- No need to use limited supply of autogenous bone

- Commercially available
- Expanded patient population
- No need for allograft

The risks of INFUSE[®] Bone Graft include:

- Failure to induce bone or induces less bone growth than desired
- Potential hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or other components of the formulation
- Potential adverse effects: if used in the vicinity of a resected or extant tumor; in patients with any active malignancy; patients undergoing treatment for a malignancy; in pregnant women, or in nursing mothers.
- Theoretical risks that are addressed in warnings on INFUSE[®] Bone Graft labeling:
 - Potential adverse effect on fetal development
 - Hepatic and Renal Impairment
 - Ectopic, heterotopic or undesirable exuberant bone formation
 - Immunogenicity

Benefits of autogenous bone graft include

- Effective bone formation
- Long history of success in oral maxillofacial bone grafting applications
- Current standard of care for this indication.

Risks of autogenous bone graft include

- Requires second surgery to harvest bone
- Morbidity and complications associated with harvesting bone.
- Adverse events associated with bone harvest
 - Pain
 - edema
 - erythema

- arthralgia (sensory loss)
- gait disturbance.
- Patients who, due to their particular physiology, are unable to be harvested for autogenous bone
- Fear of the procedure (patients would rather not fix their oral problem than undergo the morbidity of the harvest procedure)

In light of the disadvantages associated with autogenous bone grafting procedures, rhBMP-2/ACS provides a good treatment option that is a safe and effective alternative for oral maxillofacial procedures. The benefits of INFUSE[®] Bone Graft clearly outweigh the risks.

III.E.9. Conclusions

INFUSE[®] 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.



The morbidity associated with harvesting bone is a significant issue which is overcome by the INFUSE[®] Bone Graft product. In light of the disadvantages associated with autogenous bone grafting procedures, rhBMP-2/ACS provides a good treatment option that is a safe and effective alternative for oral maxillofacial procedures. The benefits of INFUSE[®] Bone Graft clearly outweigh the risks.