

PROPOSED SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Bone grafting material containing a therapeutic biologic

Device Trade Name: Augment® Bone Graft

Applicant's Name and Address: Wright Medical Technology, Inc.
BioMimetic Therapeutics, LLC
389 Nichol Mill Lane
Franklin, Tennessee 37067

Date of Panel Recommendation: May 12, 2011

Premarket Approval Application (PMA) Number: P100006

Date of FDA Notice of Approval: September 1, 2015

II. INDICATIONS FOR USE

Augment® Bone Graft is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination), due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material.

III. CONTRAINDICATIONS

Augment® Bone Graft **should not**:

- be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products.
- be used in patients with active cancer.
- be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- be implanted in patients with an active infection at the operative site.
- be used in situations where soft tissue coverage is not achievable.

- be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes.
- be used as a substitute for structural graft.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

Augment® Bone Graft is a combination device/drug indicated for use as an alternative to autograft in arthrodesis (i.e., fusion procedures) of the ankle and/or hindfoot indicating the need for supplemental graft material. The use of Augment® Bone Graft eliminates the need for a second surgery to harvest autologous bone, thereby avoiding donor site morbidity which may occur (e.g., pain, infection, etc.).

Augment® Bone Graft combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable synthetic bone matrix (beta-tricalcium phosphate or β -TCP). The rhPDGF-BB is chemotactic for fibroblasts, neutrophils, and monocytes, cell types important for the early phases of tissue repair. The rhPDGF-BB is mitogenic for fibroblasts, osteoblasts, chondrocytes, and mesenchymal stem cells, which are important for later-stage tissue formation. The rhPDGF-BB functions as a chemo-attractant and mitogen for cells involved in wound healing and through its promotion of angiogenesis at the site of healing. The β -TCP acts as bone void filler to prevent soft tissue from collapsing into the void. When the β -TCP is placed near a viable host bone, it acts as a scaffold for new bone growth (osteoconductive).

These two components are packaged together and are physically combined immediately prior to use as follows:

- 1.5, 3, 6, or 9cc of synthetic β -TCP in granule form (nominal particle size 1 to 2 mm) provided in a 44mm PETG/PE laminate cup closed with a heat-sealed PET/PE/Foil laminate lid. The β -TCP cup is packaged into a PETG tray closed with a heat-sealed coated *Tyvek*® lid. The finished component (cup/tray subassembly) is terminally sterilized by gamma irradiation.
- 1.5, 3, 6, or 9 mL of rhPDGF-BB (0.3 mg/mL in 20mM USP sodium acetate buffer, pH 6.0) is aseptically filled into a single or multiple 3 mL USP Type I borosilicate glass vial(s) (Kimble or Schott) with a 13 mm chlorobutyl rubber stopper (West Pharma S2-F451 4432/50 Gray Butyl Rubber with B2-40 Coating) and a flip-off tear cap. The rhPDGF-BB vial is packaged into a PETG tray closed with a heat-sealed coated *Tyvek*® lid. The finished component (vial/tray subassembly) is terminally sterilized by ethylene oxide gas.

The surgeon estimates the volume of graft material required, which is dependent on the size of the voids to be filled, and selects the appropriate number of kits for the surgery. Equal volumes

of rhPDGF-BB and β -TCP are mixed in a sterile surgical bowl. Any remaining material is discarded.



Figure 1: Augment® Bone Graft

The two sub-assemblies of equal size are included in each kit, along with the package insert, and are packed together in an SBS carton as the final product (Figure 2).

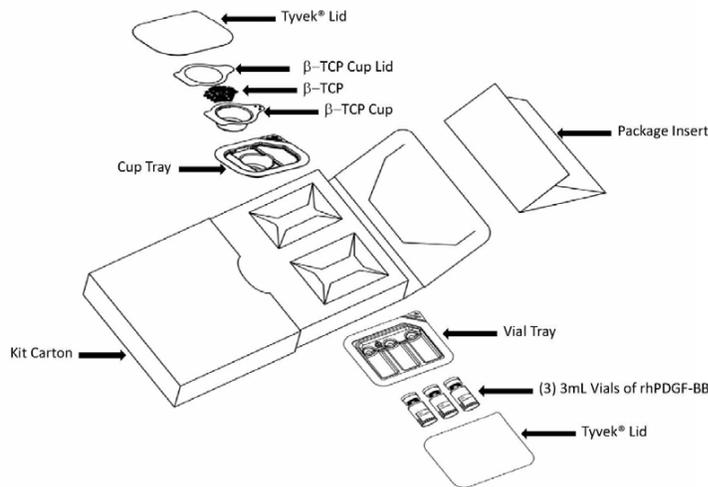


Figure 2. Augment® Bone Graft 9cc final kit (finished product) showing the assembly of the β -TCP device component (filled cup in a tray) and the rhPDGF-BB drug component (filled vial in a tray). The package insert is placed in the flipside of the carton when pulled open.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Currently, there are no generally accepted alternatives to autograft for arthrodesis procedures of the ankle or hindfoot. Ankle and hindfoot arthrodesis procedures, such as triple arthrodesis

(three hindfoot articulations), double arthrodesis (two hindfoot articulations), subtalar arthrodesis, talonavicular arthrodesis, calcaneocuboid arthrodesis, and ankle arthrodesis involve the same treatment principles of creating a peri-articular osteotomy, stabilizing the joint with rigid fixation, placing harvested autograft bone, and following standard post-operative regimen of physical therapy and gradually increasing load on the fusion.

One of the most widely used options for bone graft is autologous bone, because there is no risk of cross contamination with autologous bone in contrast to allografts. However, clinical difficulties have been associated with autograft. Most of these difficulties result from the harvest of the bone graft, including increased operative time, hospital stay and cost, increased blood loss, post-operative pain, risk of infection, and/or fracture.

Other reported complications associated with autograft include a potential nidus for infection associated with avascular bone, limited tissue supply, and variability in cellular activity of the bone graft (Younger et al. 1989 ¹). In addition to these complications, limitation exists in the amount of bone graft that may be harvested. The morbidity associated with autograft and its limited amount available to be harvested has directed surgeons to look for a better alternative for a chemotactic, mitogenic, and angiogenic bone graft substitute to accelerate healing (St. John et al. 2003 ²).

VII. MARKETING HISTORY

BioMimetic Therapeutics, LLC, received approval from Health Canada (2009) to begin marketing Augment® Bone Graft in Canada for ankle and hindfoot arthrodesis indications. Approval was granted from Australia (2011), New Zealand (2011), and Mexico (2013) to market Augment® Bone Graft for ankle and hindfoot indications. The components of Augment® Bone Graft (rhPDGF-BB and β -TCP) have been independently marketed in the United States, Canada, and internationally. Neither Augment® Bone Graft, nor any of its separate components, have ever been withdrawn from a market for any safety or effectiveness reason.

In addition, a chemically identical combination of β -TCP and rhPDGF-BB was developed by BioMimetic Therapeutics, LLC, under the trade name GEM 21S®. This product was approved in 2005, under PMA #P040013, to treat patients who have dental bone defects due to periodontal disease. This product is currently marketed in the United States and Canada by Osteohealth Company, a Division of Luitpold Pharmaceuticals, Inc., and over 200,000 units have been implanted. It has not been withdrawn from any market. The data from this PMA formed part of the basis for the IDE approval of Augment® Bone Graft.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Patients may experience any of the following adverse events that have been reported in the literature with regard to the use of autograft or bone graft substitute products: swelling, pain, bleeding, hematoma, superficial or deep wound infection, cellulitis, wound dehiscence, incomplete or lack of osseous ingrowth, transient hypercalcemia, neuralgia and loss of sensation

locally and peripherally, and anaphylaxis. Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Augment® Bone Graft identified from the Augment® Bone Graft clinical trial results and published scientific literature including: (1) those associated with any surgical procedure; (2) those associated with ankle and hindfoot arthrodesis surgery; and (3) those associated with bone graft substitute products for use in ankle and hindfoot arthrodesis, such as Augment® Bone Graft. In addition to the risks listed below, there is also the risk that surgery may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional surgery may be required to correct some of the adverse effects and may also require removal of the grafting material.

1. Risks associated with any surgical procedure include: infection; pneumonia; atelectasis; septicemia; injury to blood vessels; soft tissue damage; phlebitis, thromboembolus, or pulmonary embolus; hemorrhage; respiratory distress; pulmonary edema; reactions to the drugs or anesthetic agent used during and after surgery; reactions to transfused blood; failure of the tissue to heal properly (e.g., hematoma, seroma, dehiscence, etc.) which may require drainage, aspiration, or debridement or other intervention; incisional pain; heart attack; stroke; and death.
2. Risks associated with ankle and hindfoot arthrodesis surgery with or without the use of graft material include: swelling; bleeding; hematoma; superficial or deep wound infection; cellulitis; wound dehiscence; transient hypercalcemia; neuralgia and loss of sensation locally and peripherally; anaphylaxis; incomplete or lack of osseous ingrowth, postoperative muscle and tissue pain; surgery may not reduce the preoperative pain experienced; pain and discomfort associated with the presence of implants used to aid in the arthrodesis surgery or reaction to the metal used in the implant, as well as the cutting and healing of tissues; the ankle and/or hindfoot may undergo adverse changes or deterioration including loss of height, and/or reduction, or malalignment, and another surgery may be required; and adverse bone/implant interface reaction.
3. Risks associated with bone graft substitute products, including Augment® Bone Graft, include non-unions, allergies or immunogenic response to implant materials, hypersensitivity, migration of the graft material into the surrounding soft tissue, musculoskeletal and connective tissue disorders, nervous system disorders, arthralgia, pain in extremities, and infections.

Adverse events that occurred in the Augment® Bone Graft clinical trial are listed in Section IX.

IX. SUMMARY OF NON-CLINICAL STUDIES

Pre-clinical studies were conducted to assess the safety and effectiveness of the individual and combined components contained in Augment® Bone Graft. BioMimetic Therapeutics, LLC conducted an extensive preclinical evaluation of rhPDGF-BB in combination with β -TCP

matrices to provide sufficient data supporting its safe and effective use in treating orthopedic indications.

The structure, biology, and function of the rhPDGF-BB protein has been characterized and reported in the scientific literature. It has been reported that rhPDGF-BB functions to stimulate wound healing by attracting healing cells to wound sites, inducing them to proliferate, and supporting neovascularization to help establish an adequate blood supply. There is no evidence of systemic toxicity, acute or chronic, associated with rhPDGF-BB.

The efficacy of rhPDGF-BB combined with β -TCP for stimulating bone repair was evaluated in a variety of animal preclinical studies. Several animal models of bone repair demonstrated the local pharmacological activity and safety of rhPDGF-BB in combination with β -TCP and other matrix materials.

To evaluate the biocompatibility, toxicology, stability, and ADME/pharmacokinetics of rhPDGF-BB alone, and in combination with β -TCP, a series of studies were performed. The sponsor conducted a panel of biocompatibility/toxicology studies in compliance with ISO 10993 and USP guidelines. These studies evaluated β -TCP alone or in combination with rhPDGF-BB, and on β -TCP from several sources with or without rhPDGF-BB. The totality of the data from the biocompatibility studies demonstrated that rhPDGF-BB combined with β -TCP is non-toxic and biocompatible, which helps to define the safety profile for Augment® Bone Graft. In addition, a repeat-dose toxicity study to evaluate bone tissue responses to rhPDGF-BB in rats and an acute toxicity study to evaluate systemic toxicity following intravenous administration of rhPDGF-BB in rats were also performed. The results from these studies showed no signs of toxicity for rhPDGF-BB administered either locally or intravenously in animal models.

Stability

Primary analytical data of an on-going stability study were provided supporting label storage claims and drug product expiration dating for 36 months. The study was performed on six (6) lots of 0.3 mg/mL rhPDGF-BB (three lots each of 1.5mL and 3.0 mL in 3 mL vials). The study assessed stability of the samples stored under real-time conditions (2°C - 8°C) and accelerated aging room temperature conditions (22°C - 27°C). All drug product stored at 2°C - 8°C met the specification limits for all evaluated attributes through the 36 month time point. The rhPDGF-BB met the stability criteria under accelerated aging conditions for a duration corresponding to 36 months of real-time storage at 2°C - 8°C.

Chronic Toxicity and Carcinogenicity

A study was conducted to evaluate the chronic toxicity and carcinogenicity of rhPDGF-BB mixed with β -tricalcium phosphate (β -TCP) matrix (Augment® Bone Graft) implanted in a rat model. Three hundred (150 male/150 female) Sprague-Dawley rats were randomly distributed into three groups (test article, control article, and sham surgery). Test or control article were implanted adjacent to the femur underneath the overlying muscle. The test article dose administered was 30 μ g of rhPDGF-BB, which is approximately four times the maximum clinical dose. Animals were treated on day 0 and euthanized after 30, 180, or 365 days. Both

macroscopic and microscopic evaluations were performed to evaluate toxicity and tumor incidence. Serum was collected for hematology, coagulation, and clinical chemistry determinations. Bone marrow was also collected from all animals at all time-points. Additionally, anti-PDGF-BB antibody formation was determined using ELISA.

No treatment-related mortality or effects on the clinical condition of the rats were observed. No remarkable article-related changes in body weight or body weight gain were observed. No significant changes in urinalysis parameters across treatment groups and gender were observed. Similarly, no significant changes in bone marrow parameters across treatment groups and gender were observed. In general, minor changes in clinical chemistry were observed, but due to the sporadic changes across treatment groups, gender, and time point, the changes were not attributed to treatment with rhPDGF-BB.

There were no test article-related microscopic findings on days 30, 180, or 365 of the study. On day 30, minimal foreign body granulomas were present at the implant site within the skeletal muscle across groups (control article, test article, and sham surgery) in the majority of animals examined. These granulomas contained material consistent with surgical sutures and were considered a result of the operative procedure. Minimal to mild granulation tissue was noted at the implant site in animals from the control and the test article groups (no animals from the sham surgery group displayed this change) on days 30, 180, and 365. This finding was likely related to the β -TCP matrix and was not considered rhPDGF-BB related. Mild hyperostosis was present on the periosteal surface of the femur where the granulation tissue was present at days 180 and 365, but not at day 30. It consisted of well-differentiated bone that was indistinguishable from the normal femoral bone. This hyperostosis was considered secondary to a local effect of the β -TCP matrix on the periosteal surface of the femur.

An adenocarcinoma of the mammary gland was noted in one of the 10 females of the test article (rhPDGF-BB) group on day 180. This finding was considered incidental, based on its unique occurrence and the absence of any hyperplastic changes noted in this group. There were no test article-related neoplastic microscopic observations noted in either sex on day 365. Serum test article antibody analysis of 590 samples found one sample to be positive for anti-rhPDGF-BB antibodies. This animal was treated with the control article, i.e., a false positive.

The results of this study demonstrated that implantation of the test article was not associated with any unexpected mortality, clinical findings, or changes in body weight or food consumption. In addition, implantation of the test article was not associated with any treatment-related changes in hematology, coagulation, clinical chemistry, or bone marrow parameters. Upon necropsy and histopathologic evaluation, no differences were noted in tissue response between the sham or control treated animals and the test article implanted animals. The results of this study demonstrate that implantation of the test article did not result in any toxicity or tumorigenicity and, in addition, demonstrate that the test article was biocompatible.

Pharmacokinetics

Two animal studies were presented that provide data characterizing the pharmacokinetics of ¹²⁵I-rhPDGF-BB, its metabolism and excretion, and tissue distribution in a rat model. Both studies indicated that rhPDGF-BB is cleared rapidly from the blood (mainly in the urine), with lesser amounts eliminated in the feces following intravenous administration. There is limited systemic exposure to the protein following intramuscular implantation of ¹²⁵I-rhPDGF-BB combined with Augment® Bone Graft's β-TCP and clearance is again mainly in the urine. Overall, the toxicology and pharmacokinetic data demonstrated that rhPDGF-BB combined with Augment® Bone Graft's β-TCP does not lead to any signs of acute or chronic toxicity and the protein is eliminated rapidly from the body following administration with limited systemic exposure. However, while the evaluations provide information regarding the relative clearance rates of injected or implanted rhPDGF-BB, they only approximate how the product will be implanted in ankle or hindfoot bone grafting procedures.

The characterization of the release kinetics, biological potency, and biochemical integrity of rhPDGF-BB combined with β-TCP from different sources was also studied. Both *in vivo* and *in vitro* preclinical data demonstrated that rhPDGF-BB is released rapidly from Augment® Bone Graft's β-TCP and other sources of β-TCP in a similar fashion. The protein retains its biological potency and is biochemically intact following release from β-TCP matrices as determined by *in vitro*, cell-based analyses. Thus, the data support Augment® Bone Graft's β-TCP as an appropriate matrix as the device component of this combination product.

Reproductive Development/Teratology

A reproductive development/teratology study in female Sprague-Dawley rats was conducted at two dose levels (1 times and 10 times the maximum single, clinical dose) repeated daily over 21 days starting on day zero of gestation, i.e., the low dose group received 21 times (21 days of 1x dose amounts) and the high dose group 210 (21 days of 10x dose amounts) times the maximum clinical dose during the extended period of administration. The rats were divided into three groups: 22 rats served as the control group; 22 rats received 0.04 mg/ml rhPDGF-BB 40 µg/kg/day (“the low dose group”); and 22 rats received 0.4 mg/ml rhPDGF-BB 400 µg/kg/day (“the high dose group”). Detailed examinations, which included measurement of body weight and food consumption, were performed on gestation days 0, 3, 6, 9, 12, 15, 18, and 21. Maternal blood sampling was performed on gestation days 0 and 21 and fetal blood sampling was performed on day 21 of gestation.

The fetuses were evaluated macro- and microscopically for visceral and skeletal development anomalies. No visceral or skeletal anomalies were observed in the control or the low dose rhPDGF-BB groups; no visceral anomalies were found in the first generation fetuses. There were indications of somewhat accelerated ossification of the interparietal and hyoid bones and slight (not significant) increase in the presence of a rudimentary 14th rib in first generation fetuses from maternal rats (dams) receiving rhPDGF-BB. The low dose group had a higher incidence of incomplete ossification of the hyoid bone, while the high dose group had lower incidence of incomplete ossification of the interparietal bone. However, this finding was not dose-dependent; the incidence of incomplete ossification of the hyoid bone in the high dose group was not different from the control group. These observations were made in comparison to the control group.

No detectable amount of rhPDGF-BB was found in the maternal and fetal plasma samples. Anti-rhPDGF-BB antibodies were detected in one out of 15 dam pretreatment samples analyzed. All dam and fetal post-treatment samples analyzed were negative for antibodies to rhPDGF-BB.

The administration of rhPDGF-BB at 0.040 and 0.40 mg/kg/day, by intravenous injection, to female rats from Gestation Days 0 to 20 resulted in neither maternal toxicity, nor adverse effects on embryo-fetal development, in this study. Based on these results, 0.40 mg/kg/day (i.e., the highest dose tested in this study) was the no-observed-effect-level for maternal toxicity and the no observed-adverse-effect-level for embryo-fetal development.

Table 1 summarizes the biocompatibility studies and Table 2 summarizes the preclinical animal studies performed. See below.

Table 1: Biocompatibility Studies

Test	Standard	Methods	Result	Pass
Genotoxicity of β -TCP	ISO 10993 Part3	Reverse Mutation Assay using NaCl and CSO Extracts (Salmonella typhimurium and Escherichia coli)	Nonmutagenic to Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, and to Escherichia coli strain WP2	Pass
Intracutaneous Reactivity of β -TCP	ISO 10993 Part 11	Intracutaneous Injection Test using NaCl and CSO Extracts in New Zealand White Rabbits	Negligible irritant	Pass
Sensitization of β -TCP	ISO 10993 Part 10	Klingman Maximization Test using NaCl and CSO Extracts in Guinea Pigs	Grade I Reaction (0% sensitization)	Pass
Cytotoxicity of β -TCP	ISO 10993 Part 5	L929 MEM Elution Test	Non-cytotoxic. Grade 2 Reaction (slight)	Pass
Intramuscular Reactivity of β -TCP	ISO 10993 Part 6	Intramuscular Implantation Test (4 Week Implantation) in New Zealand White Rabbits	Moderate Bioreactivity Rating of 9.5-15.0	Pass
Acute Toxicity of β -TCP	ISO 10993 Part 11	Systemic Injection Test in Swiss Albino Mice	No biological response when compared to control.	Pass
Genotoxicity of Augment® Bone Graft Bone Graft	ISO 10993 Part3	Reverse Mutation Assay using NaCl and CSO Extracts (Salmonella typhimurium and Escherichia coli)	Nonmutagenic to Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, and to Escherichia coli strain WP2	Pass
Intracutaneous Reactivity of Augment® Bone Graft	ISO 10993 Part 11	Intracutaneous Injection Test using NaCl and CSO Extracts in New Zealand White Rabbits	Negligible irritant	Pass
Sensitization of Augment® Bone Graft	ISO 10993 Part 10	Klingman Maximization Test using NaCl and CSO Extracts in Guinea Pigs	Grade I Reaction (0% sensitization)	Pass
Cytotoxicity of Augment® Bone Graft	ISO 10993 Part 5	L929 MEM Elution Test	Non-cytotoxic. Grade 1 Reaction (slight)	Pass
Intramuscular Reactivity of Augment® Bone Graft	ISO 10993 Part 6	Intramuscular Implantation Test (4 Week Implantation) in New Zealand White Rabbits	Bioreactivity Rating of 0.5	Pass
Acute Toxicity of Augment® Bone Graft	ISO 10993 Part 11	Systemic Injection Test in Swiss Albino Mice	No biological response when compared to a control.	Pass

Table 2: Pre-Clinical Animal Studies

Test	Methods	Result
Acute Toxicity of rhPDGF-BB Following Intravenous Administration in Rats (Acute, single dose Systemic Toxicity)	Single IV injection of 0.2 and 4.0 mg/kg of rhPDGF-BB; follow-up 2 and 15 days The high dose (4,000 µg/kg), was approximately 100 times the maximum clinical dose (39 µg/kg)	<ul style="list-style-type: none"> • Intravenous rhPDGF-BB at 0.15 or 3.0 mg/mL did not elicit significant toxicity in rats • rhPDGF-BB has a high margin of safety in this assay when administered intravenously
Evaluation of the chronic toxicity and carcinogenicity of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) mixed with β-tricalcium phosphate (β-TCP) matrix (Augment® Bone Graft) implanted in a rat model (Chronic Local Toxicity and carcinogenicity)	Single implantation of 0.175 mg/kg of Augment® Bone Graft bone graft; follow-up 30, 180 and 365 days	<ul style="list-style-type: none"> • No evidence of carcinogenicity • No treatment-related mortality or effects on body weight, hematology, coagulation, clinical chemistry, bone marrow parameters, or histopathology • No differences in local tissue response between groups • No anti-PDGF-BB antibodies seen in the Augment® Bone Graft-treated group
Bone Response to Intramuscular Injections of rhPDGF-BB (Acute Local Toxicity; Repeated dose)	Repeated IM injections in muscle next to femur; doses of 13.9; 41.2 and 138.8 µg/kg/day every other day for 2 weeks; follow-up 2 and 6 weeks	<ul style="list-style-type: none"> • Effects at the high dose for both soft tissue and bone were consistent with the mechanism of action of PDGF • The responses were transient and not present 6 weeks after the last dose
Recombinant Human Platelet-derived Growth Factor-BB (rhPDGF-BB): an Intravenous Injection Teratology Study in the Rat (Reproductive and developmental Toxicity)	Repeated IV injections daily on gestation days 0-020; assessment of maternal and fetal toxicity	<ul style="list-style-type: none"> • No maternal toxicity • No adverse effects on embryo-fetal development • Minor transitory increases in the rate of ossification in the high dose fetuses. • No detectable neutralizing antibodies against rhPDGF-BB • NOAEL for maternal toxicity is 400 µg/kg/day • NOAEL for embryo fetal development is 400 µg/kg/day
Bacterial Mutagenicity Test - AMES Assay (Genotoxicity)	<ul style="list-style-type: none"> • Potential of rhPDGF-BB to induce: <ul style="list-style-type: none"> · histidine (His) reversion in <i>S. typhimurium</i> · tryptophan reversion in <i>E. coli</i> • Six dose levels with the top dose tested at 10 mg/mL (1.0 mg/plate) 	The highest dose tested: 10 mg/mL (1.0 mg/plate) rhPDGF-BB was non-mutagenic

Test	Methods	Result
Fracture Healing of the Tibia in Geriatric-Osteoporotic Rats	<ul style="list-style-type: none"> • Treatment groups (n=110 rats): <ul style="list-style-type: none"> • 1.0 mg/mL rhPDGF-BB + collagen/β-TCP • 0.3 mg/mL rhPDGF-BB + collagen/β-TCP • sodium acetate + collagen/β-TCP • untreated fracture • Model: <ul style="list-style-type: none"> • Unilateral fracture model (Einhorn model) • Outcomes: <ul style="list-style-type: none"> • Cellular proliferation – 4 days post-fracture (n=26) • Biomechanical testing – 6 and 8 weeks post fracture (n=66) • Histomorphometry – 12 weeks post-fracture (n=18) 	<ul style="list-style-type: none"> • At five weeks, the mechanical strength of Augment® Bone Graft-treated tibias was not different from the non-fractured contralateral tibia • There were no untoward tissue responses
Diabetic Rat Fracture Model	<ul style="list-style-type: none"> • Treatment groups (n=110 rats): <ul style="list-style-type: none"> • 1.0 mg/mL rhPDGF-BB + collagen/ β-TCP • 0.3 mg/mL rhPDGF-BB + collagen/ β-TCP • sodium acetate + collagen/ β-TCP • untreated fracture • Model: <ul style="list-style-type: none"> • Unilateral fracture model (Einhorn model) • Outcomes: <ul style="list-style-type: none"> • Cellular proliferation – 4 days post-fracture (n=26) • Biomechanical testing – 6 and 8 weeks post fracture (n=66) • Histomorphometry – 12 weeks post-fracture (n=18) 	<ul style="list-style-type: none"> • Augment® Bone Graft treatment in diabetic rats resulted in: <ul style="list-style-type: none"> • Increased cell proliferation at 4 days • Increased biomechanical strength as early as 6 weeks • Increased bone content of the fracture callus at 12 weeks • No evidence of either abnormal or ectopic bone formation
Partial arthrodesis of the carpus in dogs	<ul style="list-style-type: none"> • Treatment groups (n=30 dogs): <ul style="list-style-type: none"> • Autologous bone graft • rhPDGF-BB + Autologous bone graft • β-TCP • rhPDGF-BB + β-TCP • Collagen/β-TCP • rhPDGF-BB + Collagen/β-TCP • Model: <ul style="list-style-type: none"> • Two-level arthrodesis of the carpus • Outcomes: <ul style="list-style-type: none"> • Manual palpation – 5 and 12 weeks post-surgery (n=7; n=3) • Radiograph – 5 and 12 weeks post-surgery (n=7; n=3) • Histology – 12 weeks post-surgery (n=13) 	<ul style="list-style-type: none"> • Addition of rhPDGF-BB to the graft materials increased the number and extent of fused joints compared to the materials alone • New bone formed was normal • No evidence of ectopic bone formation • No evidence of acute or chronic toxicity

Test	Methods	Result
Biological Assessment of a Bone Repair Model (Rabbit Tibial Osteotomy)	<ul style="list-style-type: none"> • Unicortical 5-mm osteotomies • Treated with cylinders of: <ul style="list-style-type: none"> · β-TCP · β-TCP + 25 μg rhPDGF-BB · β-TCP+ 75 μg rhPDGF-BB • Histomorphometric analysis at 4 and 8 weeks post-implantation 	<ul style="list-style-type: none"> • Residual β-TCP detected at four weeks was significantly reduced by eight weeks • no statistically significant differences among the treatment groups
Vertical ridge bone augmentation in a dog model	<ul style="list-style-type: none"> • Critical sized chronic defect • Treated with implants of deproteinized cancellous block • \pm rhPDGF-BB • Evaluation 4 months post-op 	<ul style="list-style-type: none"> • Matrix with rhPDGF-BB created 1 cm vertical bone growth as compared with matrix alone • Histology analysis confirmed accelerated bone remodelling with rhPDGF-BB treated sites
Tissue distribution and mass balance of radioactivity in Sprague-Dawley rats following an intravenous injection of 125 I-rhPDGF-BB	<ul style="list-style-type: none"> • Single IV Injection 0.31 mg/kg • Whole body autoradiography, blood, urine, feces and cage residue collected for radioactivity analysis at different time points up to 7 days 	<ul style="list-style-type: none"> • rhPDGF-BB is widely distributed and cleared rapidly from the circulation. <ul style="list-style-type: none"> · T_{max}: 30 min · 18% of C_{max} at 4 hours • Radioactivity was excreted in urine and feces primarily as unbound 125I with smaller amounts of bound 125I also excreted in feces
Pharmacokinetics of radioactivity in Sprague-Dawley rats following intravenous administration or intramuscular implantation of 125 I-labeled recombinant human Platelet-Derived Growth Factor-BB (rhPDGF-BB) combined with β -Tricalcium Phosphate (β -TCP)	<ul style="list-style-type: none"> • Single IV Injection 0.31 mg/kg • Single IM Implantation adjacent to femur 0.29 mg/kg • blood, urine, feces and cage residue collected for radioactivity analysis at different time points up to 7 days 	<ul style="list-style-type: none"> • The systemic bioavailability of the test article was similar by both routes of administration • rhPDGF-BB is rapidly released from the β-TCP matrix over the 24 hours following IM implantation, and is nearly depleted from the implant site by 168 hours post-dose: <ul style="list-style-type: none"> · T_{max}: 8 hours · $t_{1/2}$: 30.3 hours · 3% of C_{max} at 168 hours
Evaluation of In Vivo Release of 125 I-Recombinant Human Platelet-Derived Growth Factor (125 I-rhPDGF-BB) from β -TCP/COLLAGEN and β -TCP Matrices Implanted in a Rat Calvarial Bone Defect	<ul style="list-style-type: none"> • Single Implantation in Calvarial defect <ul style="list-style-type: none"> · β-TCP: 56 μg/kg · β-TCP /Collagen: 112 μg/kg • Radioactivity at implantation site measured at different intervals up to 7 days 	<ul style="list-style-type: none"> • Rapid release of 50% in the first 60 minutes and 80% in the first 24 hours • Only 2% of input counts at 7 days • No differences between groups
Evaluation of In Vivo Release of 125 I-Recombinant Human Platelet-Derived Growth Factor (125 I-rhPDGF-BB) from β -TCP (β -Tricalcium Phosphate) and β -TCP/Human Bone Allograft Matrices Implanted in a Rat Calvarial Bone Defect	<ul style="list-style-type: none"> • Single Implantation in Calvarial defect <ul style="list-style-type: none"> · β-TCP (1000 – 2000 μm): 182.4 μg/kg · β-TCP (250 – 1000 μm): 187.5 μg/kg · Allograft+β-TCP (250 - 1000 μm): 237.6 μg/kg • Radioactivity at implantation site measured at different intervals up to 3 days 	<ul style="list-style-type: none"> • Rapid release of 50% in the first 30 minutes • Only 10% of the initial radioactivity was present at the implantation site at 72 hours (3 days) • No differences among groups

Summary of Human Pharmacokinetic Study

BioMimetic Therapeutics, LLC, conducted a clinical study to evaluate the pharmacokinetic profile of the rhPDGF-BB in Augment compared to autograft control subjects when implanted in the human hindfoot or ankle. A total of 11 subjects were treated: 4 subjects received standard rigid fixation plus autologous bone graft and 7 subjects received standard rigid fixation plus Augment Bone Graft. Blood samples were collected from each subject prior to treatment and at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 1 day, 2 days, 3 days, and 7 days. The blood samples were processed to obtain serum, which was frozen and stored until analysis of the PDGF-BB concentration.

Serum PDGF-BB levels after the administration of 6-9 cc of Augment used in this study fell within the PDGF-BB concentration range of the autograft control subjects receiving comparable volumes of autologous bone graft. Seventeen of the 119 serum samples tested showed quantifiable levels of PDGF-BB (above 7.8 ng/mL). The 17 samples with quantifiable levels of PDGF-BB were found in three subjects; two of three subjects received autograft. The data suggest a low systemic exposure to rhPDGF-BB following one time implantation of Augment (up to 2.7 mg of rhPDGF-BB) in the human hindfoot or ankle and may be supportive of the safety of Augment. Caution should be taken when interpreting these data because the assay for measuring rhPDGF-BB in human serum has not been fully validated.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The data used as the basis for this PMA approval came from a prospective, randomized, controlled, non-inferiority, multi-center clinical trial to evaluate the safety and effectiveness of Augment® Bone Graft compared to autologous bone graft in bone grafting procedures. The trial enrolled subjects requiring a bone grafting procedure in either the ankle or hindfoot that necessitated the placement of bone graft. The trial was performed in the United States and Canada under IDE # G050118. A summary of the clinical trial is presented below.

A. Study Design

Subjects were treated between April 2007 and January 2009. The database for this PMA reflected data collected through January 2010, and included 434 subjects (414 subjects with surgery). There were 37 sites in the US and Canada.

The clinical trial was a prospective, randomized, concurrently controlled, non-inferiority, multi-center clinical trial to evaluate the safety and effectiveness of Augment® Bone Graft compared to autograft as the concurrent control to fill bony defects used in conjunction with supplemental hardware in the treatment of ankle and hindfoot arthrodesis procedures.

This was a frequentist non-inferiority study with a pre-specified primary endpoint of proportion of patients with fusion and a non-inferiority margin of 10%. The statistical model for this endpoint was two independent binomial proportions.

Fusion was assessed using CT imaging for the full complement of joints, defined as evaluating all joints, and was classified as a success only if all treated joints possessed at least 50% bridging osseous bone. An alternative approach analyzed each joint separately.

Joints were assessed via plain films in four imaging planes (medial, lateral, anterior/superior, posterior/inferior). Each plane was classified as fused, not fused, or not evaluable; a joint had to be classified as fused by three of these images to be called fused. An alternative approach required only two of the images to be classified as fused.

Letting $p_{\text{Augment}^{\circledR} \text{ Bone Graft}}$ and $p_{\text{Autograft}}$ represent the proportions with 24-week fusion success for the Augment[®] and autograft bone groups, respectively, and $\delta = 0.10$ being the non-inferiority margin, the statistical hypotheses for the pre-specified primary endpoint were:

$$H_0 : p_{\text{Augment}^{\circledR} \text{ Bone Graft}} - p_{\text{autograft}} \leq -\delta$$

$$H_a : p_{\text{Augment}^{\circledR} \text{ Bone Graft}} - p_{\text{autograft}} > -\delta$$

These statistical hypotheses were assessed via one-sided 95% confidence intervals on the difference in the proportion of responders in the Augment[®]-treated group minus the proportion of responders in the autograft-treated group.

Quality-of-life and functional outcomes scores which were studied included SF-12, Foot Function Index (FFI), and AOFAS Ankle-Hindfoot questionnaires. In addition, there were three VAS pain assessments: bone graft harvest site pain, fusion site pain, and pain with weight-bearing. By definition, Augment[®] Bone Graft subjects had no harvest site pain and were classified as 0 for that aspect. Asymptotic methods were used to calculate all p -values.

Importantly, because the assessment of radiographic fusion for Augment[®] Bone Graft patients at 24 weeks was inconclusive, demonstration of effectiveness relied primarily on the clinical secondary endpoints and, in particular, the endpoint of weight bearing pain. Please refer to the Effectiveness Results section for a more detailed discussion of this issue.

The study sample size calculation was based on testing the original primary endpoint of fusion and assumed a one-sided 0.05 significance level, 2:1 randomization, 10% non-inferiority margin, and an expected 24-week fusion rate of 85% for both treatment groups. The resulting sample size was 238 Augment[®] Bone Graft and 119 bone graft, yielding 80% power. The proposed sample size was increased to 396 to account for an anticipated 10% dropout.

Upon confirmation of eligibility, patients were randomized into one of two treatment groups: standard rigid fixation plus Augment[®] Bone Graft or standard rigid fixation plus autologous bone graft (autograft). Randomization was conducted at a 2:1 ratio of Augment[®] Bone Graft to autograft. The subjects then underwent an ankle/hindfoot bone grafting procedure using an open surgical technique with supplemental bone graft or Augment[®] Bone Graft, according to the randomization assignment. The bone grafting construct required adequate reduction and

stabilization with rigid fixation intra-operatively to meet final study eligibility. Both treatment groups were immobilized according to standardized operative and post-operative protocols.

The investigators, who were fellowship trained and Board Certified ankle and hindfoot surgeons, performed clinical and radiographic assessments (as required by protocol) to monitor healing/union status. A masked independent radiographic assessment was performed by a designated fellowship trained and Board Certified musculoskeletal radiologist who assessed radiographic parameters for fusion.

All enrolled subjects were to be monitored over a 12-month period to evaluate for clinical and safety outcomes, including incidence of loss of reduction, infection, non-union, need for revision surgery, and associated complications with ankle and hindfoot arthrodesis procedures, in addition to the occurrence of other adverse device effects. A Data Safety Monitoring Board (DSMB) supervised the reporting of unanticipated, device-related, and serious adverse events.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Augment® Bone Graft IDE clinical trial was limited to patients who met the following inclusion criteria.

- a. The patient signed the IRB-approved Informed Consent Form specific to this study prior to enrollment.
- b. The patient had a bone defect (surgically created osseous defects or osseous defects resulting from pathology or traumatic injury to the bone) in the ankle or hindfoot requiring fusion using open surgical technique with supplemental bone graft/substitute, requiring one of the following procedures:
 - i. Ankle joint fusion (tibiotalar fusion)
 - ii. Subtalar fusion
 - iii. Calcaneocuboid fusion
 - iv. Talonavicular fusion
 - v. Double fusions
 - vi. Triple fusions
- c. The fusion site was able to be rigidly stabilized with no more than 3 screws across the fusion site. Supplemental pins may have been used. Supplemental screws external to the fusion site(s) were also allowed.
- d. The patient was independent, ambulatory, and could comply with all post-operative evaluations and visits.
- e. The patient was at least 18 years of age and considered to be skeletally mature.

Patients were not permitted to enroll in the Augment® Bone Graft IDE clinical trial if they met any of the following exclusion criteria.

- a. The patient had undergone previous fusion surgery of the joints to be fused.
- b. The fusion site required plate fixation*, more than 3 screws across the fusion site to achieve rigid fixation, or more than 3 kits (9 cc) of graft material.

- c. There was radiographic evidence of bone cysts, segmental defects or growth plate fracture around the fusion site that may negatively impact bony fusion.
- d. The patient currently had untreated malignant neoplasm(s) at the surgical site, or was currently undergoing radio- or chemotherapy.
- e. The patient had a pre-existing sensory impairment (e.g., diabetes with baseline sensory impairment) which limited the ability to perform objective functional measurements and may have placed patients at risk for complications. For the purpose of this protocol, diabetics that were not sensitive to the 5.07 monofilament (Semmes-Weinstein) were to be excluded.
- f. The patient had a metabolic disorder known to adversely affect the skeleton, other than primary osteoporosis or diabetes (e.g., renal osteodystrophy or hypercalcemia).
- g. The patient used chronic medications known to affect the skeleton (e.g., glucocorticoid usage > 10 mg/day). Non-steroidal anti-inflammatory drug (NSAID) use was excluded during the first 6 weeks post-operatively.
- h. The patient had a pre-fusion neuromuscular or musculoskeletal deficiency which limited the ability to perform objective functional measurements.
- i. The patient was physically or mentally compromised (e.g., currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, etc.) to the extent that the investigator judged the patient to be unable or unlikely to remain compliant.
- j. The patient had an allergy to yeast-derived products.
- k. The patient had received an investigational therapy or approved therapy for investigational use within 30 days of surgery or during the follow-up phase of this study.
- l. The patient was a prisoner, known or suspected to be transient, or had a history of drug/alcohol abuse within the 12 months prior to screening for study entry.
- m. The patient was pregnant or a female intending to become pregnant during the study period. A urine pregnancy test was to be administered within 21 days of the surgical visit to any female unless she was post-menopausal, had been sterilized, or was practicing a medically-accepted method of contraception.
- n. The patient was deemed morbidly obese (body mass index [BMI] > 45 kg/m²).

*Screw fixation was used in all study subjects to reduce the number of variables.

2. Follow-up Schedule

All patients were scheduled to return for follow up examinations at 7-21 days post-operative, 6 weeks (±1 week), 9 weeks (±1 week), 12 weeks (±1 week), 16 weeks (±1 week), 24 weeks (±2 weeks), 36 weeks (±2 weeks), and 52 weeks (±2 weeks).

Clinical assessments included the primary effectiveness variable of bridging bone at the involved level, in addition to secondary pain/disability status, general health status, and graft site pain. The protocol also included measurements of antibodies for anti-rhPDGF-BB screening in the Augment® Bone Graft group at baseline (prior to grafting procedure), visit 3 (day 7-21), visit 4 (week 6), visit 6 (week 12), and visit 8 (week 24). The objective parameters measured preoperatively and postoperatively during the study are included in Table 3 below. Adverse events and complications were recorded at all visits.

The key time-points are shown below in the tables summarizing safety and effectiveness.

Table 3. Schedule of Study Assessments

Procedure	Screening	Surgery	Post-Treatment Follow-up Evaluation							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Within 21 Days of Surgery	Day 0	Day 7-21	Wk 6 ±7 Days	Wk 9 ±7 Days	Wk 12 ±7 Days	Wk 16 ±7 Days	Wk 24 ±14 Days	Wk 36 ±14 Days	Wk 52 ±14 Days
Informed Consent	X ¹									
Urine Pregnancy Test (if applicable)	X									
Medical History / Non-Union Risk Factors	X									
Physical Examination of Foot / Ankle Region	X	X	X	X	X	X	X	X	X	X
Eligibility Criteria Verification	X	X								
Identification of Target Bone Defect	X									
Serum for rhPDGF-BB Ab Testing	X ²		X	X		X		X		
Patient Randomization		X ³								
Intraoperative Report		X								
Volume of Graft Material Placed (if applicable)		X								
Physical Therapy				X	X	X	X	X	X	
Radiographic Outcomes	X ⁴	X	X	X	X	X	X	X	X	X
CT Scans ⁵					X		X	X	X	
Clinical / Functional Assessments ⁶	X			X	X	X	X	X	X	X
Pain Assessments	X	X	X	X	X	X	X	X	X	X
Quality-of-Life Assessments	X			X		X	X	X	X	X
Adverse Events /Complications		X	X	X	X	X	X	X	X	X ⁷
Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X

Ab = antibody; CT = computed tomography
1 Must have occurred prior to any study-specific procedures.
2 Peripheral blood sample for antibody evaluation was to be taken at baseline (prior to grafting), Day 7-21, Week 6, Week 12, and Week 24. For patients who tested positive for antibodies to rhPDGF-BB, additional serum samples were to be requested in order to monitor patients until antibody titers returned to baseline. Patients testing positive for anti-rhPDGF-BB antibodies were to be tested for neutralizing activity.
3 Interactive web randomization within 48 hours of scheduled surgery.
4 Pre-operative radiographic films may have been taken within 6 months of surgery. Radiologic assessments including osseous bridging across subchondral surfaces (primary endpoint for union), callus formation, % osseous bridging, and heterotopic bone formation were to be used to assess overall fusion site healing. Plain film radiographs were to be the primary source of data for clinical assessment of fusion.
5 CT scans (0.5-0.7 mm thickness at 0.2-0.3mm intervals, pitch of 0.7, and kVp of 130-140) were to be taken at Week 9, 16, 24, and 36. A baseline CT scan may have been taken to confirm that there were no radiographic signs of cysts that would exclude the patient. CT scans were to be assessed for radiographic union by independent radiologist.
6 VAS pain assessment, SF-12 quality-of-life assessment and functional assessments include range of motion, and weight bearing (Foot Function Index and AOFAS Hindfoot / Ankle scale).
7 Non-unions (therapeutic failures) after 12-month follow-up were to be collected

3. Clinical Endpoints

The following clinical, functional, radiologic, and safety endpoints were used to evaluate the risk-benefit profile of Augment® Bone Graft:

Safety Endpoints:

- Presence of treatment emergent adverse events (TEAEs)
- Secondary Surgeries
- Serum sample analysis for presence of anti-rhPDGF-BB antibodies.

Clinical / Functional Endpoints:

- Pain on weight bearing
- Fusion site pain
- Foot Function Index (FFI)
- American Orthopaedic Foot and Ankle Society (AOFAS) Score
- SF-12 (PCS)
- Non-union rate
- Graft harvest site pain

Radiologic Endpoint:

- $\geq 50\%$ osseous bridging across the joint space as determined using computed tomography (CT) images at 24 weeks post-operative

Clinical and Functional Endpoints Used to Determine Individual Success by FDA

- Pain on weight bearing
- FFI
- AOFAS Score

B. Accountability of PMA Cohort

There were three patient populations separately accounted for: Intent to Treat (ITT), modified Intent to Treat (mITT), and Safety or “All Treated.” The ITT population consisted of 434 patients. Of these, 285 were implanted with Augment® Bone Graft and 149 received autograft. The mITT population, submitted as the primary effectiveness analysis for the radiographic evaluation of bridging bone, consisted of 397 patients (414 patients in the Safety, or “All Treated”, group minus an additional 17 subjects excluded post-operatively) divided into 260 with Augment® Bone Graft and 137 with autograft. (Figure 3)

Efficacy results, based on the radiographic interpretation of bridging bone with a “full complement of joints” analysis, was assessed on the mITT population, which included 397 evaluable patients (597 joints) who were considered by the investigator as eligible, properly randomized, and received treatment in accordance with the clinical trial protocol (“per protocol population”). Of these, 260 subjects (394 joints) received Augment® Bone Graft and 137 subjects (203 joints) received autograft. However, because interpretation of the primary radiographic endpoint for the study was inconclusive due to the radiographic attenuation of the Augment® Bone Graft implant, it was necessary to consider success or failure of the product in terms of success or failure of the individual with clinical outcome measures of pain and function

(VAS on weight bearing, FFI, and AOFAS score). Therefore, in order to determine individual success, those individuals who had medically relevant protocol deviations and missing data were not considered in this analysis (Figure 3).

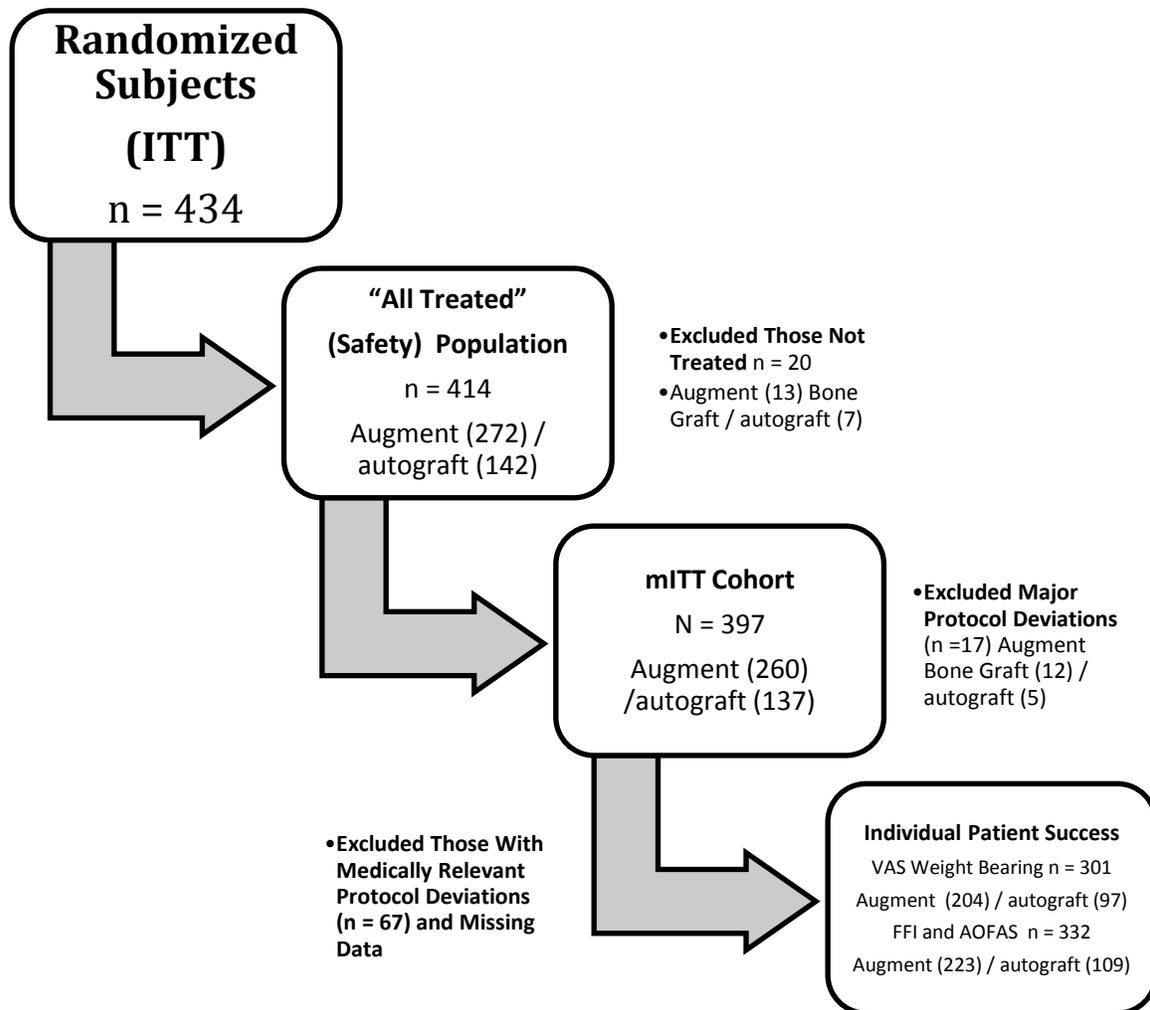


Figure 3: Subject Accounting Tree

The “All Treated” population consisted of 414 randomized and treated subjects (272 Augment® Bone Graft and 142 autograft). The mITT population consists of 397 subjects, as 17 subjects were removed due to post-operative exclusions. This group of 17 included subjects who required hardware prohibited by the protocol (5), had an excluded joint fused (9), had chronic steroid use (1), were weight bearing at two weeks (1), and required more than the allowed amount of graft material (1). Of the 397 per protocol subjects, 260 were implanted with Augment® Bone Graft and 137 received the autograft control treatment. This group was used to assess the success or failure of the study’s radiographic primary endpoint for bridging bone at 24 weeks. Regarding the assessment for Individual Patient Success, overall there were 301 individuals for VAS on weight bearing (204 Augment® Bone Graft and 97 autograft), and 332

for the FFI and AOFAS functional outcome measures (223 Augment® Bone Graft and 109 autograft).

Patient accounting at the week 24 time point of the primary endpoint is presented in Table 4.

Table 4: 24 Week Data Accounting for Augment® Bone Graft

Parameter	Augment® Bone Graft	Autograft
Randomized	285	149
Withdrawn prior to treatment	13	7
Subjects Treated	272	142
Failed Study Inclusion Criteria	12	5
Per protocol cohort	260	137
Death	1 ¹	0
Device Related Serious Adverse Event (SAE)	1	0
Secondary Procedures Among treated ²	5	4
Medically Relevant Protocol Deviations ³	38	29

¹Death due to pulmonary embolus was not evaluated by the investigator as being related to Augment® Bone Graft, but was likely procedure related.

²Subjects with secondary procedures due to non-union, delayed union, or application of bone stimulator to prevent one of these outcomes prior to Week 24.

³Subjects who were considered as individual failures due to protocol deviations that materially impacted the outcome assessments of pain and function.

C. Study Population Demographics and Baseline Parameters for “All Treated” Patients

Subject demographics are summarized in Table 5.

Table 5: Demographic & Clinical Characteristics at Baseline – “All Treated” Population

	Augment® Bone Graft (n=272)			Autograft (n=142)		
Gender						
Male	129	(47.4%)		81	(57.0%)	
Female	143	(52.6%)		61	(43.0%)	
Affected Ankle/Hindfoot						
Right	135	(49.6%)		77	(54.2%)	
Left	128	(47.1%)		56	(39.4%)	
Bilateral	9	(3.1%)		9	(6.3%)	
Arthrodesis Procedure Performed						
Ankle	102	(37.5%)		53	(37.3%)	
Subtalar	68	(25.0%)		38	(26.7%)	
Calcaneocuboid	3	(1.1%)		0	(0.0%)	
Talonavicular	15	(5.5%)		9	(6.3%)	
Double arthrodesis	23	(8.5%)		12	(8.5%)	
Triple arthrodesis	61	(22.4%)		30	(21.1%)	
Surgery Site						
Hindfoot	170	(62.5%)		88	(62.0%)	
Ankle	102	(37.5%)		54	(38.0%)	
Description of Injury/Deformity						
Primary Arthritis	91	(33.5%)		56	(39.4%)	
Rheumatoid Arthritis	23	(8.5%)		5	(3.5%)	
Post-traumatic injury/deformity	135	(49.6%)		63	(44.4%)	
Ankylosing spondylitis	0	(0.0%)		0	(0.0%)	
Non-Specified	23	(8.5%)		18	(12.8%)	
Comorbidities						
Smoking history within last 5 years	66	(24.3%)		33	(23.2%)	
Obesity (BMI >= 30 kg/m ²)	125	(46.0%)		77	(54.2%)	
Previous revision surgery ¹	63	(23.2%)		32	(22.5%)	
Diabetes history (type 1 or 2)	31	(11.4%)		19	(13.4%)	
Other Factors	n	Mean	SD	n	Mean	SD
Age at surgery (years)	272	55.9	14.5	142	57.6	13.4
BMI (kg/m ²)	272	0.5	0.5	142	0.5	0.5
Age of injury (weeks)	170	266.6	468.8	88	325.5	464.5
Baseline Functional Status						
Foot Function Index (FFI) Total	272	51.8	18.7	142	48.8	18.4
AOFAS Total	272	39.7	17.9	142	40.8	18.3
SF12 PCS (Physical)	272	30.9	9.0	142	31.5	9.3
VAS - Fusion site pain	242	52.9	29.3	128	49.3	28.0
VAS- Weight bearing pain	240	67.8	26.2	125	65.5	23.7

Note: Percent values are based on the number of treated subjects (N=414).

¹This includes any surgery at the revision site(s).

As part of FDA’s review, the sponsor provided information on how patients were enrolled based on the absence or presence of a “bone defect.” The sponsor assessed baseline radiographs for the presence of 16 parameters, which physicians would use to indicate the need for bone graft in ankle and hindfoot arthrodesis surgery as described in a survey article by Baumhauer, et al.³ The results of this review are included in Table 6.

Table 6: Radiographic Assessment of the Need for Graft Material

Radiographic Parameters Observed Indicating Need for Graft Material	n	%
Total number subjects with evaluable radiograph at baseline	400	100.0
Convexity/concavity mismatch of the articulating surfaces of the joint	394	98.5
Large surface areas to be fused	374	93.5
Irregular bony surfaces of joints to be fused	285	71.2
Evidence of potential incongruous apposition	247	61.8
Intra-articular deformity	206	51.5
Joint malalignment	194	48.5
Subchondral cysts	143	35.8
Radiographic evidence of bone loss	125	31.3
More than one joint to be fused	119	29.8
Osteoporosis or post-traumatic with subchondral collapse	89	22.3
Osseous defects resulting from pathology or traumatic injury to the bone	64	16.0
Extra-articular deformity	49	12.3
Bony step-offs	19	4.8
Prior adjacent joint fusions	18	4.5
Avascular necrosis (AVN)	2	0.5
Summary of Radiologic Findings		
At least one radiologic parameter	400	100.0
At least two radiologic parameters	396	99.0
At least three radiologic parameters	368	92.0
At least four radiologic parameters	332	83.0
At least five radiologic parameters	275	68.8

Of the 400 subjects with an evaluable baseline radiograph, 400 (100%) demonstrated at least 1 of the 16 radiographic findings that required bone graft to treat the subject. Three-hundred ninety six (99.0%) demonstrated at least 2 such findings, 368 (92.0%) demonstrated at least 3, and 332 (83.0%) demonstrated at least 4 radiographic findings.

The most common parameters observed (those seen in at least 50% of subjects) were convexity/concavity mismatch of the articular surfaces (394, 98.5%), large surface area to be fused (374, 93.5%), irregular bony surfaces of the joint to be fused (285, 71.3%), evidence of potential incongruous apposition (247, 61.8%), and intra-articular deformity (206, 51.5%).

D. Safety and Effectiveness Results

Safety Results

The safety of the investigational product was assessed using a separate analysis population at 24 weeks and was not part of the primary study endpoint. Safety was assessed by evaluating graft harvest site pain scores as the primary safety endpoint, and operating room time and surgical wound infection rate as secondary safety endpoints. Safety was also evaluated based on the nature and frequency of adverse events which occurred in the Augment® Bone Graft group, as compared to those that occurred in the autograft group.

Reported adverse events were classified as systemic and product-specific. The MedDRA was used to classify systemic adverse events. Product-specific complications were collected according to seven subgroups pre-defined by the sponsor’s protocol: 1) “Pre-treatment signs and symptoms”; 2) “Treatment Emergent Adverse Events” (TEAEs) defined as AEs reported on or after the day of surgery; 3) “Complications” defined as complications associated with surgical procedures, a subset of the TEAEs; 4) “Serious Complications”; 5) Infections; 6) Related TEAEs; and 7) Serious TEAEs.

All Adverse Events

The adverse events, as shown in the tables below, are reported from the “Safety Population” which included 272 Augment® Bone Graft patients and 142 autograft control patients enrolled in the multi-center clinical study. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

A total of 212 (77.9%) of Augment® Bone Graft patients had at least one adverse event within 52 weeks versus 105 (73.9%) autograft control patients. A total of 657 events were reported in the Augment® Bone Graft patients and 316 events were reported in the controls. The 24-week data analysis was used as the primary effectiveness endpoint. The summary of AEs by System Organ Classification (SOC) and Preferred Term (PT) in either treatment group is provided in Table 7.

Table 7– Adverse Events Summary by MedDRA SOC and PT

System Organ Class Preferred Term	All Patients (N=414)		Augment® Bone Graft (N=272)		Autologous Bone Graft (N=142)	
	Subjects	Events	Subjects	Events	Subjects	Events
Any Adverse Event	317 (76.6%)	973	212 (77.9%)	657	105 (73.9%)	316
Blood and lymphatic system disorders	2 (0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Cardiac disorders	9 (2.2%)	10	3 (1.1%)	3	6 (4.2%)	7
Congenital, familial and genetic disorders	2 (0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Ear and labyrinth disorders	3 (0.7%)	3	1 (0.4%)	1	2 (1.4%)	2
Endocrine disorders	2 (0.5%)	3	2 (0.7%)	3	0 (0.0%)	0

Eye disorders	5 (1.2%)	6	2 (0.7%)	3	3 (2.1%)	3
Gastrointestinal disorders	52 (12.6%)	66	35 (12.9%)	45	17 (12.0%)	21
General disorders and administration site conditions	56 (13.5%)	61	37 (13.6%)	40	19 (13.4%)	21
Hepatobiliary disorders	1 (0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Immune system disorders	12 (2.9%)	13	10 (3.7%)	11	2 (1.4%)	2
Infections and infestations	89 (21.5%)	121	61 (22.4%)	86	28 (19.7%)	35
Injury, poisoning and procedural complications	104 (25.1%)	125	67 (24.6%)	82	37 (26.1%)	43
Medical device pain	21 (5.1%)	21	14 (5.1%)	14	7 (4.9%)	7
Investigations	9 (2.2%)	9	6 (2.2%)	6	3 (2.1%)	3
Metabolism and nutrition disorders	8 (1.9%)	9	4 (1.5%)	5	4 (2.8%)	4
Musculoskeletal and connective tissue disorders	166 (40.1%)	276	117 (43.0%)	193	49 (34.5%)	83
Arthralgia	53 (12.8%)	63	38 (14.0%)	46	15 (10.6%)	17
Pain in extremity	69 (16.7%)	80	48 (17.6%)	56	21 (14.8%)	24
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.7%)	7	5 (1.8%)	5	2 (1.4%)	2
Nervous system disorders	58 (14.0%)	65	43 (15.8%)	49	15 (10.6%)	16
Psychiatric disorders	16 (3.9%)	18	11 (4.0%)	13	5 (3.5%)	5
Renal and urinary disorders	28 (6.8%)	29	17 (6.3%)	17	11 (7.7%)	12
Reproductive system and breast disorders	3 (0.7%)	3	1 (0.4%)	1	2 (1.4%)	2
Respiratory, thoracic and mediastinal disorders	25 (6.0%)	30	14 (5.1%)	15	11 (7.7%)	15
Skin and subcutaneous tissue disorders	61 (14.7%)	69	41 (15.1%)	47	20 (14.1%)	22
Surgical and medical procedures	14 (3.4%)	16	9 (3.3%)	9	5 (3.5%)	7
Vascular disorders	27 (6.5%)	29	18 (6.6%)	20	9 (6.3%)	9

* Serious Adverse Events are defined by FDA's Medwatch Adverse Event program as any death, any life-threatening event (*i.e.*, an event that placed the patient, in the view of the investigator, at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form, might have caused death), any event that required or prolonged in-patient hospitalization, any event that resulted in persistent or significant disability/incapacity, any congenital anomaly/birth defect diagnosed in a child of a patient who participated in this study following the study procedure, any other medically important events that in the opinion of the investigator may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed above, or any serious problem associated with the device that related to the rights, safety or welfare of study patients.

There are five categories of adverse events in which the Augment® Bone Graft group is greater than or equal to two percentage points higher than the autograft control group: immune system disorders (3.7% vs 1.4%); musculoskeletal and connective tissue disorders (43.0% vs 34.5%); arthralgia (14.0% vs 10.6%); pain in extremity (17.6% vs 14.8%); and nervous system disorders (15.8% vs 10.6%). There are two categories of adverse events in which the autograft control group had a higher rate by two percentage points or more than the Augment® Bone Graft group: cardiac disorders (4.2% vs. 1.1%); and respiratory, thoracic and mediastinal disorders (7.7% vs. 5.1%). The correlation of high rates of pain measured as adverse events with secondary outcome measures for product effectiveness is unclear. Infections and infestations are higher in the investigational group by over 2 percentage points (22.4% vs. 19.7%). Although infections and infestations rates are similar rates, these rates are clinically concerning for hind foot and ankle arthrodesis. No inferential statistical comparison of adverse events between investigational and autograft control groups was performed.

There were 1.8% (5/272) of adverse events in Augment® Bone Graft patients categorized as Neoplasms (i.e., cancers, either benign or malignant) and 1.4% (2/142) in autograft control patients. Please see the section “Observed Cancer Incidence in Pivotal Trials” for additional details.

Serious Adverse Events

Table 8 summarizes the SAEs by treatment group and System Organ Class (SOC) for each visit and in total during the study for all 414 randomized and treated subjects (272 Augment® Bone Graft and 142 autograft subjects).

Table 8: SAEs by Treatment Group and System Organ Class (SOC)

System Organ Class	Visit																Total events	
	Week 3		Week 6		Week 9		Week 12		Week 16		Week 24		Week 36		Week 52			
	(Day 1 to 31)		(Day 32 to 52)		(Day 53 to 73)		(Day 74 to 97)		(Day 98 to 139)		(Day 140 to 209)		(Day 210 to 307)		(Day 308 to 421)			
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C		
Cardiac disorders		1				2	1						1				1	4
Congenital, familial and genetic disorders												1					0	1
Gastrointestinal disorders		1	1				1			1			1		1	1	4	3
General disorders and administration site conditions	1				1				1				2		1		6	0
Infections and infestations							2	1	2	3	1	1			2		7	5
Injury, poisoning and procedural complications		1		1	1							1		1			3	2
Investigations												1					1	0
Musculoskeletal and connective tissue disorders	1		1									3	2	2			7	2
Neoplasms benign, malignant and unspecified (incl cyst)		1							1		1		1	1			3	2
Nervous system disorders	1											1					2	0
Psychiatric disorders										1				1			1	1
Respiratory, thoracic and mediastinal disorders	1	2										1		1			1	4
Surgical and medical procedures									1								1	0
Vascular disorders	2	2		1	1	1	2		1		1				1	1	8	5

Total events	6	8	2	2	3	3	6	1	6	5	9	6	8	2	5	2	45	29
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Note:

I= Investigational (Augment), C=Control (autograft)

As the above table shows, a total of 74 SAEs occurred during the study, of which 45 were in Augment® Bone Graft subjects and 29 were in autograft subjects. Twenty eight of the 272 (10.3%) Augment® Bone Graft subjects experienced the 45 SAEs in that treatment group while 21 of the 142 (14.8%) autograft subjects experienced the 29 SAEs in that treatment group.

There were three Augment® Bone Graft subjects who were withdrawn from the study due to SAEs. There were no autograft control subjects withdrawn due to SAEs. The three Augment® Bone Graft subjects withdrew for the following reasons: one infection was noted during surgery and the fusion procedure was not performed and no graft material was implanted, one death due to pulmonary embolism, and one bilateral MRSA infection of both knees.

Nine surgical wound infections were classified as SAEs: four infections in Augment® Bone Graft subjects and five infections in autograft control subjects.

All but five of the subjects (three Augment® Bone Graft and two autograft control subjects) who experienced SAEs were reported as recovered/resolved.

The table of treatment-emergent SAEs by SOC and PT is presented in Table 9 below. Defined: WHO Grade 3 or 4; N=272 Augment® Bone Graft patients and N=142 autograft controls.

Table 9: Treatment-Emergent SAEs by SOC and PT

System Organ Class (Preferred Term)	All Patients (N=414)		Augment® Bone Graft (N=272)		Autologous Bone Graft (N=142)	
	Subjects	Events	Subjects	Events	Subjects	Events
Any Adverse Event	49(11.8%)	74	28(10.3%)	45	21(14.8%)	29
Cardiac disorders	4 (1.0%)	5	1 (0.4%)	1	3 (2.1%)	4
Acute myocardial infarction	1(0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Atrial flutter	1(0.2%)	1	1(0.4%)	1	0 (0.0%)	0
AV block complete	1(0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Cardiac failure congestive	1(0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Myocardial infarction	1(0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Congenital, familial and genetic	1 (0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Congenital foot malformation	1(0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Gastrointestinal disorders	6 (1.4%)	7	3 (1.1%)	4	3 (2.1%)	3
Gastritis	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Gastrointestinal haemorrhage	4 (1.0%)	5	2 (0.7%)	3	2 (1.4%)	2
Megacolon	1 (0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
General disorders and administration site conditions	6 (1.4%)	6	6 (2.2%)	6	0 (0.0%)	0
Chest pain	1 (0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Impaired healing	2(0.5%)	2	2 (0.7%)	2	0 (0.0%)	0
Non-cardiac chest pain	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Pyrexia	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Cardiac chest pain	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Infections and infestations	9 (2.2%)	12	5 (1.8%)	7	4 (2.8%)	5
Cellulitis	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0

Clostridium difficile colitis	1 (0.2%)	1	0 (0.0%)	0	1 (0.7%)	1
Infection	1(0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Osteomyelitis	3(0.7%)	3	1 (0.4%)	1	2 (1.4%)	2
Pneumonia	2(0.5%)	2	2 (0.7%)	2	0 (0.0%)	0
Postoperative wound infection	2(0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Staphylococcal infection	2(0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Injury, poisoning and procedural complications	5 (1.2%)	5	3(1.1%)	3	2(1.4%)	2
Device related infection	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Medical device complication	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Overdose	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Postoperative wound infection	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Wound infection staphylococcal	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Investigations	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Prothrombin level abnormal	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Musculoskeletal and connective tissue	9 (2.2%)	9	7(2.6%)	7	2(1.4%)	2
Foot fracture	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Joint instability	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Joint range of motion decreased	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Muscle strain	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Osteoarthritis	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Osteoporosis	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Pain in extremity	3 (0.7%)	3	3(1.1%)	3	0(0.0%)	0
Neoplasms benign, malignant and unspecified (incl cyst)	5 (1.2%)	5	3(1.1%)	3	2(1.4%)	2
Endometrial cancer	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Lung neoplasm malignant	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Prostate cancer	2 (0.5%)	2	2(0.7%)	2	0(0.0%)	0
Renal cell carcinoma stage unspecified	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Nervous system disorders	2 (0.5%)	2	2(0.7%)	2	0(0.0%)	0
Cerebrovascular accident	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Convulsion	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Psychiatric disorders	2 (0.5%)	2	1(0.4%)	1	1(0.7%)	1
Alcohol withdrawal syndrome	1 (0.2%)	1	0(0.0%)	0	1(0.7%)	1
Suicide attempt	1 (0.2%)	1	1(0.4%)	1	0(0.0%)	0
Respiratory, thoracic and mediastinal	4(1.0%)	5	1(0.4%)	1	3(2.1%)	4
Atelectasis	1(0.2%)	1	1(0.4%)	1	0(0.0%)	0
Chronic obstructive pulmonary disease	1(0.2%)	2	0(0.0%)	0	1(0.7%)	2
Hypoxia	1(0.2%)	1	0(0.0%)	0	1(0.7%)	1
Pulmonary embolism	1(0.2%)	1	0(0.0%)	0	1(0.7%)	1
Surgical and medical procedures	1(0.2%)	1	1(0.4%)	1	0(0.0%)	0
Osteotomy	1(0.2%)	1	1(0.4%)	1	0(0.0%)	0
Vascular disorders	12(2.9%)	13	7(2.6%)	8	5(3.5%)	5
Aortic stenosis	1(0.2%)	1	0(0.0%)	0	1(0.7%)	1
Deep vein thrombosis	7(1.7%)	7	4(1.5%)	4	3(2.1%)	3
Pulmonary embolism	4(1.0%)	4	3(1.1%)	3	1(0.7%)	1
Thrombosis	1(0.2%)	1	1(0.4%)	1	0(0.0%)	0

Highlighted=higher by >1 percentage point in the investigational group (yellow) and autograft control group (blue). See AE discussion above for further information.

There were eight categories where rates differed by greater than one percentage point:

- Augment ® Bone Graft higher: general disorders and administrative site conditions, which included chest pain, non-cardiac chest pain, cardiac chest pain, impaired healing and pyrexia (2.2% vs 0%); and musculoskeletal and connective tissue disorders, which includes foot fracture, joint instability, joint range of motion decreased, and muscle strain (2.6% vs 1.4%); and pain in extremity (1.1% vs 0%).

- Autograft control higher: cardiac disorders (2.1% vs 0.4%); GI disorders (2.1% vs 1.1%); infections and infestations (2.8% vs 1.8%); osteomyelitis (1.4% vs 0.4%); and respiratory, thoracic and mediastinal disorders (2.1% vs 0.4%).

The median time to first SAE was 109 days for Augment® Bone Graft and 64 days for autograft (p = 0.249 based on Wilcoxon-Gehan test statistic of 1.33 for comparing equality of time to first SAE in subjects who experienced an SAE). The analysis did not detect any significant differences between the treatment groups in the number of subjects with SAEs, or the time to first SAE in those subjects experiencing an SAE.

Detailed Information on Specific Adverse Event Categories

Infection Rates

Table 10 summarizes the incidence of fusion-related, procedure-related, graft harvest site related, and other-site related infections by treatment group at 24, 36, and 52 weeks after implantation of the graft material.

Table 10: Incidence of Fusion-Related, Procedure, Graft Harvest Site, and Other Site Related Infections by Treatment Groups at 24, 36, and 52 Weeks After Implantation

Site	Total events through week 24		Total Patients through week 24 (%)		p-value	Total events through week 52		Total Patients through week 52 (%)		p-value
	I	C	I	C		I	C	I	C	
Fusion site related*	19	17	15(5.5)	12(8.5)	0.2951	24	17	19(7.0)	12(8.5)	0.6944
Procedure site related*	24	19	20(7.4)	14(9.9)	0.4509	29	20	24(8.8)	15(10.6)	0.5968
Graft harvest site related*	0	2		2(1.4)	0.1171		2		2(1.4)	0.1171
Other site related*	52	18	33(12.1)	16(11.3)	0.8734	65	25	40(14.7)	20(14.1)	>0.999
All Infections*	78	38	55(20.2)	31(21.8)	0.7035	96	46	66(24.3)	36(25.4)	0.8111

Note:

I-Investigational (Augment, N=272), C-Control (Autologous Bone Graft, N=142)

p-value of two-tailed Exact Fisher's test using patient counts.

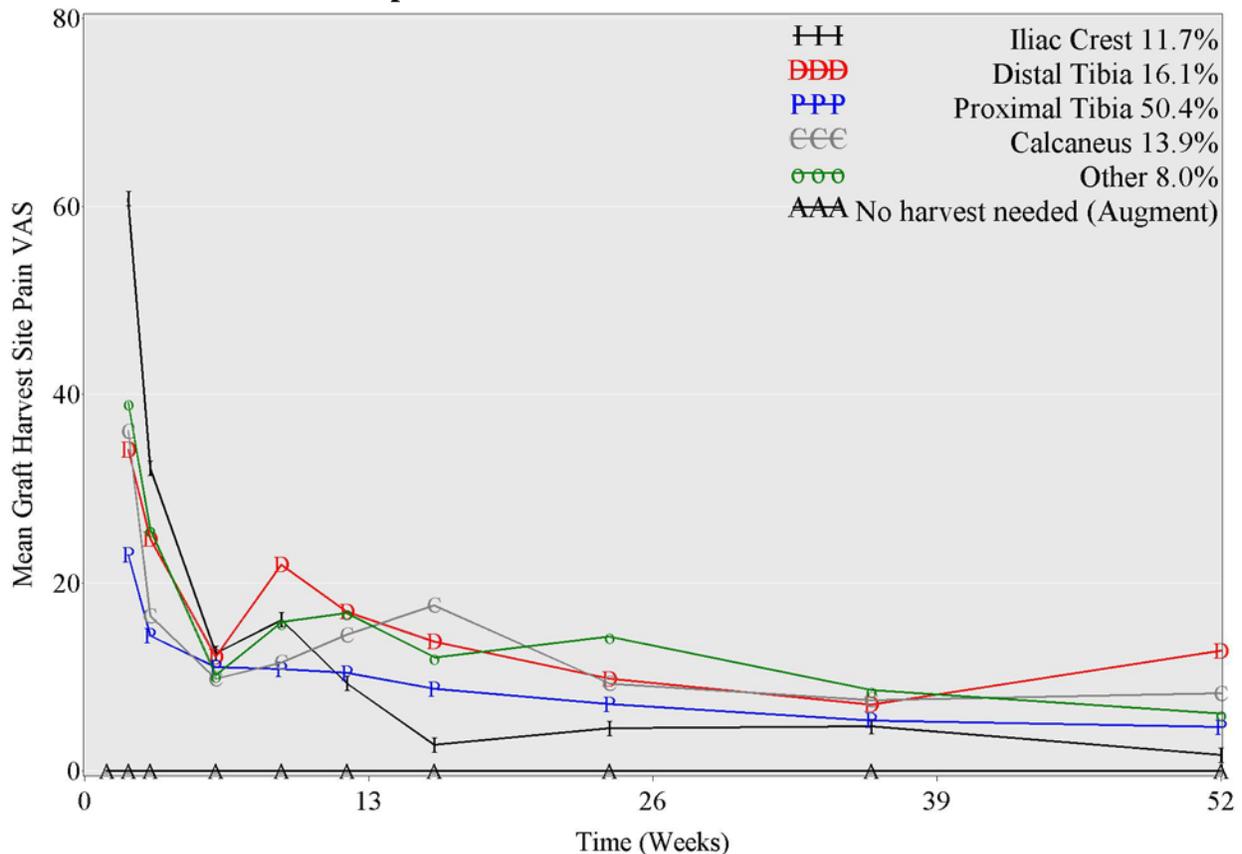
* a patient may have more than one infection event and an infection event may be classified into more than one site category.

As table 10 above shows, fusion site related, procedure site related, and graft harvest site related infections demonstrated no significant differences between treatment groups. Augment® Bone Graft reported a higher infection rate for “other” site related infections (e.g., sinus infection, thrush, UTI), which were not related to arthrodesis surgery. When looking at all infections, infection and infestation rates between the two groups were similar (Augment® Bone Graft, 20.2% and autograft control, 18.3%). Although infections and infestations rates are similar rates, these rates are clinically concerning for hind foot and ankle arthrodesis.

Graft Harvest Site Pain

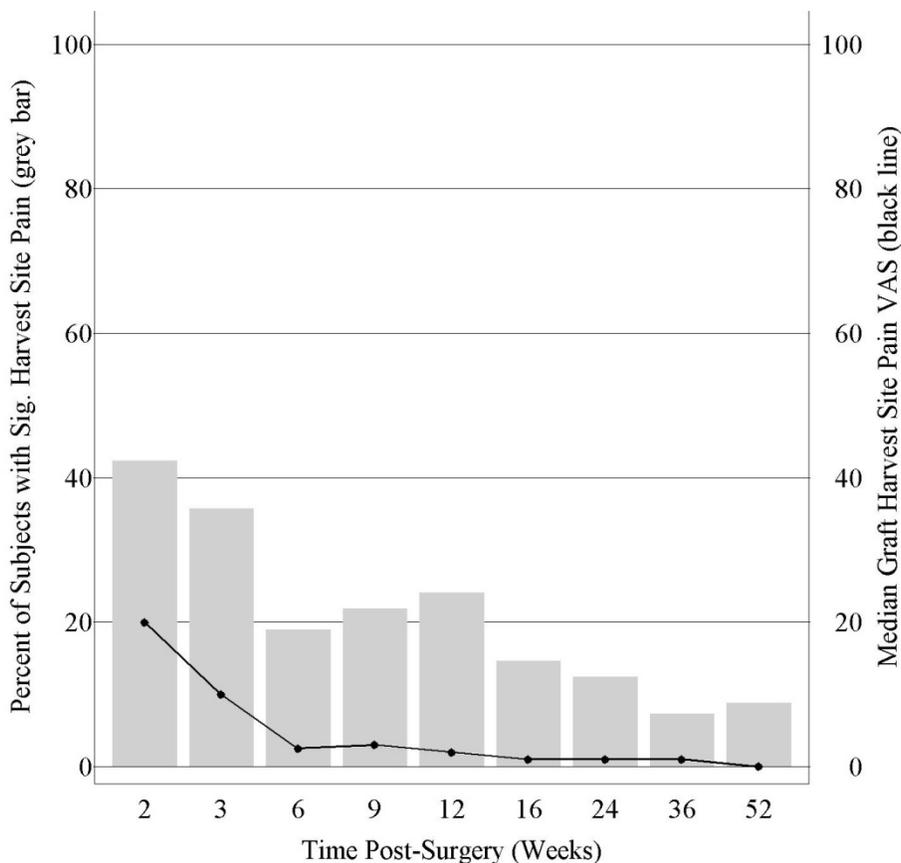
Subjects in the autologous bone graft group report clinically significant pain at the graft harvest site (≥ 20 mm) on VAS at and after the week 24 visit: 12.4% of autologous bone graft subjects at week 24 and 8.8% at week 52. A breakdown of the different anatomical areas from which graft material was obtained showed that the iliac crest with a higher morbidity constituted only 11.7% of all site materials used. Distal tibia (16.1%) and calcaneus (13.9%) were also used. The remaining autograft subjects utilized some other autograft source location.

Graph 1: Pain at Harvest Site Over Time



As shown in Graph 1, only patients with Iliac Crest Bone Graft (ICBG) achieved a VAS score greater than 40 mm and this was in the post-operative period (approximately 3 weeks) as presented in Graph 1 above.

Graph 2: Clinically Significant Graft Site Pain of at Least 20mm



As shown by the bars in Graph 2, the majority of autograft subjects did not report graft harvest site pain of at least 20 mm (the cut-off point for inclusion). Because the VAS pain scores were skewed in the remaining minority of subjects, a line was incorporated in the graph to denote the median pain score, which is a more representative measure than the mean. The highest median overall VAS score was 20 mm at two weeks post-surgery.

Anti-rhPDGF-BB Antibodies

All randomized and treated subjects were tested for anti-rhPDGF-BB antibodies before implantation and at 2, 6, 12, and 24 weeks after implantation. In accordance with the protocol, additional serum samples were not obtained from subjects that tested negative for anti-rhPDGF-BB antibodies at 6 months. Anti-rhPDGF-BB antibodies were detected in 14.5% (41 out of 282) of patients receiving Augment® Bone Graft and in 3.5% (5 out of 141) in those that received an autograft. Anti-rhPDGF-BB antibodies persisted for up to six months with no data available beyond that time. Neutralizing activity was observed in 6 out of the 41 patients that confirmed positive for anti-rhPDGF-BB antibodies (6 out of 282 ~ 2.12%). No neutralizing antibodies were detected in patients that received an autograft. The clinical significance of the anti-rhPDGF-BB antibodies or any neutralizing activity is not known.

Per FDA request, BioMimetic Therapeutics, LLC, developed a cell-based assay to determine the presence of neutralizing anti-rhPDGF-BB antibodies in human samples and then used that assay

to test the stored serum samples of the pivotal study subjects who tested positive for anti-rhPDGF-BB antibodies during the study. Seven subjects tested positive for neutralizing activity at a single visit. All subjects returned to baseline levels at the next visits. Therefore the presence of neutralizing antibodies was transient. None of those seven subjects had any reported allergic reactions or hypersensitivity. Thus, there does not appear to be a correlation between detectable anti-rhPDGF-BB antibodies with neutralizing activity and clinical outcomes and adverse events.

A summary of the key safety results for the safety population is presented in Table 11 below.

Table 11: Safety Results

	Augment® Bone Graft (n=272)	Autograft (n=142)
Pre-Treatment Signs and Symptoms	2.6%	2.8%
Treatment Emergent Adverse Events (TEAEs)	77.9%	73.9%
Serious TEAEs	10.3%	14.8%
Related TEAEs	2.2%	4.2%
Overall complications	35.3%	38.7%
Complications associated with surgical procedure	23.9%	30.3%
Serious complications	5.1%	6.3%
Infections by SOC	22.4%	19.7%
Cancer/Neoplasm	1.8%	1.4%
Transient Antibody (non-neutralizing)	13.9%	3.6%
Transient Antibody (neutralizing)	2.6%	0%

Observed Cancer Incidence in Pivotal Trial

Observations of cancer incidence in the treated population during the 1-year follow-up in the pivotal trial were 1.8% (5 of 272) in Augment® Bone Graft treated subjects and 1.4% (2 of 142) in autograft treated subjects. Although the incidences of cancer were collected under the term “neoplasm”, FDA uses the term “cancer” in this document, which includes neoplasms that are both malignant and benign. In the randomized subject cohort, there were seven events (five investigational and two autograft controls) noted as the category of “Neoplasms” for this trial, with five of these categorized by the sponsor as serious adverse events (SAEs). Two patients with neoplasms in the investigational group were not considered as SAEs because the sponsor considered these of a benign nature (one pre-cancerous hyperplastic colon polyp and one plantar fibroma).

Notably, the IDE study for Augment® Bone Graft has an exclusion criterion that only excludes for “untreated malignant neoplasm(s) at the surgical site, or was currently undergoing radio- or chemotherapy.” Therefore, it is possible that patients that received the product may have had pre-existing cancer because only subjects with cancer at the surgical site and subjects currently undergoing cancer treatment were excluded from the study.

Of these events, all were classified as not related to the product. There was no clear relationship to any demographic or other parameter among the Augment® Bone Graft patients with cancer reported to 24 months according to gender (3 males and 4 females); time to diagnosis (range 20 days to 9 months); or age at surgery (range 42-75).

Brief summaries of the types of cancer cases and subsequent treatment, are detailed in the Table 12 below:

Table 12 - Summary of Cancer Events to 52 Weeks

Treatment Group	Sex	Age at Surgery	Surgery Type	Cancer Type	Time of Diagnosis Post-Treatment	Treatment	Outcome
Augment® Bone Graft	M	65	Not provided	Prostate	7 months	Radiation	Recovered
Augment® Bone Graft	F	57	Not provided	Breast	4 months	Bilateral total mastectomy and 2 rounds chemotherapy	Unresolved
Augment® Bone Graft	M	64	Not provided	Prostate	6 months	Chemotherapy	Unresolved
Augment® Bone Graft	F	61	Not provided	Hyperplastic Colon Polyp	9 months	Removal	Resolved
Augment® Bone Graft	F	42	Not provided	Plantar fibroma	9 months	Removal	Resolved
autograft control	M	75	Not provided	Renal Cell Carcinoma	20 days	Right ureterectomy and radical nephrectomy	Recovered
autograft control	F	60	Not provided	Endometrial cancer	7 months	No additional information past diagnosis at time of biopsy	Unresolved

Cancer Types Observed in the Investigational Group:

The cancer types at 52 weeks listed as SAEs include two prostate cancers and one breast cancer. Further information on the two neoplasms listed under “All Adverse Events,” but not classified as SAEs, include one hyperplastic colon polyp and one plantar fibroma. Information on the three investigational patients with SAE cancers revealed that there were two males and one female; 5.6 average months (range - 4 to 7 months) time to diagnosis; 62 average age (range - 57 to 65 years) at diagnosis; and subsequent treatments as outlined in Table 12. The outcomes on two of these three patients remain “unresolved.” The most notable related parameter was the time to cancer diagnosis, being 9 months or less for all subjects.

Cancer Types Observed in the Autograft Control:

The cancer types seen in the autograft control group were renal cell carcinoma and endometrial carcinoma. There was one male and one female; average 4 months (20 days and 7 months) to diagnosis; ages 60 and 75; with subsequent treatments as outlined in the table 12 above.

Relative Risks of Products Containing Becaplermin (rhPDGF-BB)

Augment® Bone Graft contains becaplermin (rhPDGF-BB), which promotes cellular chemotaxis, proliferation and angiogenesis. rhPDGF-BB is also the active ingredient of two FDA-approved products: Regranex® gel, which is a topical gel formulation indicated for the treatment of lower extremity diabetic neuropathic ulcers; and GEM 21S®, which is a synthetic grafting system for bone and periodontal regeneration.

The labeling of Regranex® gel contains a black box warning describing an increased rate of mortality secondary to malignancy in patients treated with three or more tubes of this product. This warning is based on a numerical imbalance in the number of patients with malignancies distant from the site of application in clinical studies as well as a finding of an increase in mortality from existing cancers in patients exposed to three or more tubes of Regranex® from a retrospective pharmacoepidemiology study⁴. However, a subsequent study that presented extended follow-up data in the same cohorts of patients found no conclusive evidence that cancer incidence rate or cancer mortality was higher in becaplermin (rhPDGF-BB) users than in comparators⁵.

Regranex® gel is applied up to 3 times daily to skin ulcers for up to 20 weeks, thereby exposing the patient to repeated doses of rhPDGF-BB over long time periods at significantly higher maximum exposure than occurs with the use of Augment® Bone Graft for treating ankle and hindfoot arthrodeses. The typical single use application of Augment® Bone Graft involves the use of one or more kits containing 1.5 to 9 ml rhPDGF-BB at 0.3 mg/ml (0.45 - 2.70 mg), resulting in a total exposure of 450 - 2,700 µg, whereas the minimum amount of Regranex® in the label warning represents repeated daily use of Regranex® in a significantly higher total exposure of 4500 µg or more of rhPDGF-BB (3 tubes or more).

The product label of REGRANEX® Gel contains a warning identifying an increased rate of mortality secondary to malignancy in patients treated with three or more tubes of this product based on the results of the first of three post-approval studies of REGRANEX® Gel.

Summary of the Three REGRANEX® Post-Approval Studies' Findings Regarding Cancer

First, in a retrospective study¹⁸ of a medical claims database, cancer rates and overall cancer mortality were compared between 1622 patients who used REGRANEX® Gel and 2809 matched comparators. Estimates of the incidence rates reported below may be under-reported due to limited follow-up for each individual.

- The incidence rate for all cancers was 10.2 per 1000 years for patients treated with REGRANEX® Gel and 9.1 per 1000 years for the comparators. Adjusted for several possible confounders, the rate ratio was 1.2 (95% confidence interval 0.7-1.9). Types of cancers varied and were remote from the site of treatment.
- The incidence rate for mortality from all cancers was 1.6 per 1000 person years for those who received REGRANEX® Gel and 0.9 per 1000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.7-4.9).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX® Gel was 3.9 per 1000 years and 0.9 per 1000 person years for the comparators. The rate ratio for cancer mortality among those who received 3 or more tubes relative to those who received none was 5.2 (95% confidence interval 1.6-17.6), although this estimate ignored confounders in the incidence model due to the small number of events in this group.

These results are based on follow-up information, post-treatment out to 3 years. The information indicates that patients treated with REGRANEX® Gel did not have a greater incidence of post-treatment cancer, but patients treated with 3 or more tubes of REGRANEX® Gel had a statistically significant increased rate of mortality, i.e., a 5.2 fold greater rate, secondary to malignancy, unadjusted for other confounders. The malignancies observed were distant from the site of application in becaplermin (PDGF) users evaluated in the post-marketing study.

Second, in the follow-up epidemiologic study of these same patient cohorts (post-treatment years 3 to 6), investigators found that the becaplermin treated group receiving 3 or more tubes of REGRANEX® Gel did not have an increased incidence of cancer as compared to the control group. While the cancer mortality rate remained higher (the adjusted rate ratio was 2.4 with 95% confidence interval 0.8-7.4) in the becaplermin treated group receiving 3 or more tubes of REGRANEX® Gel, the rate was not statistically different than the rate of cancer mortality of the control group during this observation period. The findings of the second study of patients in post-treatment years 4 to 6 are not considered to negate the findings of the first study of patients in post-treatment years 1 to 3, just as the findings of the first study are not considered to negate the findings of the second study.

Third, a study evaluating cancer risk associated with the use of Becaplermin (rhPDGF-BB) for the treatment of diabetic foot ulcers was conducted by the Veterans Administration. This study

compared cancer rates and overall cancer mortality between 6429 patients who used REGRANEX® Gel and 6429 matched comparators followed over 11 years (1998 through 2009). The hazard ratio for cancer mortality among those who received 3 or more tubes of REGRANEX® Gel relative to those who received none was 1.04 (95% confidence interval 0.73-1.48). This study provided no evidence of a cancer risk among becaplermin users, and did not indicate an elevated risk of cancer mortality.

These three studies have limited relevance to the use of *Augment® Bone Graft* in bone grafting procedures of the ankle and hindfoot due to:

- higher doses of rhPDGF-BB with REGRANEX® Gel compared to *Augment® Bone Graft*
- their different intended uses,
- the locations where the products containing PDGF were placed,
- possible gender bias, and
- limited statistical power to detect small incident cancer death risks.

Comprehensive preclinical studies including long term carcinogenicity, acute and repeated dose toxicity, reproductive/development toxicity, and animal and human pharmacokinetic studies were conducted to evaluate the safety and carcinogenic potential of rhPDGF-BB at doses far in excess of the usual orthopedic dose of a single administration of *Augment® Bone Graft*. The human pharmacokinetic study included seven patients receiving the *Augment® Bone Graft* implantation, and the data showed no increase in circulating levels of PDGF-BB in serum, i.e., no systemic effect of the administration of *Augment® Bone Graft* in ankle and hindfoot arthrodesis. Overall, these studies have shown no adverse findings or any indication of an increase in cancer incidence or cancer mortality. Furthermore, there is no reported evidence of increased cancer incidence or mortality associated with rhPDGF-BB in data from human clinical trials of *Augment® Bone Graft* or similar products containing rhPDGF-BB and β -TCP.

Treatment Emergent Adverse Events

Of 973 reported treatment emergent adverse events (TEAEs), there were fewer related TEAEs in the *Augment® Bone Graft* group (2.2% versus 4.2%) than in the autograft group. There were also fewer serious TEAEs in the *Augment® Bone Graft* group (10.3% versus 14.8%). Total TEAEs were similar between groups with an overall rate of 77.9% for *Augment® Bone Graft* (212 of 272 subjects) and 73.9% for autograft (105 of 142 subjects).

Treatment emergent adverse event terms that occurred in at least 5% of the subjects in the trial are listed in Table 13. Adverse event rates are similar for the two treatment groups for the three adverse event types identified in Table 13.

Table 13: Treatment Emergent Adverse Events Found in $\geq 5\%$ of Subjects

	Augment® Bone Graft (n=272)		Autograft (n=142)	
	Subjects	Events	Subjects	Events

Any Adverse Event	212 (77.9%)	657	105 (73.9%)	316
Medical device pain	14 (5.1%)	14	7 (4.9%)	7
Arthralgia	38 (14.0%)	46	15 (10.6%)	17
Pain in extremity	48 (17.6%)	56	21 (14.8%)	24

Treatment emergent adverse events are those events that occurred on or after the day of surgery.

The incidence of TEAEs that were considered by the investigator to be possibly, probably, or definitely related to clinical trial treatment was low in both treatment groups, reported in only six Augment® Bone Graft subjects (2.2%), and eight autograft control subjects (5.6%). Only pain in extremity is reported by more than one (0.7%) Augment® Bone Graft subject while pain in extremity (1.4%) and graft site infection (1.4%) are reported by more than one autograft subject. Graft site infection was not observed in subjects treated with Augment® Bone Graft because there is no autograft harvest site.

All the related TEAEs (defined as possibly, probably, or definitely related to clinical trial treatment) are presented in Table 14.

Table 14: Related Treatment Emergent Adverse Events

	Augment® Bone Graft (n=272)		Autograft (n=142)	
	Subjects	Events	Subjects	Events
All adverse events	6 (2.2%)	9	8 (5.6%)	12
Arthralgia	1 (0.4%)	1	0 (0.0%)	0
Bone pain	0 (0.0%)	0	1 (0.7%)	1
Cellulitis	0 (0.0%)	0	1 (0.7%)	1
Foot deformity	1 (0.4%)	1	0 (0.0%)	0
Graft site infection	0 (0.0%)	0	2 (1.4%)	2
Impaired healing	1 (0.4%)	1	0 (0.0%)	0
Medical device pain	0 (0.0%)	0	1 (0.7%)	1
Edema peripheral	0 (0.0%)	0	1 (0.7%)	1
Pain in extremity	2 (0.7%)	2	2 (1.4%)	2
Pruritus	0 (0.0%)	0	1 (0.7%)	1
Skin ulcer	1 (0.4%)	2	0 (0.0%)	0
Swelling	0 (0.0%)	0	1 (0.7%)	1
Tenderness	0 (0.0%)	0	1 (0.7%)	1
Tendonitis	0 (0.0%)	0	1 (0.7%)	1
Ulcer	1 (0.4%)	1	0 (0.0%)	0
Wound dehiscence	1 (0.4%)	1	0 (0.0%)	0

Related adverse events are those events categorized as having a possible or probable/definite relationship to treatment. Treatment emergent adverse events are those events that occurred on or after the day of surgery.

Table 15 summarizes the secondary surgeries through week 24 and week 52 for all randomized and treated subjects.

Table 15: Categorization of Secondary Surgeries

Type	Total Procedures through Week 24		Total Subjects through Week 24 (%)		Total Procedures through Week 52		Total Subjects through Week 52 (%)	
	I	C	I (n=272)	C (n=142)	I	C	I (n=272)	C (n=142)
Revisions	13	7	12 (4.4)	6 (4.2)	24	9	22 (8.1)	8 (5.6)
Removals	3	0	3 (1.1)	0	8	1	7 (2.6)	1 (0.7)
Supplemental fixations	0	0	0	0	1	0	1 (0.4)	0
Reoperations	2	2	2 (0.7)	2 (1.4)	2	2	2 (0.7)	2 (1.4)
Hardware Removals	12	6	11 (4)	5 (3.5)	23	8	21 (7.7)	7 (4.9)
Others	6	7	6 (2.2)	7 (4.9)	10	10	10 (3.7)	9 (6.3)
Total procedures	36	22	23 (8.5)	15 (10.6)	68	30	42 (15.4)	20 (14.1)

Notes:

I-Investigational (Augment® Bone Graft, N = 272)

C- (autograft control, N = 142)

Following the FDA Guidance entitled “Clinical Data Presentations for Orthopedic Device Applications,” definitions of the categories for a subject’s secondary procedure may be classified into one or more categories. For purposes of this accounting, revisions are defined as any adjustment, modification, or removal of a part of the original implant configuration. Removals are defined as removal of the original system, with or without replacement. A supplemental fixation is defined as the implantation of additional instrumentation not under study. Reoperations are defined as any surgeries that do not include removal, modification, or addition of the components of the system. Hardware removals are defined as adjustments to supplemental hardware (e.g., screws) not under study. The other category refers to surgeries unrelated to the arthrodesis procedure. Augment® Bone Graft and autograft demonstrated similar rates of secondary surgeries across the clinical trial.

Vascular Events

As with any lower extremity surgery, ankle and hindfoot surgery carries an increased risk of subjects developing deep vein thrombosis (DVT) or pulmonary embolism (PE). There are known risk factors which include any trauma to the lower extremity, post-operative immobilization, increased age, history of myocardial infarction (MI) or congestive heart failure (CHF), use of estrogen therapy or pregnancy, obesity, presence of varicose veins and smoking.

The incidence of serious “complications” coded as vascular disorders was reported as 13 events for 12 patients, or by treatment group of 2.9% Augment® Bone Graft and 2.8% for autograft controls (DVT: 2.2% Augment® Bone Graft versus 2.1% autograft control; Pulmonary Embolus: 0.7% Augment® Bone Graft versus 0.7% autograft control; and Thrombosis: 0.4% Augment® Bone Graft and 0% autograft control).

Deaths

There was one death in the Augment® Bone Graft group and none in the autograft group through the 52-week reporting time. The patient died of a pulmonary embolism 14 days after surgery. This SAE was assessed as being “not related” to the study device. This event, however, was likely related to the surgical procedure. The following Table 16 provides all known information on the one death reported.

Table 16-Summary of Deaths to 52 Weeks

Case ID	Patient No	Treatment Group	Reported Term	Preferred Term	Investigator Causality	Event Outcome
GEM	44-07 HVH	Augment® Bone Graft	PULMONARY EMBOLISM	Pulmonary Embolism	Not related	Death

Effectiveness Results

Primary Endpoint

The primary endpoint was fusion, defined as at least 50% osseous bridging on the full complement of joints in the ankle or hindfoot, based on computerized tomography (“CT”) scans at 24 weeks.

The hypothesis for the primary endpoint was that Augment® Bone Graft, in comparison to autograft, would be non-inferior to the primary endpoint defined as CT evidence of greater than 50% osseous bridging at 24 weeks. Patients who received secondary procedures (bone growth stimulation or revision surgery) were considered as failures. Subjects with one or more serious adverse events that were medically-relevant (i.e., relative to the safety and effectiveness of the product) and led to secondary surgical procedures were classified as failures for effectiveness. The autograft control arm received autograft harvested from external sites; harvest of graft from the iliac crest occurred in a minority of the patients (11.7%).

For the “full complement of joints” assessment, the sponsor deemed 61.2% (159/260) of Augment® Bone Graft subjects and 62.0% (85/137) of autograft control subjects as successful and, therefore, statistically non-inferior to the autograft control group in the mITT population ($p=0.038$), but not in the ITT population ($p=0.065$). FDA had several concerns with the clinical and statistical relevance of the “full complement of joints” and the methodology used to determine bridging bone by CT scan. Therefore, FDA requested a review of radiographs and CT scans collected from the clinical trial. This information was needed to adequately evaluate the product’s effectiveness in promoting fusion, and to specifically answer questions regarding whether or not Augment® Bone Graft contributed to the bridging bone in the fusion mass over time, or conversely, whether Augment® Bone Graft impedes or prevents the formation of bridging bone where the material was placed in relation to the bones being fused.

Radiologic Observations

FDA reviewed a random sampling of x-rays and arrived at the following conclusions:

1. There is high attenuation of the Augment® Bone Graft seen radiographically that precludes the assessment of bridging bone. In areas where Augment® Bone Graft is present it is not possible to determine whether bridging bone is present because Augment® Bone Graft obscures visualization. One can evaluate bony bridging in a joint with Augment® Bone Graft, but only in the areas of the joint where no Augment® Bone Graft is present. Conversely, one can evaluate joints with autograft for the presence of bony bridging.
2. FDA believes that the high attenuation of the Augment® Bone Graft is attributed to the β -TCP component of the product. Observation of high attenuation, or density, equal to that of cortical bone does not equate to the presence of bridging bone.
3. Because the assessment of radiographic fusion for Augment® Bone Graft patients at 24 weeks was inconclusive, outcome evaluations and benefit/risk assessments should be based on clinical functionality by evaluating pain and function scores at specified intervals post operatively.
4. Quantitative assessment of radiographic fusion (objectively measuring) by CT is very challenging because the method of assessment is subjective for determining successful fusion using imaging.
5. The Augment® Bone Graft was observed in the soft tissue in a few of the CTs evaluated. This would indicate there was migration of the graft material during application or over time.

The results from the statistical analysis of the primary endpoint for the assessment of bridging bone at 24 weeks, as a measure of effectiveness, were inconclusive for the reasons discussed above.

Because of the high attenuation of Augment® Bone Graft’s β -TCP matrix still observed on the CT scans at the 24-week time point, the evaluation of bridging bone in the Augment® Bone Graft group could not definitively be assessed in contrast to the bridging bone seen in the autograft control group. The sponsor defined fusion as the coalescence of the Augment® Bone Graft particles at 24 weeks with no radiolucencies observed in the Augment® Bone Graft success group. While these criteria may be consistent with a progression toward fusion, they would not in and of themselves provide conclusive evidence of fusion. Consensus could not be reached regarding how to interpret these radiologic findings. Therefore, FDA relied primarily on the evaluation of endpoints such as weight bearing pain and functional assessments to help determine the clinical effectiveness of Augment® Bone Graft in individual subjects as compared to autograft at the 24 and 52 week time points.

Clinical Endpoints

There were five clinical measurements that evaluated the clinical benefit of Augment® Bone Graft compared to autograft when used for ankle and hindfoot arthrodesis. These clinical measurements were Pain on Weight Bearing (via VAS), Pain at Fusion Site (via VAS), Foot Function Index (FFI), AOFAS Hindfoot and Ankle Score, and SF-12 (PCS). Of these assessments, FDA chose to analyze VAS on weight bearing, FFI, and AOFAS in a post-hoc manner. The analysis demonstrated equivalent improvements in outcomes for both Augment® Bone Graft and autograft at weeks 24 and 52, postoperatively.

Pain on Weight Bearing

Graph 3 displays data on pain on weight bearing (measured by VAS) at week 24 as assessed in the cohort used to determine individual success and taking into account the 2:1 randomization. (Graph 3 and subsequent Graphs 4 and 5 omit the 67 medically relevant protocol derivations and missing data). Table 17 presents data in the “Per Protocol” population. In the data presentations, the “clinically significant improvement” group was defined by a greater than 20mm decrease in VAS score compared to baseline, the “improved” group was defined by a 10-20mm decrease in VAS score compared to baseline, and the maintained group was defined by a change in VAS of -10 to 10mm as compared to baseline.

Graph 3 - VAS on Weight Bearing Assessed for Individual Success at 24 Weeks

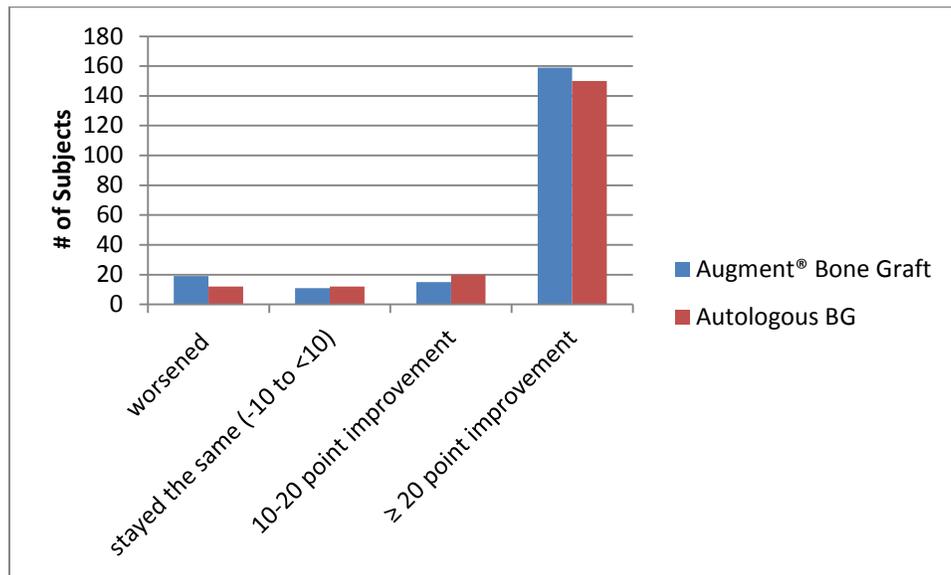


Table 17: Reduction in Pain on Weight Bearing at 24 and 52 weeks – “Per Protocol” Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Clinically Significant Improvement ¹	76.3% (167/219)	74.4% (87/117)	79.1% (170/215)	80.5% (95/118)
Detectable Improvement ²	6.4% (14/219)	10.3% (12/117)	9.3% (20/215)	6.8% (8/118)
Maintained ³	11.4% (25/219)	10.3% (12/117)	8.8% (19/215)	9.3% (11/118)
Deteriorated ⁴	5.9% (13/219)	5.1% (6/117)	2.8% (6/215)	3.4% (4/118)

¹Clinically significant improvement: ≥20mm decrease from baseline

²Detectable improvement: 10-20mm decrease from baseline

³Maintained: <10mm decrease from baseline and <10mm increase from baseline

⁴Deteriorated: >10mm increase from baseline

Both Augment® Bone Graft and autograft control demonstrated comparable postoperative improvement in pain on weight bearing according to VAS. The vast majority of subjects in both treatment groups showed maintained or improved values in pain on weight bearing, as compared to baseline levels at these time points.

Pain at Fusion Site

Table 18 displays pain at fusion site (measured by VAS) at week 24 and week 52. In the data presentations, the “clinically significant improvement” group was defined by a greater than 20mm decrease in VAS score compared to baseline, the “improved” group was defined by a 10-20mm decrease in VAS score compared to baseline, and the maintained group was defined by a change in VAS of -10 to 10mm as compared to baseline.

Table 18 Fusion Site Pain at 24 and 52 Weeks – “Per Protocol” Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Clinically Significant Improvement ¹	64.6% (144/223)	61.7% (71/120)	63.8% (139/218)	67.5% (81/120)
Detectable Improvement ²	9.0% (20/223)	12.5% (15/120)	12.4% (27/218)	9.2% (11/120)
Maintained ³	17.5% (39/223)	17.5% (21/120)	20.2% (44/218)	15.8% (19/120)
Deteriorated ⁴	9.0% (20/223)	8.3% (10/120)	3.7% (8/218)	7.5% (9/120)

¹Clinically significant improvement: ≥ 20 mm decrease from baseline

²Detectable improvement: 10-20mm decrease from baseline

³Maintained: < 10 mm decrease from baseline and < 10 mm increase from baseline

⁴Deteriorated: > 10 mm increase from baseline

Both Augment® Bone Graft and autograft demonstrated comparable postoperative improvement in fusion site pain according to VAS. The majority of subjects in both treatment groups showed maintained or improved relief in fusion site pain as compared to baseline levels at each time point.

Foot Function Index (FFI)

Graph 4 displays data displays on functional improvement measured by the Foot Function Index (FFI) at week 24, as assessed in the cohort used to determine individual success and taking into account the 2:1 randomization. Table 19 presents data in the “Per Protocol” population. In the data presentations, the “clinically significant improvement” group was defined by a greater than 10 point decrease in FFI score compared to baseline, the “improved” group was defined by a 5-10 point decrease in FFI score compared to baseline, and the maintained group was defined by a change in FFI of -5 to 5 points as compared to baseline.

Graph 4: FFI Assessed for Individual Success at 24 Weeks

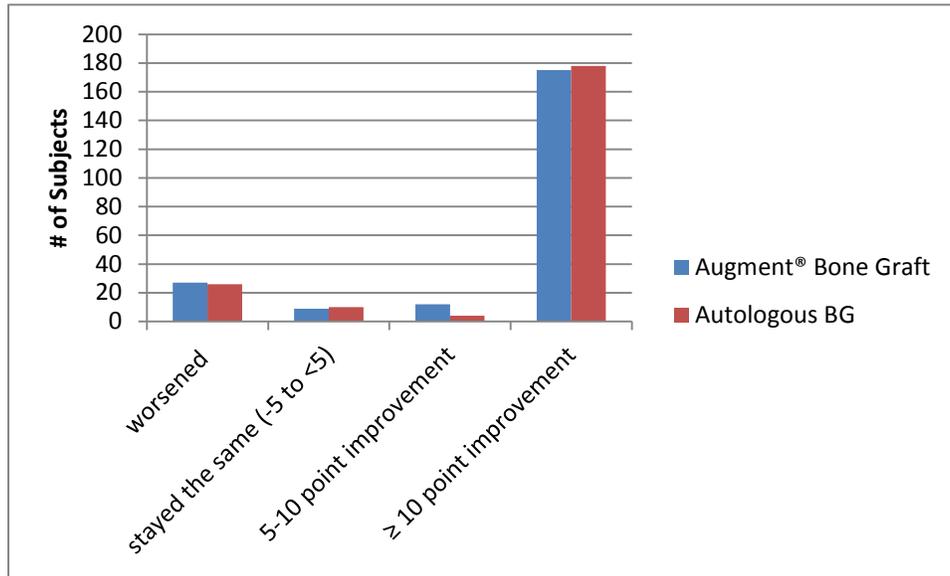


Table 19: Foot Function Index at 24 and 52 Weeks – “Per Protocol” Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Clinically Significant Improvement ¹	76.3% (190/249)	79.7% (106/133)	86.7% (209/241)	86.6% (114/132)
Improved ²	7.6% (19/249)	3.0% (4/133)	3.3% (8/241)	0.8% (1/132)
Maintained ³	6.4% (16/249)	10.5% (14/133)	5.0% (12/241)	8.8% (12/132)
Deteriorated ⁴	9.6% (24/249)	6.8% (9/13)	5.0% (12/241)	3.6% (5/132)

¹Clinically significant improvement: ≥10 point decrease from baseline

²Improved: 5-10 point decrease from baseline

³Maintained: <5 point decrease from baseline and <5 point increase from baseline

⁴Deteriorated: >5 point increase from baseline

Both Augment® Bone Graft and autograft demonstrated comparable postoperative improvement in FFI. Mean scores were similar between the Augment® Bone Graft group and autograft. The vast majority of subjects in both treatment groups maintained, or showed improvement in, foot function as compared to baseline levels at each time point.

AOFAS Hindfoot and Ankle Score

Graph 5 displays data on functional improvement measured by AOFAS Hindfoot and Ankle Score at week 24, as assessed in the cohort used to determine individual success and taking into account the 2:1 randomization. Table 20 presents data in the “Per Protocol” population. In the data presentations, the “clinically significant improvement” group was defined by a greater than 20 point increase in AOFAS score compared to baseline, the “improved” group was defined by a

10-20 point increase in AOFAS score compared to baseline, and the maintained group was defined by a change in AOFAS of 10 to -10 points as compared to baseline.

Graph 5 - AOFAS Assessed for Individual Success at 24 Weeks

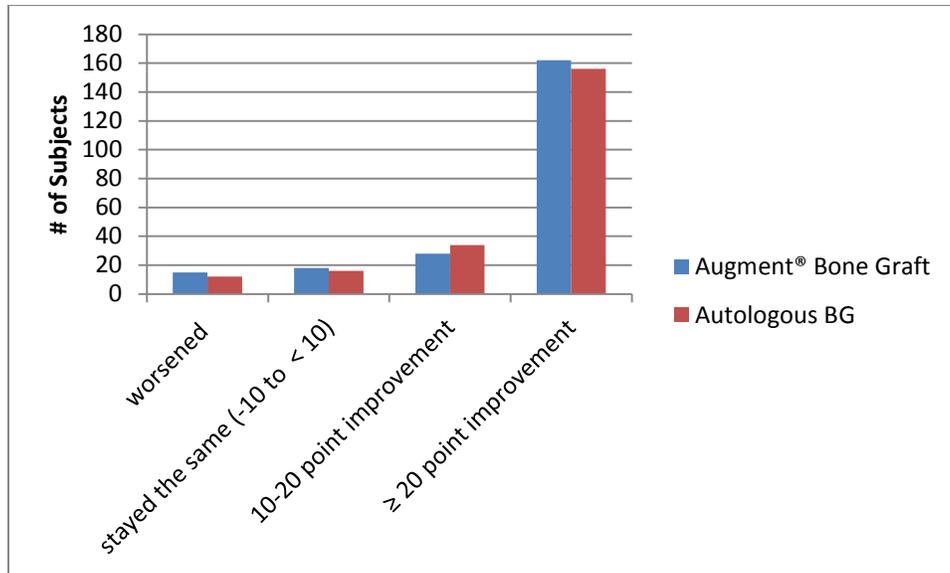


Table 20: AOFAS Hindfoot and Ankle Score at 24 and 52 Weeks – “Per Protocol” Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Clinically Significant Improvement ¹	72.6% (180/248)	70.1% (94/133)	80.90% (195/241)	80.3% (106/132)
Improved ²	10.9% (27/248)	14.3% (19/133)	9.1% (22/241)	7.6% (10/132)
Maintained ³	13.3% (35/248)	10.5% (14/133)	7.9% (19/249)	8.3% (11/132)
Deteriorated ⁴	3.2% (8/248)	4.5% (6/133)	2.1% (5/249)	3.8% (5/132)

¹Clinically significant improvement: ≥20 point increase from baseline

²Improved: 10-20 point increase from baseline

³Maintained: <10 point increase from baseline and <10 point decrease from baseline

⁴Deteriorated: >10 point decrease from baseline

Both Augment® Bone Graft and autograft demonstrated comparable postoperative improvement in function according to AOFAS scores. The vast majority of subjects in both treatment groups showed maintained or improved function as compared to baseline levels at each time point.

SF-12 Physical Component Score

Table 21 presents data on overall quality of life measured by SF-12 Physical Component Score (PCS) at weeks 24 and 52. In the data presentations, the “maintenance or improvement” group was defined by an increase in SF-12 PCS as compared to baseline.

Table 21: SF-12 Physical Component Score (PCS) at 24 and 52 Weeks – “Per Protocol” Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Maintenance or Improvement ¹	81.5% (203/249)	79.7% (106/133)	85.5% (206/241)	88.6% (117/132)
Slight Decline ²	15.3% (38/249)	16.5% (22/133)	13.7% (33/241)	10.6% (14/132)
Deteriorated ³	3.2% (8/249)	3.8% (5/133)	0.8% (2/241)	0.8% (1/132)

¹Maintenance or improvement: ≥ 0 point increase from baseline

²Slight Decline: 0-10 point decrease from baseline

³Deteriorated: >10 point decrease from baseline

Both Augment® Bone Graft and autograft demonstrated comparable postoperative maintenance or improvement in overall quality of life according to SF-12 PCS. The vast majority of subjects in both treatment groups showed maintained or improved overall quality of life as compared to baseline levels at each time point.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 82 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL RECOMMENDATION

A. Panel Meeting Recommendation

The Orthopedic and Rehabilitation Devices Panel reviewed this PMA at a May 12, 2011, panel meeting. Based on the data and labeling available at time of panel meeting, the panel voted 12 to 6 that there is a reasonable assurance that the product is safe, 10 to 8 that there is a reasonable assurance that the product is effective, and 10 to 8 that the benefits of the product do outweigh the risks in patients who meet the criteria specified in the proposed indication. The panel recommended a sufficiently powered post approval study (PAS) be performed to allow for the surveillance of both effectiveness and adverse events. sponsor agreed to perform a PAS to

evaluate both effectiveness and adverse events associated with the use of Augment® Bone Graft.

B. FDA's Post Panel Meeting Action

Subsequent to the panel meeting, the FDA requested the CT studies to help determine if the CT primary endpoint was acceptable. Based upon the review of the CT studies of Augment® Bone Graft, high attenuation was observed with the β -TCP of the Augment Bone Graft at 24 weeks prevented assessment of bridging bone. Therefore, the clinical endpoints of weight bearing pain and function were used as the bases of comparison between Augment® Bone Graft and autograft.

XII. CONCLUSIONS DRAWN FROM NON-CLINICAL & CLINICAL STUDIES

Augment® Bone Graft is a combination of a highly porous, osteoconductive scaffold (β -TCP) which provides an environment for cellular ingrowth and bone formation, and recombinant human Platelet Derived Growth Factor BB (rhPDGF-BB).

The scientific evidence presented in the preceding sections provides reasonable assurance that Augment® Bone Graft is a safe and effective alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular and calcaneocuboid joints) due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material.

Non-clinical studies provide support for the safety of Augment® Bone Graft, including local and systemic genotoxicity and cytotoxicity studies, acute and chronic high dose exposure studies, as well as pharmacokinetic evaluations. Animal studies were conducted to evaluate Augment® Bone Graft's role in bone healing. These studies show the addition of rhPDGF-BB demonstrated superior biomechanical and histologic healing as compared to matrix only autograft controls, particularly at early time points. No evidence of ectopic or heterotopic bone formation has been demonstrated in these animal studies.

Augment® Bone Graft demonstrated a reasonable assurance of safety and effectiveness as a bone graft substitute in a randomized clinical trial involving 434 subjects. These conclusions are based upon clinical and functional measurements. The results of this clinical trial also demonstrate that Augment® Bone Graft patients do not require a second surgical incision site for the harvest of autograft bone. Autograft harvest site complications can include morbidities such as infection, fracture, hematoma or seroma formation, sensory nerve injury, and chronic pain or dysesthesia at the autograft harvest site affecting patient quality of life and/or function.

A. Effectiveness Conclusions

In the pivotal trial, 434 subjects were enrolled and a total of 414 subjects completed study surgery. Of these, 397 were treated per protocol and comprise the primary analysis population for the radiographic assessment of bridging bone at 24 weeks as the primary outcome measure. The autograft control group for the clinical trial was autologous bone graft (autograft), which is considered the gold standard for graft material for ankle and hindfoot arthrodesis procedures. Analysis of patient demographics showed no differences between the treatment groups. However, because of the high attenuation of β -TCP at 24 weeks, radiographic analyses for the assessment of bridging bone in the Augment® Bone Graft group was inconclusive.

Because the radiographic review was inconclusive, effectiveness of Augment® Bone Graft was evaluated using clinical and functional, outcome measures as an assessment of individual subject success. The following outcome measures demonstrated equivalence of Augment® Bone Graft and autograft at 24 and 52 weeks post-operatively:

- Pain on weight bearing (VAS)
- Fusion site pain (VAS)
- FFI
- AOFAS Hindfoot and Ankle Score
- SF-12 (PCS)

In conclusion, the clinical trial data indicate that, at 24 and 52 weeks postoperatively, Augment® Bone Graft is at least as effective as the autograft control treatment, for the patient population and indications studied in this investigation, in terms of the individual patient success for clinical and functional outcomes. Further benefits of Augment® Bone Graft are realized without the pain and morbidity resulting from harvesting autograft.

B. Safety Conclusions

The key safety conclusions from the trial are that subjects treated with Augment® Bone Graft had overall similar rates of treatment-emergent adverse events (TEAEs), serious TEAEs, treatment-related TEAEs, complications, and infections compared to subjects treated with autograft. The clinical trial revealed one adverse event directly attributable to Augment® Bone Graft. The elimination of pain and morbidity resulting from the surgical approach in harvesting autograft provides additional benefit to patients receiving Augment® Bone Graft. This is clinically important to surgeons and patients due to the elimination of complications, patient pain, and morbidity associated with a separate surgical incision site to harvest autograft bone.

The data demonstrate that use of Augment® Bone Graft resulted in comparable clinical healing to autograft as determined by the individual subjects and the surgeons. The Augment® Bone Graft clinical trial results demonstrate a similar safety profile when compared to autograft.

C. Benefit-Risk Conclusions

The probable benefits of Augment® Bone Graft are based on data collected in the clinical trial as described above. Benefits of Augment® Bone Graft demonstrated over the 52-week time period studied include:

Augment® Bone Graft and autograft control subjects achieved comparable clinical and functional improvements in outcomes (pain on weight bearing, Foot Function Index (FFI), and AOFAS Score). Augment® Bone Graft patients did not require the need for autograft from a secondary harvest site. Clinically significant pain was present at the harvest site through 24 and 52 weeks for 12.4% and 8.8% of autograft subjects, respectively.

Regarding risk, as previously mentioned, subjects treated with Augment® Bone Graft had overall similar rates of treatment-emergent adverse events (TEAEs), serious TEAEs, treatment-related TEAEs, complications, and infections compared to subjects treated with autograft.

In conclusion, the data support that the probable clinical benefits of Augment® Bone Graft for bone grafting procedures outweigh the probable risks through 24 and 52 weeks of follow-up. However, because the radiographic assessment of bridging bone at 24 weeks was inconclusive, uncertainty remains in interpreting the effectiveness of Augment® Bone Graft for bony fusions, although it can be stated that radiographic evidence showing the lack of radiolucencies and coalescence of the Augment® Bone Graft material may be consistent with a progression toward bony fusion.

D. Overall Conclusions

The preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of Augment® Bone Graft when used in accordance with the indications for use when compared to autograft. Based on the clinical trial results, the clinical benefits of the use of Augment® Bone Graft outweigh the risks in terms of pain and functional improvements and the elimination of harvest site complications, when used in the intended population in accordance with the directions for use, and as compared to the autograft control treatment in the same intended population. The valid scientific evidence presented in the preceding sections provides reasonable assurance that Augment® Bone Graft is a safe and effective alternative to autograft for use in arthrodesis procedures of the ankle and/or hindfoot when bone grafting procedures of the ankle and/or hindfoot are warranted.

XIII. CDRH DECISION

CDRH issued an approval order on September 1, 2015.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

The sponsor will conduct two post-approval studies as described below:

1. *Extended Follow-up of Premarket Cohort (Long-term PAS Study)*: The applicant has agreed to a study outline on October 23, 2014 (email). This PAS is a continued follow-up of the Augment Bone Graft and Autologous graft premarket IDE cohort. It is a prospective, controlled study within the US and Canada comparing Augment Bone Graft to Autograft (in a 2:1 ratio) in hind foot and ankle arthrodesis at 5 or more years post-treatment. The study will address the following objectives: (1) Can it be assessed and confirmed that bridging bone occurs in the long-term after Augment has been resorbed? (2) Are the improvements in clinical outcomes associated with the use of Augment sustained long-term? (3) Does the promotion of existing tumors from a nonmalignant to malignant state at longer time-points in patients treated with Augment exceed the expected rate of promotion in patients not treated with Augment or other growth factors used to promote fusion?

The primary effectiveness endpoints will consist of the following:

- Demonstration of bridging bone via CT
- Patient Function as determined by Pain on Weight Bearing (via VAS), AOFAS Score and Foot Function Index (FFI)

The primary safety endpoints will consist of the following:

- Presence of all adverse events (i.e., description, frequency, incidence, time to onset of first event, severity, duration, treatments administered, etc.)
- Presence of serious unanticipated adverse device effects (UADE)
- rhPDGF-BB antibody status
- At evaluation, subjects will be interviewed regarding significant medical conditions, including incidence of cancer
- Presence of clinically important events as defined below:
 - Musculoskeletal and connective tissue disorders (severe pain, swelling and/or arthralgia in the treated foot/ankle joint(s));
 - Additional surgery of the original treated joint due to non-union.
 - Neoplasms benign, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)
 - Complications related to bone graft harvest site

The study will require 150 subjects (100 Augment; 50 Autograft) to be evaluated at a single visit at 5 years or more after original treatment under BMTI-2006-01 study. Hypothesis testing for maintenance of improvements within the Augment group on pain on weight bearing, AOFOS and FFI will be conducted.

2. *2-year New Enrollment Study*: The applicant has agreed to a study outline on October 23, 2014 (email). This is a prospective, single arm, new enrollment study of patients with ankle and hind foot fusion procedures using Augment Bone Graft. The study will address the following objectives: (1) Can it be assessed and confirmed that bridging bone occurs after Augment has been resorbed? (2) Are the improvements in clinical outcomes associated with the use of Augment in the IDE study confirmed? (3) Does the promotion of existing tumors from a nonmalignant to malignant state in patients treated with Augment exceed the expected rate of promotion in patients not treated with Augment or other growth factors used to promote fusion?

The primary effectiveness endpoints will consist of the following:

- Pain on Weight Bearing (via VAS) (Pre-op, Week 12, Week 24, Year 1, Year 2)
- Confirmation of bridging bone via CT (Year 1, Year 2)
- Patient Function (Pre-op, Week 12, Week 24, Year 1, Year 2) as determined by AOFAS Score and Foot Function Index (FFI)

The primary safety endpoints will consist of the following:

- Presence of all adverse events (i.e., description, frequency, incidence, time to onset of first event, severity, duration, treatments administered, etc.)
- Presence of serious unanticipated adverse device effects (UADE)
- rhPDGF-BB antibody status
- At evaluation, subjects will be interviewed regarding significant medical conditions, including incidence of cancer
- Presence of clinically important events as defined below:
 - Musculoskeletal and connective tissue disorders (severe pain, swelling and/or arthralgia in the treated foot/ankle joint(s));
 - Additional surgery of the original treated joint due to non-union.
 - Neoplasms benign, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)

The study will require 118 Augment subjects at year two. The frequency of follow up will be as follows: Pre-op, Post-op, 12 weeks, 24 weeks, 1 year, and 2 years.

There will be 3 comparators and are outlined as follows:

Comparator 1 Patients serve as own control: Baseline pain and function parameters will be used as comparators in analysis that demonstrates that clinical improvements observed at 2 years post-treatment are clinically meaningful (>20 point difference for Pain on weight bearing (VAS) and AOFAS and 10 point difference for Foot Function Index (FFI), as defined in the SSED.)

Comparator 2 Historical Comparator –Augment IDE Cohort –Will be used to compare success rates for fusion, pain and function endpoints in Augment arm of IDE study to success rates for these endpoints in the 2 year New Enrollment study participants treated with Augment .

Comparator 3 Historical Comparator –Autograft IDE Cohort –Will be used to compare success rates for pain and function in Autograft arm of IDE study to success rates for these endpoints in the 2 year New Enrollment study participants treated with Augment.

Primary hypothesis testing for maintenance of improvements as outlined above in “Comparator 1” on pain on weight bearing, AOFOS and FFI will be conducted.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See labeling.

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

Post Approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *Journal of orthopaedic trauma*. 1989; 3(3):192-195.
2. St John TA, Vaccaro AR, Sah AP, Schaefer M, Berta SC, Albert T, Hilibrand A. Physical and monetary costs associated with autogenous bone graft harvesting. *Am J Orthop (Belle Mead NJ)*. 2003 Jan; 32(1):18-23.
3. Baumhauer, et al. "Survey on the Need for Bone Graft in Foot and Ankle Fusion Surgery" *Foot and Ankle International* 34(12) 1629-1633.
4. Seeger, et al. "A Cohort Study of the Risk of Cancer in Regranex (Becaplermin) Users and Matched Comparators" *Pharmacoepidemiology and Drug Safety*, 2007.
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