SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Bone grafting material containing a therapeutic biologic

Device Trade Name: AUGMENT® Injectable

Device Procode: NOX

Applicant's Name and Address: BioMimetic Therapeutics, LLC, a wholly owned subsidiary of Wright Medical Group, N.V.
389 Nichol Mill Lane
Franklin, Tennessee 37067

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100006/S005

Date of FDA Notice of Approval: June 12, 2018

The original PMA, P100006, for AUGMENT® Bone Graft was approved on September 1, 2015, and 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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted for a new product, AUGMENT® Injectable. This new formulation incorporates a modification of the device component of AUGMENT® Bone Graft utilizing beta tricalcium phosphate (β-TCP) granules of a different particle size combined with a collagen material. This results in a 'flowable' consistency for the product, which can then be placed at the bone fusion site via a syringe.

II. INDICATIONS FOR USE

AUGMENT® Injectable 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® Injectable **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® Injectable labeling.

V. DEVICE DESCRIPTION

AUGMENT® Injectable (AI) is a combination product bone graft material consisting of multiple components – a two-part matrix (device components) and a recombinant human protein (drug component).

Matrix component
The matrix component contains two constituents - β-TCP granules and a collagen matrix.

The β-TCP granules are a purified, multicrystalline, porous form of calcium phosphate with a calcium to phosphate ratio similar to human cancellous bone. The granules have a nominal diameter of 100-300μm.

The collagen matrix consists of Type I bovine collagen derived from the inner layer stratum corium of hides. All animals are sourced from a single, closed US-based herd that receives routine veterinary monitoring and feed in compliance with 21 CFR 589. The animals are slaughtered at a USDA-approved abattoir, receive pre- and post-mortem veterinary inspections and all hides are removed before the head and spinal cord. The collagen complies with ASTM F2212 (*Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPS)).*

The stratum corium is processed until an acid soluble slurry is produced. At this point the collagen is combined with the β-TCP granules to form a composite matrix that is 80% β-TCP and 20% bovine Type I collagen. The matrix is then lyophilized, mechanically shredded and sieved. The shredded β-TCP/collagen mixture is then loaded into 10ml syringes. The matrix component is provided in one of two sizes - 0.5g or 1.0g per syringe.

The filled syringes are loaded into trays that also contain an empty syringe, a female luer coupler, a blunt fill needle and a dispensing cannula. This combination of the device component and the mixing and delivery components is packaged and terminally sterilized after exposure to gamma irradiation.

Recombinant human protein component:
The recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) component of AUGMENT® Injectable is identical to the rhPDGF-BB contained in AUGMENT® Bone Graft (P100006).

rhPDGF-BB, also referred to as becaplermin, is a recombinant form of the endogenous PDGF-BB. It is a highly purified human therapeutic protein of approximately 24.5 kDa that is expressed in the yeast, *Saccharomyces cerevisiae*, by recombinant DNA technology. The active ingredient is a homodimer comprising two antiparallel identical polypeptide chains of 109 amino acids that are linked by two intermolecular disulfide bonds at Cys_{43} and Cys_{52} of each chain. rhPDGF-BB supports angiogenesis by upregulating vascular endothelial growth factor (VEGF) to stimulate new capillary outgrowth, and recruits smooth muscle cells to the ends of sprouting capillaries to help stabilize the capillary bed. The protein attracts and stimulates the proliferation of mesenchymal cells at the wound site including osteoblast progenitor cells and mesenchymal stem cells (MSCs), leading to new bone formation.

The AUGMENT drug product is formulated by diluting the rhPDGF-BB drug substance in 20 mM USP sodium acetate, pH 6.0 to a concentration of 0.3 mg/mL. This solution is aseptically filled into 1.5 or 3cc glass vials. A tray containing the vial is terminally sterilized using ethylene oxide.

When mixed at the time of surgery, the matrix combines with the rhPDGF-BB and creates a flowable putty-like consistency that allows the surgeon to place the product at the fusion site through a 14 gauge needle (included).

The components of AUGMENT® Injectable are provided as two sterile tray configurations:

- The matrix tray contains a 10 ml polypropylene syringe containing either 0.5 or 1.0 grams of a milled β-TCP/bovine Type I collagen (ratio=4:1) matrix. Also included are one 10 ml empty polypropylene syringe, one 14 gauge blunt tip needle for administration of the combination product, one 18 gauge blunt tip needle for drawing

up the rhPDGF-BB and one female-to-female luer-lock connector for mixing of the two components. The tray is sterilized by gamma irradiation.

- The vial tray contains one 3 cc vial, dependent on the kit configuration, aseptically filled with either 1.5 ml or 3.0 ml of rhPDGF-BB solution (0.3mg/ml). The vial tray is sterilized by ethylene oxide.

Figure 1: AUGMENT® Injectable

The two sub-assemblies are included in each kit, along with the package insert.

AUGMENT® Injectable must be used in combination with metallic fixation hardware in order to provide appropriate stabilization of the fusion site.

AUGMENT® Injectable must be stored at refrigerated temperature (2-8°C, 36- 46°F) and cannot be frozen.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives to accomplish arthrodesis of the ankle and/or hindfoot, 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. Arthrodesis procedures of the ankle and/or hindfoot may use autograft, allograft, or synthetic bone void fillers for the grafting procedure.

While autograft is the most widely used graft material, its use is associated with clinical concerns, such as graft harvesting, 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. In addition to these complications, a limited amount of autograft bone is available.

The supply of allograft bone is unlimited; however, the risk of disease transmission exists. While synthetic bone graft materials are also associated with unlimited supply and

do not carry the risk of disease transmission, their effectiveness is variable and dependent on the specific material from which they are manufactured. A non-injectable granular form of AUGMENT® Bone Graft is also available (P100006).

Each of these alternative graft materials has its own advantages and disadvantages and is associated with its own set of benefits and risks which must be weighed before being used in a specific clinical situation. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

AUGMENT® Injectable has been available in markets outside of the United States since 2013. The product has not been withdrawn from the market for any reason relating to the safety and effectiveness of the product. The countries in which AUGMENT® Injectable is available are as follows: Canada, Australia, New Zealand and Mexico.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

As with any surgery, ankle and hindfoot arthrodesis surgery is not without risk. A variety of complications related to surgery or the use of AUGMENT® Injectable Bone Graft may occur. 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 AUGMENT® Injectable identified from the AUGMENT® Injectable 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® Injectable. 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® Injectable, 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.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The safety and effectiveness of the three-component product was evaluated in a series of non-clinical studies. These studies revealed that the presence of residual peroxide from the processing of the collagen component resulted in oxidation of the rhPDGF-BB component. Because this could have an impact on the effective bioactivity of the complete product and its ability to stimulate bone formation, data from the analysis of the recombinant protein combined with only the β-TCP component would not generally be representative of the behavior of the complete product under simulated clinical conditions. Some evaluations of the protein alone or protein combined with β- TCP, *e.g.*, biocompatibility and pharmacology/toxicology studies, would be relevant to assessing the safety of the final product. The same was true for certain studies of the various components of the product in anatomic locations that differed from that of the clinical use, *i.e.*, they were useful for addressing certain safety questions, but not product effectiveness. A separate set of studies was performed to characterize the effect of the oxidation on the bioactivity and stability of the recombinant protein component.

A series of studies were performed to evaluate the biocompatibility, toxicology, stability, and ADME/pharmacokinetics of rhPDGF-BB alone and in combination with β-TCP. The sponsor conducted a panel of biocompatibility/toxicity studies in compliance with ISO 10993 and USP guidelines. These studies evaluated β-TCP/collagen matrix, β-TCP/collagen in combination with rhPDGF-BB, as well as 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. 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 lots of rhPDGF-BB stored under real-time conditions (2°C - 8°C) and accelerated aging room temperature conditions (22°C - 27°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 implanted in a rat model. Sprague-Dawley rats were randomly distributed into three groups (test article (rhPDGF-BB combined with β-TCP), control article (β-TCP combined with vehicle), and sham surgery). Test or control articles were implanted adjacent to the femur underneath the overlying muscle. The test article dose administered was 30 µg 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 enzyme-linked immunosorbent assay (ELISA).

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 demonstrated that implantation of the test article did not result in any toxicity or tumorigenicity and, in addition, demonstrated that the test article was biocompatible.

Pharmacokinetics

Two animal studies were performed to characterize pharmacokinetics of ^{125}I-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 ^{125}I- rhPDGF-BB combined with β-TCP and clearance is again mainly in the urine. Overall, the toxicology and pharmacokinetic data demonstrated that rhPDGF-BB combined with 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 β-TCP alone, AUGMENT® Injectable β-TCP/collagen matrix 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® Injectable Bone Graft's β-TCP/collagen matrix as an appropriate 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 (1x - 0.04 mg/ml rhPDGF-BB 40 μg/kg/day and 10x - 0.4 mg/ml rhPDGF-BB 400 μg/kg/day 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. 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.

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 14^{th} 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, 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 (NOEL) for maternal toxicity and the no observed-adverse-effect-level (NOAEL) 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/collagen matrix	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 WP2uvrA	Pass
Genotoxicity of AUGMENT Injectable Bone Graft	ISO 10993 Part 3	Reverse Mutation Assay using NaCl and CSO Extracts (*Salmonella typhimurium* and *Escherichia coli*); conducted with 10x concentration of rhPDGF-BB (3.0 mg/ml) combined with β -TCP/collagen	Nonmutagenic to Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, and to Escherichia coli strain WP2uvrA	Pass
Intracutaneous Reactivity of β -TCP/collagen matrix	ISO 10993 Part 11	Intracutaneous Injection Test using NaCl and CSO Extracts in New Zealand White Rabbits	Negligible irritant	Pass
Intracutaneous Reactivity of AUGMENT Injectable	ISO 10993 Part 10	Intracutaneous Injection Test using NaCl and CSO Extracts in New Zealand White Rabbits	Negligible irritant	Pass
Sensitization of β-TCP/collagen	ISO 10993 Part 10	Kligman Maximization Test using NaCl and CSO Extracts in Guinea Pigs	Grade I Reaction (0% sensitization)	Pass
Sterilization of AUGMENT Injectable	ISO 10993 Part 10	Kligman Maximization Test using NaCl and CSO Extracts in Guinea Pigs	Grade I Reaction (0% sensitization)	Pass
Cytotoxicity of β-TCP/collagen	ISO 10993 Part 5	L929 MEM Elution Test	Non-cytotoxic Grade 1 Reaction	Pass
Cytotoxicity of AUGMENT Injectable Bone Graft	ISO 10993 Part 5	L929 MEM Elution Test	Non-cytotoxic Grade 1 Reaction (slight)	Pass
Intramuscular Reactivity of β-TCP/collagen matrix	ISO 10993 Part 6	Intramuscular Implantation Test (4 Week Implantation) in New Zealand White Rabbits	Bioreactivity Rating of 0.5	Negative. No signs of toxicity. Toxicity rating of 0.5 (non-toxic)

Test	Standard	Methods	Result	Pass
Intramuscular Reactivity of AUGMENT Injectable Bone Graft	ISO 10993 Part 6	Intramuscular Implantation Test (4 Week Implantation) in New Zealand White Rabbits	Bioreactivity Rating of 0.5	Negative. No signs of toxicity. Toxicity rating of 0.5 (non-toxic)
Acute Toxicity of β-TCP/collagen matrix	ISO 10993 Part 11	Systemic Injection Test in Swiss Albino Mice	No biological response when compared to control	Pass
Acute Toxicity of AUGMENT Injectable Bone Graft	ISO 10993 Part 11	Systemic Injection Test in Swiss Albino Mice	No biological response when compared to control	Pass
Hemolytic β-TCP/collagen matrix	ISO 10993 Part 4	Hemolysis - Rabbit Blood using NaCl Extract	Non-hemolytic	Pass
Hemolytic Assessment of AUGMENT Injectable Bone Graft	ISO 10993 Part 4	Hemolysis - Rabbit Blood using NaCl Extract	Non-hemolytic	Pass
TCP/collagen matrix	ISO 10993 Part 11	Rabbit Pyrogen Test in New Zealand White Rabbits	Non-pyrogenic	Pass
Pyrogenicity of AUGMENT Injectable Bone Graft	ISO 10993 Part 11	Rabbit Pyrogen Test in New Zealand White Rabbits	Non-pyrogenic	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)	Treatment groups: • 0.2 mg rhPDGF-BB/kg body mass • 4.0 mg rhPDGF-BB/kg body mass Model: Normal rats; single IV tail-vein injection Timepoints: 2 and 15 days Dose rationale: The high dose (4.0 mg/kg), was approximately 100 times the maximum human clinical dose (39 µg/kg body mass)	• Intravenous rhPDGF-BB at 0.2 mg/kg and 4.0 mg/kg did not elicit significant toxicity in rats • rhPDGF-BB has a high margin of safety in this assay when administere 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 implanted in a rat model (Chronic Local Toxicity and carcinogenicity)	Treatment groups: • Single parafemoral, intramuscular implantation of 0.175 mg/kg of rhPDGF-BB + β-TCP; Timepoints: 30, 180 and 365 days Dosing rationale: Dose in this study of 150 ug/kg body mass exceeded maximum human clinical dose by 4 times (39 ug/kg body mass)	• 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 rhPDGF-BB + β-TCP test group
Bone Response to Intramuscular Injections of rhPDGF-BB (Acute Local Toxicity; Repeated dose)	Treatment groups: 13.9; 41.2 and 138.8 µg/kg/day every other day for 2 weeks Model: Normal rats; repeat intramuscular injections next to femur and first metatarsal bones in each animal Timepoints: 2 and 8 weeks Dosing rationale: Single dose in study of 160 ug/kg body mass was 4 times the maximum human clinical dose (39 ug/kg body	• Effects at the high dose for both soft tissue and bone were consistent with the mechanism of action of PDGF-BB • 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)	Treatment groups: • 40 ug/kg body mass per injection 400 ug/kg body mass per injection Model: Normal gravid, female rats; repeat IV tail-vein injections daily on gestation days 0-20 Timepoint: 21 days Dosing rationale: The maximum cumulative dose for this study exceeded the maximum human clinical dose (39 ug/kg body mass) by 210 -fold. Outcomes: Assessment of maternal and fetal toxicity	• 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
New Zealand white rabbit 6-month paravertebral muscle implantation study	Treatment groups: • β-TCP/collagen combine with 20 mM sodium acetate vehicle • β-TCP/collagen combined with 0.3 mg/ml rhPDGF-BB (AUGMENT® Injectable) • β-TCP-collagen combined with 1.0 mg/ml rhPDGF-BB (AUGMENT® Injectable) Model: Rabbit paravertebral intramuscular implantation Timepoints: 28 and 180 days	• No signs of acute or chronic toxicity • All animals survived to scheduled endpoint • Fine to 30 x 20 µm "black specks" of material observed histologically after 180 days in rabbit intramuscular sites
Geriatric non-human primate (baboon) spine vertebral body injection safety study	Treatments: • β-TCP/collagen combined with 1.0 mg/ml rhPDGF-BB (AUGMENT® Injectable) • β-TCP/collagen combined with 20 mM sodium acetate, pH 6.0 vehicle • Vehicle alone Model: Geriatric, non-human primate (baboon) percutaneous injection of 3 lumbar vertebra per animal Timepoint: 9 months	• All animals survived to their scheduled endpoint • No signs of acute or chronic toxicity • 9-months post-injection, was moderate to marked new bone formation in the injected areas of the vertebral bodies with or without rhPDGF-BB • No signs of local toxicity or neurotoxicity in neighboring lumbar spinal cord segments

Acute Toxicity of rhPDGF-BB Following Intravenous Administration in Rats (Acute, single dose Systemic Toxicity)	Treatment groups: • 0.2 mg rhPDGF-BB/kg body mass • 4.0 mg rhPDGF-BB/kg body mass Model: Normal rats; single IV tail-vein injection Timepoints: 2 and 15 days Dose rationale: The high dose (4.0 mg/kg), was approximately 100 times the maximum human clinical dose (39 µg/kg body mass)	• Intravenous rhPDGF-BB at 0.2 mg/kg and 4.0 mg/kg • 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 implanted in a rat model (Chronic Local Toxicity and carcinogenicity)	Treatment groups: • Single parafemoral, intramuscular implantation of 0.175 mg/kg of rhPDGF-BB + β-TCP; Timepoints: 30, 180 and 365 days Dosing rationale: Dose in this study of 150 ug/kg body mass exceeded maximum human clinical dose by 4 times (39 ug/kg body mass)	• 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 rhPDGF-BB + β-TCP test group
Bone Response to Intramuscular Injections of rhPDGF-BB (Acute Local Toxicity; Repeated dose)	Treatment groups: • 13.9; 41.2 and 138.8 µg/kg/day every other day for 2 weeks; Model: Normal rats; repeat intramuscular injections next to femur and first metatarsal bones in each animal Timepoints: 2 and 8 weeks Dosing rationale: Single dose in study of 160 ug/kg body mass was 4 times the maximum human clinical dose (39 ug/kg body mass)	• Effects at the high dose for both soft tissue and bone were consistent with the mechanism of action of PDGF-BB • 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)	Treatment groups: • 40 ug/kg body mass per injection 400 ug/kg body mass per injection Model: Normal gravid, female rats; repeat IV tail-vein injections daily on gestation days 0-20 Timepoint: 21 days Dosing rationale: The maximum cumulative dose for this study exceeded the maximum human clinical dose (39 ug/kg body mass) by 210 -fold.	• 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

New Zealand white rabbit 6-month paravertebral muscle implantation study	Treatment groups: • β-TCP/collagen combine with 20 mM sodium acetate vehicle • β-TCP/collagen combined with 0.3 mg/ml rhPDGF-BB (AUGMENT® Injectable) • β-TCP-collagen combined with 1.0 mg/ml rhPDGF-BB (AUGMENT® Injectable) Model: Rabbit paravertebral intramuscular implantation Timepoints: 28 and 180 days	• No signs of acute or chronic toxicity • All animals survived to scheduled endpoint • Fine to 30 x 20 μm "black specks" of material observed histologically after 180 days in rabbit intramuscular sites
Geriatric non-human primate (baboon) spine vertebral body injection safety study	Treatments: • β-TCP/collagen combined with 1.0 mg/ml rhPDGF-BB (AUGMENT® Injectable) • β-TCP/collagen combined with 20 mM sodium acetate, pH 6.0 vehicle • Vehicle alone Model: Geriatric, non-human primate (baboon) percutaneous injection of 3 lumbar vertebra per animal Timepoint: 9 months	• All animals survived to their scheduled endpoint • No signs of acute or chronic toxicity • 9-months post-injection, was moderate to marked new bone formation in the injected areas of the vertebral bodies with or without rhPDGF-BB • No signs of local toxicity or neurotoxicity in neighboring lumbar spinal cord segments
Bacterial Mutagenicity Test - AMES Assay (Genotoxicity)	• Potential of rhPDGF-BB to induce: – histidine (His) reversion in S. typhimurium – tryptophan reversion in E. coli • 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

Fracture Healing of the Tibia in Geriatric-Osteoporotic Rats	• Treatment groups (n=110 rats): – 1.0 mg/mL rhPDGF-BB + collagen/β-TCP (AUGMENT® Injectable) – 0.3 mg/mL rhPDGF-BB + collagen/β-TCP (AUGMENT® Injectable) – sodium acetate + collagen/β- TCP – untreated fracture • Model: Unilateral fracture model (osteotomy model) • Outcomes: MicroCT and Histology- 3 and 5 weeks (n=16) Radiographs and Biomechanical testing – 3 and 5 weeks post fracture (n=64) Histomorphometry – 12 weeks post-fracture (n=18)	• At five weeks, the mechanical strength of AUGMENT® Injectable -treated tibias was not different from the non-fractured contralateral tibia • There were no untoward tissue responses
Diabetic Rat Fracture Model	• Treatment groups (n=110 rats): 1.0 mg/mL rhPDGF-BB + collagen/ β-TCP (AUGMENT® Injectable); 0.3 mg/mL rhPDGF-BB + collagen/ β-TCP (AUGMENT® Injectable) sodium acetate + collagen/ β-TCP untreated fracture • Model: Unilateral fracture model (Einhorn model) • Outcomes: 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)	AUGMENT® Injectable treatment in diabetic rats resulted in: • 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	• Treatment groups (n=30 dogs): Autologous bone graft: 0.3 mg/ml rhPDGF-BB + Autologous bone graft β-TCP: 0.3 mg/ml rhPDGF-BB + β-TCP Collagen/β-TCP: 0.3 mg/ml rhPDGF-BB + Collagen/β-TCP (AUGMENT® Injectable) • Model: Two-level arthrodesis of the carpus • Outcomes: 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)	• 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
Biological Assessment of a Bone Repair Model (Rabbit Tibial Osteotomy)	• Unicortical 5-mm osteotomies • Treated with cylinders of: β-TCP β-TCP + 25 µg rhPDGF-BB β-TCP+ 75 µg rhPDGF-BB • Histomorphometric analysis at 4 and 8 weeks post-implantation	• Residual β-TCP detected at four weeks was significantly reduced by eight weeks • No statistically significant differences among the treatment groups
Tissue distribution and mass balance of radioactivity in Sprague-Dawley rats following an intravenous injection of ^{125}I-rhPDGF-BB	• 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	• rhPDGF-BB is widely distributed and cleared rapidly from the circulation. Tmax: 30 min 18% of Cmax at 4 hours • Radioactivity was excreted in urine and feces primarily as unbound ^{125}I with smaller amounts of bound ^{125}I 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)	• Single IV Injection 0.31 mg/kg • Single IM Implantation of rhPDGF + β-TCP 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	• 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: Tmax: 8 hours $t_{½}$: 30.3 hours 3% of Cmax 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	• Single implantation in calvarial defect – β-TCP: 56 µg/kg – β-TCP /Collagen: 112 µg/kg • Radioactivity at implantation site measured at different intervals up to 7 days	• 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 and β- TCP/Human Bone Allograft Matrices Implanted in a Rat Calvarial Bone Defect	• Single implantation in calvarial defect – 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	• 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

The pharmacokinetic profile was evaluated by implanting of 0.3 mg/ml rhPDGF-BB combined with β-TCP compared to autograft control subjects 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 0.3 mg/ml rhPDGF-BB combined with β-TCP. 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 rhPDGF-BB combined with β-TCP 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 suggested a low systemic exposure to rhPDGF-BB following one- time implantation of rhPDGF-BB combined with β-TCP (up to 2.7 mg of rhPDGF-BB) in the human hindfoot or ankle. 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 STUDIES

The submission consists of data from three sources that the sponsor has identified as BMTI-2006-01, BMTI-2009-01 and BMTI-2010-01. These numbers correspond to three different clinical studies that incorporated different inclusion/exclusion criteria, endpoints, etc. The first dataset (BMTI-2006-01) evaluated the behavior of a different graft substitute compared to the other two datasets. The investigational graft material in this study was AUGMENT® Bone Graft which consists of β-TCP granules and rhPDGF-BB. The investigational graft

material in the other two studies (BMTI-2009-01 and BMTI-2010-01) was AUGMENT® Injectable, consisting of different β-TCP granules, bovine collagen and the identical recombinant protein. Because of differences in the granule components, the presence of the collagen component and the action of the collagen component causing complete oxidation of the recombinant protein component, AUGMENT® Bone Graft and AUGMENT® Injectable are considered to be different products whose clinical outcome cannot be combined into a single dataset. As a result of these significant differences between the investigational product in the first study and the investigational product in the second and third studies, only the control data from the first dataset were considered in the discussion described below. Relevant details of these studies are as follows:

A. Study Designs

1st data source - BMTI-2006-01 (AUGMENT® Bone Graft clinical study performed in the US under IDE G050118)

The data from the control population of this study were used to supplement the control population data from the clinical study that evaluated AUGMENT® Injectable.

This study was designed as a prospective, randomized, controlled, non-inferiority trial. A total of 396 subjects were to be randomized 2:1 investigational:control with the control subjects receiving autograft and the investigational subjects receiving the investigational graft material. All subjects had the joints to be fused stabilized by screw fixation. Subjects requiring foot (hindfoot) or ankle fusions were eligible.

Subjects were enrolled in accordance with the following inclusion/exclusion criteria:

inclusion

- at least 18 years of age and considered to be skeletally mature
- bone defect in the hindfoot or ankle requiring fusion using open surgical technique with supplemental bone graft/substitute, requiring one of the following procedures - ankle joint fusion, subtalar fusion, calcaneocuboid fusion, talonavicular fusion, triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints) OR double fusions (talonavicular and calcaneocuboid joints)
- fusion site able to be rigidly stabilized with no more than 3 screws across the fusion site
  - supplemental pins allowed
  - supplemental screws external to the fusion site(s) allowed
  - plate fixation not allowed.
- signed informed consent document, independent, ambulatory, and can comply with all post-operative evaluations and visits

exclusion

- has undergone previous surgery of the proposed fusion site
- fusion site requires plate fixation, more than three (3) screws across the fusion site to achieve rigid fixation, or more than 3 kits/9cc of graft

- radiographic evidence of bone cysts, segmental defects or growth plate fracture around the fusion site that may negatively impact bony fusion
- current untreated malignant neoplasm(s) at the surgical site or currently undergoing radio- or chemotherapy
- pregnant or intending to become pregnant during the study period
  - a urine pregnancy test will be administered within 21 days of the surgical visit to any female unless post-menopausal, has been sterilized or is practicing a medically accepted method of contraception.
- morbidly obese defined as BMI > 45 kg/m^2
- pre-existing sensory impairment, e.g., diabetics with baseline sensory impairment, which limits ability to perform objective functional measurements and may be at risk for complications. For the purpose of this protocol, diabetics not sensitive to the 5.07 monofilament (Semmes-Weinstein) are to be excluded.
- metabolic disorder known to adversely affect the skeleton other than primary osteoporosis or diabetes, e.g., renal osteodystrophy or hypercalcemia
- use of chronic medications known to affect the skeleton, e.g., glucocorticoid usage > 10mg/day. NSAID use excluded during the first 6 weeks post-op.
- pre-fracture neuromuscular or musculoskeletal deficiency which limits ability to perform objective functional measurements
- physically or mentally compromised, e.g., current treatment for a psychiatric disorder, senile dementia, Alzheimer's disease, etc., to the extent that the Investigator judges the subject to be unable or unlikely to remain compliant
- allergic to yeast-derived products
- received an investigational therapy within 30 days of proposed surgery or during the follow-up phase of the study
- is a prisoner, known or suspected transient or a history of drug/alcohol abuse within the 12 months prior to screening

Subject evaluation consisted of a series of clinical and radiographic assessments. These were collected at up to 21 days pre-op (if not collected within 6 months of surgery), 7 to 21 days post-op, 6 weeks ± 7 days, 9 weeks ± 7 days, 12 weeks ± 7 days, 16 weeks ± 7 days, 24 weeks ± 14 days, 36 weeks ± 14 days and 52 weeks ± 14 days.

The following clinical and radiographic evaluations were performed:

- pain using VAS
  - general pain
  - pain at fusion site on weight-bearing (if applicable)
  - pain at the autograft harvest site (control subjects only)
- motion at the fusion site (+ or -)
- warmth at the fusion site (none, mild, moderate, severe)
- swelling (none, mild, moderate, severe)
- tenderness at the surgical site (+ or -)
- neuro status (intact or impaired)
- infection (+ or -)

- weight-bearing status (nonweight-bearing, touchdown, partial weight-bearing, full weight-bearing)
- clinical/radiographic assessment of healing by the investigator (union, evidence of progressive healing (≤ 6 months), delayed union (≤ 6 months), nonunion (@ 36 weeks), uninterpretable at 24 and 36 weeks
- hardware complications (none, fractured hardware, developing lucency surrounding screws)

Quality of life assessments included SF-12, American Orthopaedic Foot and Ankle Society (AOFAS) Outcomes Scores (Ankle-Hindfoot Scale) and the Foot Function Index (FFI) at 6, 12, 24, 36, and 52 weeks, post-op.

In addition to the investigator's general radiographic evaluation, a more detailed radiographic assessment was performed by an independent reviewer. This assessment was based on anterior-posterior (AP), lateral, and oblique views of the ankle and AP, lateral, and oblique views of the foot, as well as axial heel views only for subjects receiving subtalar or triple arthrodesis. Plain films were taken at each visit to assess standard clinical healing parameters, while computed tomography (CT) scans were only collected at 9, 16, 24, and 36 weeks post-op to determine the degree of fusion. A baseline CT scan was not collected. Radiographs were also obtained before and after re-reduction maneuvers, if necessary.

Serum was collected at baseline (prior to grafting procedure), the 7-21 day post-op visit and at 6, 12 and 24 weeks post-op for the presence of neutralizing and non-neutralizing antibody formation to rhPDGF-BB. Subjects testing positive for anti-rhPDGF-BB antibodies were tested for neutralizing activity.

The primary effectiveness endpoint was defined as the percent of subjects achieving fusion (≥ 50% osseous bridging on CT scans at 24 weeks post-op). A composite endpoint consisting of clinical and radiographic endpoints was also created. Individual subject success was defined as:

- surgical treatment completed per protocol
- subject determined to have union or progressive evidence of healing (as per the Investigator assessment)
- evidence of fusion >25% on CT Scan
- less than 20mm on VAS pain assessment at bone graft harvest site beyond 30 days post-study surgery
- no serious AEs possibly related to treatment
- no second surgical intervention

Fusion success was based on the independent radiographic review of bone formation (fusion) across the treated joints. Greater than or equal to 50% fusion across the joint space was defined as fusion success. For the subtalar joint, the review was isolated to the posterior facet. For procedures involving multiple joints, e.g., triple or double arthrodesis, fusion success was determined by assessment of bone bridging as a percentage of the total fusion construct. Subjects who were categorized as a fusion success at 24 weeks had a confirmatory CT scans taken at 36 weeks. If 36-week CT scans were not available, the

fusion endpoint was considered to have been achieved at 24 weeks if there was no evidence to the contrary that fusion was not sustained after 24 weeks.

Safety was assessed by the evaluating the frequency and severity of reported AEs.

2nd data source - BMTI-2009-01 (AUGMENT® Injectable clinical study performed in Canada)

This study was originally intended to incorporate an identical investigational plan (IP) to that of a US study conducted under an approved Investigational Device Exemption (IDE) application; however, it was approved by Health Canada prior to approval of the US IDE and did not incorporate modifications to the inclusion/exclusion criteria, study endpoints, or definitions of success that had been approved for the IP of the US IDE study. This Canadian study evaluated subjects undergoing foot (hindfoot) and ankle fusions.

This study was designed as a prospective, randomized, controlled, non-inferiority trial. The intent was to enroll a total of 180 subjects randomized 5:1 investigational:control resulting in 150 prospective, randomized investigational subjects and 30 prospective, randomized control subjects. These control subjects were to be combined with 120 control subjects from the original AUGMENT® Bone Graft clinical study described above (BMTI-2006-01). Enrollment was terminated after only 75 total prospective subjects had been enrolled (63 investigational and 12 control).

The control population received autograft bone and the investigational subjects received the investigational AUGMENT® Injectable graft material. All subjects had the joints to be fused stabilized by screw fixation. Subjects requiring foot (hindfoot) or ankle fusions were eligible.

Subjects were enrolled in accordance with the following inclusion/exclusion criteria:

inclusion

- at least 18 years of age and considered to be skeletally mature
- bone defect in the hindfoot or ankle requiring fusion with supplemental bone graft/substitute, requiring one of the following procedures - ankle joint fusion, subtalar fusion, calcaneocuboid fusion, talonavicular fusion, triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints) OR double fusions (talonavicular and calcaneocuboid joints)
- fusion site able to be rigidly stabilized with no more than 3 screws across the fusion site
  - supplemental pins or staples allowed
  - supplemental screws external to the fusion site(s) allowed
- signed informed consent document, independent, ambulatory, and can comply with all post-operative evaluations and visits

exclusion

- has undergone previous fusion surgery of the proposed fusion site or revision of failed total ankle arthroplasty
- fusion site requires plate fixation, more than three (3) screws across the fusion site to achieve rigid fixation, or more than 3 kits/9cc of graft
- structural bone graft, allograft, bone graft substitute, platelet-rich plasma (PRP) or bone marrow aspirate required
- requires a pantalar fusion, i.e., fusion of the ankle plus all hindfoot joints (talonavicular, subtalar, and calcaneocuboid) or a tibiotalocalcaneal (ankle and subtalar) fusion
- radiographic evidence of bone cysts, segmental defects or growth plate fracture around the fusion site that may negatively impact bony fusion
- current untreated malignant neoplasm(s) at the surgical site or currently undergoing radio- or chemotherapy or has been diagnosed with hypercalcemia
- pre-existing sensory impairment, e.g., diabetics with baseline sensory impairment, which limits ability to perform objective functional measurements and may be at risk for complications
  - diabetics not sensitive to the 5.07 monofilament (Semmes-Weinstein) are to be excluded
- metabolic disorder known to adversely affect the skeleton other than primary osteoporosis or diabetes, e.g., renal osteodystrophy or hypercalcemia
- use of chronic medications known to affect the skeleton, e.g., glucocorticoid usage > 10mg/day
- physically or mentally compromised, e.g., current treatment for a psychiatric disorder, senile dementia, Alzheimer's disease, etc., to the extent that the Investigator judges the subject to be unable or unlikely to remain compliant
- allergic to yeast-derived products or bovine collagen or other bovine-sourced products
- received an investigational therapy within 30 days of proposed surgery or during the follow-up phase of the study
- is a prisoner, known or suspected transient or a history of drug/alcohol abuse within the 12 months prior to screening
- pregnant or intending to become pregnant during the study period
  - A urine pregnancy test will be administered within 21 days of the surgical visit to any female unless post-menopausal, has been sterilized or is practicing a medically accepted method of contraception.
- morbidly obese defined as BMI > 45 kg/m^2
- currently has an acute infection at the surgical site
- history of anaphylaxis or of multiple non-environmental allergies that have precipitated an anaphylactic reaction

Subject evaluations consisted of a series of clinical and radiographic assessments. Data were collected according to the following schedule: within 21 days of scheduled surgery, intra-op,

7-21 days post-op, 6 weeks ± 7 days, 9 weeks ± 7 days, 12 weeks ± 7 days, 16 weeks ± 7 days, 24 weeks ± 14 days, 36 weeks ± 14 days and 52 weeks ± 14 days.

The following clinical and radiographic evaluations were performed:

- pain using VAS
  - general pain
  - pain at fusion site on weight-bearing (if applicable)
  - pain at the autograft harvest site (control subjects only)
- motion at the fusion site (+ or –)
- warmth at the fusion site (none, mild, moderate, severe)
- swelling (none, mild, moderate, severe)
- tenderness at the surgical site (+ or –)
- neurological status (intact or impaired)
- infection (+ or –)
- weight-bearing status (nonweight-bearing, touchdown, partial weight-bearing, full weight-bearing)
- clinical/radiographic assessment of healing by the investigator (union, evidence of progressive healing (≤ 6 months), delayed union (≤ 6 months), nonunion (@ 36 weeks), uninterpretable at 24 and 36 weeks)
- hardware complications (none, fractured hardware, developing lucency surrounding screws)

Quality of life assessments included SF-12, AOFAS Outcomes Scores (Ankle-Hindfoot Scale) and the Foot Function Index (FFI) at 6, 12, 24, 36, and 52 weeks, post-op.

Serum was collected at baseline (prior to the grafting procedure), the 7-21 day post-op visit and at 6, 12 and 24 weeks post-op for the presence of neutralizing and non-neutralizing antibody formation to rhPDGF-BB. Subjects testing positive for anti-rhPDGF-BB antibodies were tested for neutralizing activity.

The sponsor defined a series of primary and secondary radiographic and clinical effectiveness endpoints:

primary radiographic effectiveness endpoint

- 24-week fusion rate (%) by CT scans

secondary radiographic effectiveness endpoints

- mean time to clinical healing, determined by investigator's clinical/radiographic assessment
- supplemental radiographic parameters for healing as determined by the independent radiologist
- overall assessment of osseous bridging based on CT at 9, 16, 24 and 36 weeks post-op
- presence of heterotopic bone formation
- assessment of β-TCP resorption

- hardware (screw) complications

secondary clinical endpoints

- 36-week fusion rate (%) based on CT scans
- 36-week composite success
- time to fusion based on CT scan
- 36-week fusion rate based on clinical assessments
- clinical success defined as improvement in pain on weight-bearing and lack of revision surgery
- time to radiographic healing as determined by the independent radiologist
- pain on weight-bearing
- pain at graft harvest site
  - this was to be assessed prior to all other functional assessments and rehabilitation procedures at each visit
- operative time
- quality-of-life assessments based on the SF-12 (Physical Composite Score [PCS] component only), AOFAS outcomes score and the Foot Pain and Disability Index

The primary safety endpoint was defined as pain scores at any secondary surgical site. Secondary safety endpoints included total operating room time and surgical wound infection rate. In addition, all subjects were monitored over the initial 12-month post-op period for incidence of loss of reduction, infection, non-union, need for revision fusion surgery, and complications associated with hindfoot and ankle fusion procedures, as well as any other AEs that were reported.

The primary effectiveness endpoint was defined as the percent of subjects achieving fusion (≥ 50% osseous bridging on CT scans at 24 weeks post-op). Secondary effectiveness endpoints included:

- fusion rate (%) at 36 weeks based on CT scans
- radiographic assessments
- time to healing
- pain on weight-bearing
- graft harvest site pain
- quality of life evaluations
- a composite success endpoint

The composite endpoint consisted of clinical and radiographic endpoints. Success for the composite endpoint was defined as:

- surgical treatment completed per protocol
- subject determined to have union or progressive evidence of healing (as per the Investigator assessment)
- evidence of fusion >25% on CT scan
- less than 20 mm on VAS pain assessment at bone graft harvest site ≥ 6 weeks post-op
- no serious AEs possibly related to treatment

- no second surgical intervention

Fusion success was based on the independent radiographic review of bone formation (fusion) across the treated joints. Greater than or equal to 50% fusion across the joint space was defined as fusion success. Multiple fusions were to be assessed based on a defined index joint. The index joint for multiple fusions was defined as the talonavicular joint if a talonavicular joint fusion was performed. The subtalar joint was defined as the index joint if a talonavicular fusion was not performed. For the subtalar joint, the review was to be isolated to the posterior facet because this is traditionally considered the most significant area of interest for this procedure. For multi-joint fusions, e.g., triple or double arthrodesis, fusion of the index joint was to be used for the purpose of determining the primary endpoint. The independent radiologist was also instructed to assess the fusion status of each individual joint. All subjects were to have a 36-week CT scan. If the 36-week CT scans were unavailable, the fusion endpoint was considered to have been achieved at 24 weeks unless there was evidence to the contrary.

Safety was assessed by the evaluating the frequency and severity of reported AEs.

3rd data source - BMTI-2010-01 (AUGMENT® Injectable clinical study performed in the US under IDE G090133)

This study was designed as a prospective, randomized, concurrently-controlled, multi-center trial to assess the use of AUGMENT® Injectable in fusions stabilized with screw fixation compared to the same treatment using autograft bone in treating foot joint degeneration in adult subjects. The objective of the study was to demonstrate the non-inferiority of the synthetic AUGMENT® Injectable graft compared to autograft bone. Clinical (pain using a Visual Analog Scale (VAS) and function using the Foot Function Index (FFI)) and radiographic (x-rays with secondary assessments using CT scans to demonstrate presence of fusion) endpoints were assessed out to 24 months post-op. Due to the nature of the surgical procedure, i.e., the need to harvest an autograft from a site away from the fusion in the control subjects, it was not possible to blind the investigators, surgical assistants or subject with respect to treatment assignment. Subject masking existed only until the immediate post-op period. The radiographic reviewers, on the other hand, remained blinded with respect to treatment for the entirety of the study.

This study was originally approved for a total of 201 subjects randomized 2:1 investigational:control (134 investigational and 67 control) at a total of 25 sites. The investigational plan was subsequently modified by increasing enrollment to a total of 300 subjects randomized 2:1 (200 investigational and 100 control) at a total of 30 sites. The study was not designed to incorporate any control subject data from any other study. Because enrollment in this study was never completed, a total of 104 subjects were enrolled. Of these subjects, 96 were enrolled under the US IDE (G090133, 64 investigational:32 control subjects) and the remainder in Canada. There were 18 US sites and 4 Canadian sites.

The control population received autograft bone and the investigational subjects received the investigational AUGMENT® Injectable graft material. All subjects had the joints to be fused stabilized by screw fixation. Unlike the subjects eligible for the studies defined in BMTI-

2006-01 and BMTI-2009-01, the subjects eligible for enrollment in this study were determined to only need a foot fusion. Because of differences in subject selection and treatment, subjects requiring a foot fusion are not the same as those requiring an ankle fusion. In addition, subjects undergoing a primary procedure are not equivalent to those undergoing a revision procedure.

Subjects were enrolled in accordance with the following inclusion/exclusion criteria:

inclusion

- at least 21 years old and considered skeletally mature
- minimum baseline VAS full weight-bearing without assistive devices pain score of 40mm on a 100mm scale
- diagnosed with degenerative joint disease (DJD) affecting the hindfoot due to a congenital or acquired deformity, osteoarthritis, rheumatoid arthritis, post- traumatic arthritis or ankylosing spondylitis of the subtalar, calcaneocuboid, and/or talonavicular joints
- requires one of the following hindfoot fusion procedures with supplemental bone graft/substitute: subtalar fusion (talocalcaneal), calcaneocuboid fusion, talonavicular fusion, triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints) OR double fusions (any combination of any two of the following: subtalar, talonavicular and calcaneocuboid joints)
- fusion site able to be rigidly stabilized with no more than 3 screws across the fusion site
  - supplemental pins or staples allowed
  - supplemental screws external to the fusion site(s) allowed
- signed informed consent document, independent, ambulatory, and can comply with all post-operative evaluations and visits

exclusion

- undergone previous fusion surgery at the proposed location, i.e., revision of a failed fusion
- previous hindfoot surgery
  - previous procedures that do not have significant compromise of the peri-articular soft tissues are allowed. Examples include:
    - diagnostic arthrotomy and debridement
    - arthrotomy for removal of osteophytes
    - open reduction internal fixation for tibial fractures or foot fracture
    - ligament/ tendon repair or reconstruction
    - hardware removal
- more than one previous procedure at the involved joints
- retained hardware spanning the joint(s) intended for fusion
- procedure anticipated to require plate fixation (including claw plates), intramedullary (IM) nails or more than 3 screws to achieve rigid fixation based on pre-op planning
- procedure expected to require more than 9cc of graft material based on pre-op planning

- procedure expected to require structural bone graft, allograft, bone graft substitute, platelet rich plasma (PRP) or bone marrow aspirate
- procedure expected to require a pantalar fusion, i.e., fusion of ankle plus all hindfoot joints (talonavicular, subtalar, and calcaneocuboid) or an ankle fusion in combination with any hindfoot fusion
- expectation of performing a subsequent surgery of the concomitant hindfoot within 12 months of the investigational procedure
- presence of bilateral degenerative joint disease that may require fusion or surgical repair of the contralateral hindfoot with 12 months of enrollment
- radiographic evidence of bone cysts, segmental defects or growth plate fracture near the fusion site that could negatively impact the proposed fusion procedure
- tested positive or been treated for a malignancy in the past or is suspected of having a malignancy or currently undergoing radio- or chemotherapy treatment for a malignancy anywhere in the body, whether adjacent to or distant from the proposed surgical site
- pre-existing sensory impairment, e.g., diabetics with baseline sensory impairment, which limits ability to perform objective functional measurements and may be at risk for complications
  - diabetics not sensitive to the 5.07 monofilament (Semmes-Weinstein) are to be excluded
- metabolic disorder known to adversely affect the skeleton other than primary osteoporosis or diabetes, e.g., renal osteodystrophy or hypercalcemia
- use of chronic medications known to affect the skeleton, e.g., glucocorticoid usage > 10mg/day
- pre-fracture neuromuscular or musculoskeletal deficiency which limits the ability to perform objective functional measurements
- has vascular insufficiency (large or small vessel disease) or kidney insufficiency
- diagnosis or history of bi-polar disorder, schizophrenia, suicidal ideation, post-traumatic stress disorder, senile dementia or Alzheimer's disease as defined via standard, recognized methods such as the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, to the extent that the investigator judges the subject to be unable or unlikely to remain compliant
- allergic to yeast-derived products or bovine collagen or other bovine-sourced products
- received an investigational therapy within 30 days of proposed surgery or during the follow-up phase of the study
- is a prisoner, known or suspected transient or a history of drug/alcohol abuse within the 12 months prior to screening
- pregnant or intending to become pregnant within 12 months of the study procedure
  - A urine or blood pregnancy test will be administered within 2 days of the surgical visit to any female unless post-menopausal, has been sterilized or is practicing a medically accepted method of contraception.
- morbidly obese defined as BMI > 45 kg/m^2
- currently has an acute infection at the surgical site
- history of anaphylaxis or of multiple non-environmental allergies

- refuses to discontinue tobacco use prior to surgery
- medical history that contraindicates use of surgical tourniquet

Subject evaluations consisted of a series of clinical and radiographic assessments. Data were collected according to the following schedule: within 21 days of scheduled surgery, intra-op, 7-21 days post-op, 6 weeks ± 7 days, 9 weeks ± 7 days, 12 weeks ± 7 days, 16 weeks ± 7 days, 24 weeks ± 14 days, 36 weeks ± 14 days, 52 weeks ± 14 days and 104 weeks ± 14 days. Annual follow-up visits occurred until the last subject enrolled had returned for their 104 week visit.

The following clinical and radiographic evaluations were performed:

- pain using VAS
  - pain at fusion site, non weight-bearing
  - pain at fusion site on weight-bearing without assistive devices, starting at 6 weeks post-op
  - pain at the autograft harvest site (control subjects only)
- motion at the fusion site (+ or –)
- warmth at the fusion site (none, mild, moderate, severe)
- abnormal swelling (none, mild, moderate, severe)
- tenderness at the surgical site (+ or –)
- neurological status (intact or impaired)
- infection (+ or –)
- weight-bearing status (non weight-bearing, touchdown, partial weight-bearing, full weight-bearing)
- clinical/radiographic assessment of healing by the investigator (union, evidence of progressive healing (@ 24 weeks), delayed union (@ 24 weeks), nonunion (≥ 36 weeks), uninterpretable (day 7-21), secondary therapeutic intervention required)

Quality of life assessments included SF-12, AOFAS Outcomes Scores (Ankle-Hindfoot Scale) and the Foot Function Index (FFI) at 6, 12, 24, 36 and 52 weeks, post-op.

Serum was collected at baseline (prior to grafting procedure), the 7-21 day post-op visit and at 6, 12, 24, 36, 52 and 104 weeks post-op then annually until the last subject enrolled had returned for their 104 week evaluation. Serum was assessed for the presence of neutralizing and non-neutralizing antibody formation to rhPDGF-BB or to bovine Type I collagen. Subjects testing positive for anti-rhPDGF-BB or anti-bovine Type 1 collagen antibodies were tested for neutralizing activity. Subjects who tested positive for antibodies to rhPDGF-BB or bovine Type 1 collagen at their last scheduled blood draw were required to provide additional samples at 3 month intervals until titers returned to baseline.

The sponsor defined a series of primary and secondary effectiveness and safety endpoints that consisted of clinical and radiographic parameters.

primary effectiveness endpoint

The sponsor defined a composite effectiveness endpoint as follows:

- radiographic evidence of fusion at 24 weeks

- absence of significant pain defined as:
  - absence of weight-bearing pain, i.e., pain less than 20mm on a 100mm VAS scale AND graft site harvest pain, i.e., pain less than 20mm on a 100mm VAS scale
- improvement in function as demonstrated by at least a 10 point reduction in the Foot Pain and Disability Index (also referred to as the Foot Function Index or FFI); Budiman-Mak, 1991
- absence of any secondary interventions

secondary effectiveness endpoints

The sponsor defined a series of secondary effectiveness endpoints:

- CT fusion based on full complement of joints at 24 weeks post-op
- Subject Performance Composite plus CT fusion based on full complement of joints at 24 weeks post-op
- Subject Performance Composite exclusive of radiographic success
- CT fusion based on individual joints
- radiographic union (3-aspects) based on full complement of joints
- radiographic union (3-aspects) based on individual joints
- radiographic union (2-aspects) based on full complement of joints
- radiographic union (2-aspects) based on individual joints
- clinical healing at the subject level
- clinical healing at the joint level
- clinical success
- composite success
- functional success as determined by:
  - weight-bearing pain
    no pain or mild pain defined as ≤ 20mm on VAS scale in the absence of ambulatory assist devices.
  - maintenance or improvement in function; and
  - no need for a secondary surgical intervention
- therapeutic failure
- time to the binary endpoints listed above
- SF-12
- FFI
- AOFAS
- VAS pain scores (fusion site, graft harvest site, weight bearing pain)
  weight-bearing pain success defined as ≥ 20mm reduction on VAS pain assessment of fusion site (performed prior to all other functional assessments and rehabilitation procedures at each visit)
- assessment of β-TCP resorption
- hardware complications (i.e., screws)
- presence of heterotopic bone formation

primary safety endpoints

- surgical site complications associated with injury or standard surgical treatment, including non-union
- product-related AEs categorized as anticipated and unanticipated

secondary safety endpoints

- operative time
- wound infection rate
- pain scores at any secondary surgical site
- overall AEs
- pain at graft harvest site (assessed prior to collection of other functional assessments and rehab)

Subjects were also monitored over the course of the study for the loss of reduction, infection, non-union, need for revision fusion surgery, and associated complications with hindfoot fusion procedures, in addition to the incidence of other AEs. Like the effectiveness assessments, safety assessments continued annually after the 104-week visit until the last enrolled subject had their 104-week evaluation.

Safety was assessed by the evaluating the frequency, severity and relatedness of reported AEs.

B. Accountability of Combined PMA Cohort

Because each of the three datasets described above incorporated different inclusion/ exclusion criteria and endpoints, e.g., foot fusion alone versus foot and ankle fusion and minimum VAS pain score for eligibility, a propensity score matching analysis was performed in order to identify a single set of investigational and control subjects derived from the three datasets that were comparable and could be evaluated for the purpose of assessing the safety and effectiveness of AUGMENT® Injectable. Propensity score analysis involves matching and statistical adjustment for measured confounders. The sources of data and the number of eligible subjects from each dataset are outlined in Figure 2 below:

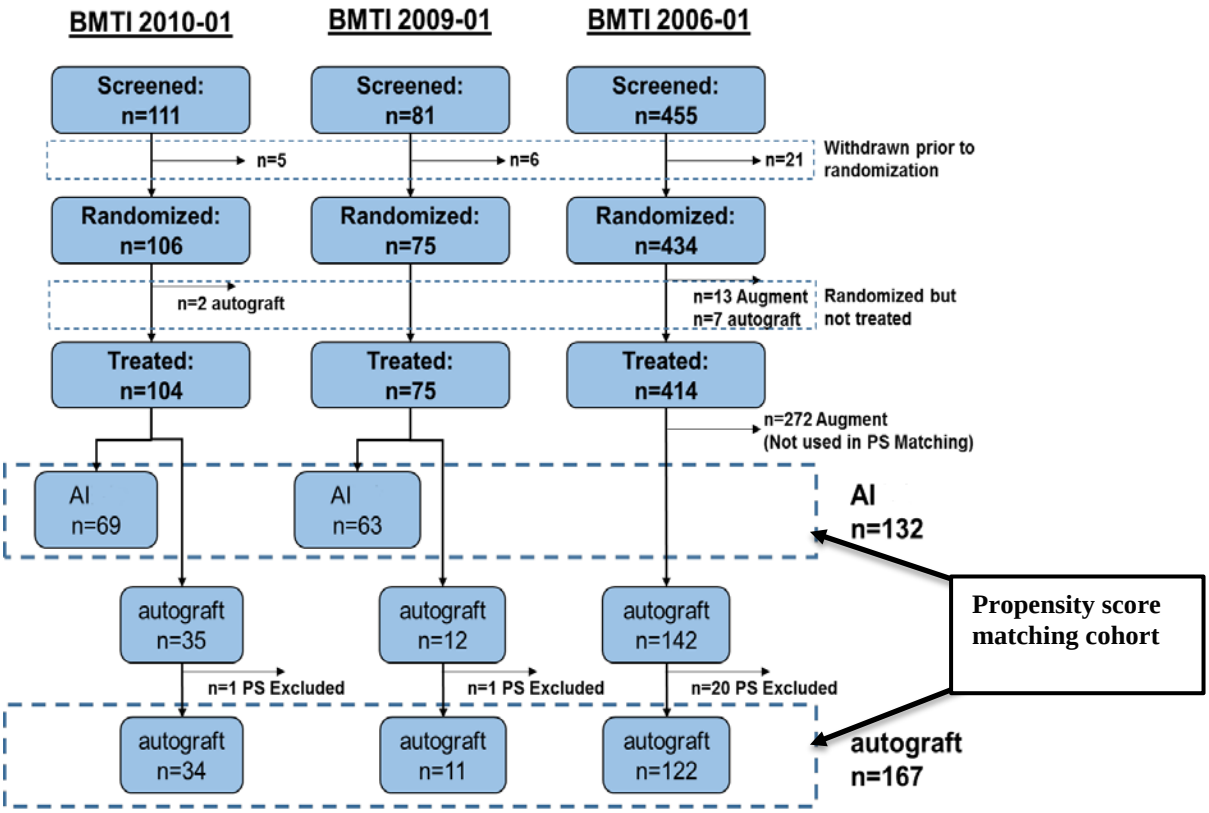

Figure 2: Subject Accounting Tree for Clinical Studies

Throughout the 52 week follow-up period for all three studies there was a high rate of subject follow up, with approximately 90% of subjects having outcome data available at 52 weeks. For the AUGMENT® Injectable group, 91.7% of subjects had endpoint data available for all assessments at 52 weeks. For the autograft group, the 52 week follow up rate for all assessments was 91.0%.

Study withdrawals prior to randomization

Table 3 presents the number of subjects who withdrew prior to randomization for each study.

Table 3: Study Withdrawals Pre-randomization

Pre-randomization withdrawal	Subjects
BMTI 2009-01	6
BMTI 2010-01	5
BMTI 2006-01	21
Total subjects withdrawn prior to randomization	**32**

Randomized but not treated

Table 4 presents the number of subjects in each study who withdrew following randomization but prior to treatment.

Table 4: Study withdrawals post-randomization/pre-treatment

Post-Randomization Withdrawal	AUGMENT® Injectable	Autograft
BMTI 2009-01	0	0
BMTI 2010-01	0	2
BMTI 2006-01	-	7
Total subjects withdrawn after randomization/prior to treatment	**0**	**9**

The primary study withdrawals post randomization and prior to treatment occurred in BMTI 2006-01. In the AUGMENT® Injectable group, there were no subjects who withdrew after randomization but prior to treatment.

C. Study Population Demographics and Baseline Parameters in Combined Dataset

The baseline demographic factors for the treated subjects in the combined dataset are presented in Table 5. Overall, the baseline subject demographics in the investigational and control groups were similar, a consequence of the propensity score matching algorithm.

Table 5: Demographics and Clinical Factors

	AUGMENT Injectable (AI) N=132	Autograft N=167	AI vs Autograft P-value*
Sex			0.816
Male	70 (53.03%)	86 (51.5%)	
Female	62 (46.97%)	81 (48.5%)	
Affected Foot/Ankle			0.131
Ankle fusion	31 (23.48%)	46 (27.54%)	
Subtalar fusion	52 (39.39%)	59 (35.33%)	
Calcaneocuboid fusion	3 (2.27%)	0 (0.0%)	
Talonavicular fusion	6 (4.55%)	9 (5.39%)	
Double fusion[1]	21 (15.91%)	17 (10.18%)	
Triple arthordesis[2]	19 (14.39%)	36 (21.56%)	
Ankle-Hindfoot fusion	0 (0.0%)	0 (0.0%)	
Ever smoked			0.562
No	61 (46.21%)	83 (49.7%)	
Yes	71 (53.79%)	84 (50.3%)	
Obese (BMI >= 30)			0.061
No	68 (51.52%)	68 (40.72%)	
Yes	63 (47.73%)	99 (59.28%)	
Older (>= 65 yo)			0.133
No	97 (73.48%)	109 (65.27%)	

Yes	35 (26.52%)	58 (34.73%)	
Baseline Weight Bearing Pain > 40mm			0.569
No	12 (9.09%)	19 (11.38%)	
Yes	120 (90.91%)	145 (86.83%)	
Graft Material Used[3]			0.000
Not recorded	0 (0.0%)	1 (0.6%)	
1-3cc	78 (59.09%)	49 (29.34%)	
4-6cc	40 (30.30%)	77 (46.11%)	
7-9cc	14 (10.61%)	40 (23.95%)	

*Fisher's exact test p-value for categorical variables; two-sample t-test p-value for continuous variables

[1] Combination of any two of the joints: subtalar, talonavicular and calcaneocuboid joint

[2] Subtalar, talonavicular, and calcaneocuboid joints

[3] Estimated amount of graft material used per subject was based on the volume of a single AUGMENT® kit; thus, estimates were made using an ordered categorical scale of "1 kit", "2 kits", or "3 kits" for AUGMENT® Injectable, corresponding to approximate amounts of autograft of "1-3cc", "4-6cc", or "7-9cc", respectively. The amount AUGMENT® Injectable was represented by the number of kits used, regardless of whether or not an entire kit was implanted. The amount of autograft used was estimated by the surgical staff during surgery and not formally measured.

D. Safety and Effectiveness Results

Clinical Endpoints

As outlined above, a variety of clinical, functional and radiographic parameters were assessed at each follow-up evaluation. After review of the radiographic data, however, the assessment of radiographic fusion for AUGMENT® Injectable subjects at 24 weeks was found to be inconclusive. It was not possible to differentiate the AUGMENT® Injectable graft material from the surrounding bone due to their similar radiodensities. Because of this, it was necessary to limit the determination of individual subject success to evaluations of only the clinical (pain) and functional endpoints (VAS on weight bearing, FFI, and AOFAS score).

The following clinical, functional, and safety endpoints were used to evaluate the effectiveness and safety of AUGMENT® Injectable:

Clinical/Functional endpoints:

- Pain on weight bearing (via VAS)
- Fusion site pain (via VAS)
- Foot Function Index (FFI)
- American Orthopaedic Foot and Ankle Society (AOFAS) Score
- SF-12 (PCS)
- Graft harvest site pain (via VAS for control subjects only)

Safety endpoints:

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

1. Safety Results

Safety was assessed by comparing the type of rate of adverse events (AEs) between the investigational AUGMENT® Injectable subjects and the control autograft subjects. Reported AEs were classified using the Medical Dictionary for Regulatory Affairs (MedDRA) and were collected according to seven subgroups pre-defined by the study protocols:

- Pre-treatment signs and symptoms defined as AEs collected prior to the day of surgery
- Treatment Emergent Adverse Events (TEAEs) defined as AEs reported on or after the day of surgery
- Complications defined as complications associated with surgical procedures, a subset of the TEAEs. Complications associated with the surgical procedure may include pain, edema, nausea, vomiting, hypoaesthesia, skin and subcutaneous tissue ulcers, hardware irritation/complication, constipation, cast irritation, swelling, stiffness, warmth, pain and discomfort following surgery (typically worse with more severe pre-operative deformities), bruising, failure of fixation, infection, wound dehiscence, and pulmonary embolism. These reported events were collected as AEs
- Infections, a subset of the TEAEs, defined as any infection in the body regardless of location
- Related TEAEs, a subset of the TEAEs considered directly related to the bone graft material
- Serious TEAEs, a subset of the TEAEs that meet the definition of "serious". Events were classified as serious if they met any of the following criteria (in accordance with 21 CFR 812.3(s)) and the recommendations of International Conference on Harmonisation [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):
  - 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
  - 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
  - Any serious problem associated with the device that related to the rights, safety or welfare of study patients
- Serious Complications, defined as Complications that meet the definition of a serious adverse event

There was a key difference in AE reporting across the three studies comprising the final dataset that influences how these data are interpreted. For BMTI-2006-01 and BMTI-

2009-01, changes in physical examination findings (e.g. swelling, warmth, tenderness, fusion site stability and weight bearing pain) were not recorded as AEs unless determined to be clinically significant by the clinical investigator. The approved protocols did not require reporting changes in these findings as AEs, as these events were collected during the post-operative clinical exams at protocol-specified visits. This is in contrast to BMTI-2010-01, where all changes in physical exam findings were reported as AEs regardless of their clinical significance. As a result, there were certain types of AEs reported in BMTI 2010-01 that would not have been treated as AEs in BMTI-2006-01 and BMTI-2009-01.

A more significant concern with AE reporting was related to differences in reporting (due to less stringent criteria for AE reporting being utilized for certain types of physical examination findings in the earlier studies) and a determination of the severity of AEs, as well as reporting independence and the degree of bias present in the assessments. These concerns were based on the following observations associated with AE collection and assessment:

- In BMTI-2006-01 and BMTI-2009-01, events which could be associated with surgery, e.g., redness or itching at the incision site, but could also be associated with an immune response to the recombinant protein component of the product, were recorded as physical exam observations, but not as AEs. This is in contrast to BMTI-2010-01, where all observations and events were reported and evaluated as AEs.
- The assessment of whether or not an event constituted an AE was made by the investigators, for example, radiologic incidences of fracture to hardware were not considered AEs unless the investigator deemed them clinically significant. Certain events, such as swelling or redness, were not considered AEs in two of the studies.
- The categorization and mapping of AEs was done by the investigators.
- Variable AE definitions were utilized by the study sites.

In response to these concerns raised by FDA as part of their review, the sponsor created a Clinical Event Committee (CEC) to "…provide a formal mechanism for adjudication of adverse events and unanticipated product effects…" Based on a review of the CEC charter, a number of concerns that would impact the ability of the CEC to perform as intended were identified:

- The composition of the CEC included only one clinical expert and included representatives of the sponsor.
- The CEC adjudicated a subset of AEs based on the assessments of the investigators.
- The definition utilized for categorizing the events was not included in the charter, and as provided to FDA, was not clearly defined and appeared to not be validated.
- The source data provided for adjudication appeared to be incomplete and inadequate for the CEC to make an independent assessment.

These concerns with the initial AE allocation and categorization and the concerns with the CEC and their potential effect on the degree of uncertainty of the safety profile of the product should be kept in mind when evaluating the safety data presented below.

Adverse effects that occurred in the PMA clinical studies:

A summary of the AEs by MedDRA class through 52 weeks follow-up is presented in Table 6. Due to the reporting differences described above between BMTI 2010-01, and BMTI 2006-01 and BMTI 2009-01, with respect to total AEs, surgical complications, and infections, results from BMTI 2010-01 for these particular categories of AEs are also presented separately.

Table 6: Summary of Treatment Emergent Adverse Events through 52 weeks post-treatment

	AUGMENT Injectable (n=132)		Autograft (n=167)	
	Events	**Subjects**	**Events**	**Subjects**
Total AEs	558	116(87.9%)	489	135(80.8%)
BMTI 2010-01	334	65/69 (94.2%)	171	34/34 (100%)
BMTI 2006-01 & 2009-01	224	51/63 (81.0%)	318	101/133 (75.9%)
Related TEAEs	3	3(2.3%)	10	6(3.6%)
Serious TEAEs	20	17(12.9%)	35	25(15%)
Surgical Complication	79	47(35.6%)	76	52(31.1%)
BMTI 2010-01	30	20/69 (28.9%)	12	9/34 (26.4%)
BMTI 2006-01 & 2009-01	49	27/63 (42.9%)	64	43/133 (32.3%)
Serious Surgical Complication	8	8(6.1%)	11	10(6%)
Infections	36	27(20.5%)	32	26(15.6%)
BMTI 2010-01	26	17/69 (24.6%)	14	9/34 (26.4%)
BMTI 2006-01 & 2009-01	10	10/63 (15.9%)	18	17/133 (12.8%)

A slightly higher rate of overall AEs and surgical complications was reported in the AUGMENT® Injectable group compared with the autograft group. It is unclear the extent to which this finding could be based on the differences in AE reporting for the majority of AUGMENT® Injectable subjects in the BMTI-2010-01 study compared with the results from the BMTI-2006-01 and BMTI-2009-01 studies, in that the protocol for BMTI-2010-01 counted expected post-surgery clinical findings, e.g., swelling and warmth, as AEs, while BMTI-2006-01 and BMTI-2009-01 did not count these types of findings as AEs.

Serious Adverse Events

The timecourse distribution of the serious TEAEs for investigational AUGMENT® Injectable subjects (I) and autograft control subjects (C) through 52 weeks follow-up is presented in Table 7.

Table 7: Timecourse Distribution of Serious Treatment Emergent Adverse Events by SOC and PT through 52 weeks post-treatment

	Visit																	
	Week 3 (Day 1 to 31)		Week 6 (Day 32 to 52)		Week 9 (Day 53 to 73)		Week 12 (Day 74 to 97)		Week 16 (Day 98 to 139)		Week 24 (Day 140 to 209)		Week 36 (Day 210 to 307)		Week 52 (Day 308 to 420)		Total Events	
System Organic Class Preferred Term	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
Blood and lymphatic system disorders															1		1	
Anaemia															1		1	
Cardiac disorders		1				2						1			1	1	1	5
Acute myocardial infarction		1																1
Arrhythmia															1		1	
Atrial fibrillation																1		1
Atrioventricular block complete												1						1
Cardiac failure congestive						1												1
Myocardial infarction						1												1
Congenital, familial and genetic disorders												1						1
Congenital foot malformation												1						1
Gastrointestinal disorders		1								1						1		3
Gastrointestinal haemorrhage										1						1		2
Megacolon		1																1
General disorders and administration site conditions			1														1	
Impaired healing			1														1	
Hepatobiliary disorders													1				1	
Gallbladder pain													1				1	

	Visit																	
	Week 3 (Day 1 to 31)		Week 6 (Day 32 to 52)		Week 9 (Day 53 to 73)		Week 12 (Day 74 to 97)		Week 16 (Day 98 to 139)		Week 24 (Day 140 to 209)		Week 36 (Day 210 to 307)		Week 52 (Day 308 to 420)		Total Events	
System Organic Class Preferred Term	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
Immune system disorders	1																1	
Hypersensitivity	1																1	
Infections and infestations	1	1								3		1	1		1	1	3	6
Clostridium difficile colitis												1						1
Infection		1											1				1	1
Osteomyelitis										1								1
Pneumonia															1		1	
Postoperative wound infection										1								1
Staphylococcal infection										1								1
Urinary tract infection	1																1	
Wound infection																1		1
Injury, poisoning and procedural complication		1		2														3
Device related infection				1														1
Overdose		1																1
Wound infection				1														1
Musculoskeletal and connective tissue disorder	1											2			2	1	3	3
Arthralgia	1																1	
Osteoarthritis												1			1		1	1
Osteoporosis												1						1
Pain in extremity															1	1	1	1
Neoplasms benign, malignant and unspecified (includes cysts and polyps)		1												1				2
Endometrial cancer														1				1
Renal cell carcinoma stage unspecified		1																1

	Visit																	
	Week 3 (Day 1 to 31)		Week 6 (Day 32 to 52)		Week 9 (Day 53 to 73)		Week 12 (Day 74 to 97)		Week 16 (Day 98 to 139)		Week 24 (Day 140 to 209)		Week 36 (Day 210 to 307)		Week 52 (Day 308 to 420)		Total Events	
System Organic Class Preferred Term	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
Pregnancy, puerperium and perinatal condition														1				1
Pregnancy														1				1
Psychiatric disorders					1					1							1	1
Alcohol withdrawal syndrome										1								1
Suicidal ideation					1												1	
Renal and urinary disorders	1													1			1	1
Ureteric injury														1				1
Urinary tract infection	1																1	
Respiratory, thoracic and mediastinal disorders	1	1										1		1	1		2	3
Chronic obstructive pulmonary disease												1		1				2
Pneumonia															1		1	
Pulmonary embolism	1	1															1	1
Skin and subcutaneous tissue disorders	1																1	
Cellulitis	1																1	
Vascular disorders	2	2	1	1		1						1			1	1	4	6
Aneurysm	1																1	
Aortic stenosis												1						1
Aortic stenosis																1		1
Deep vein thrombosis		1	1	1		1									1		2	3
Haematoma	1																1	
Pulmonary embolism		1																1

I-Investigational (AUGMENT Injectable, n=132), C-Control (Autologous Bone Graft, n=167)

Infections

The timecourse distribution of treatment emergent infections for investigational AUGMENT® Injectable subjects (I) and autograft control subjects (C) through 52 weeks

follow up is presented in Table 8. The infection types and rates were similar between the two treatment groups.

Table 8: Treatment Emergent Infections by SOC and PT through 52 weeks post-treatment

System Organic Class / Preferred Term	Visit																		Total	
	Rx Day		Week 3 (Day 1 to 31)		Week 6 (Day 32 to 52)		Week 9 (Day 53 to 73)		Week 12 (Day 74 to 97)		Week 16 (Day 98 to 139)		Week 24 (Day 140 to 209)		Week 36 (Day 210 to 307)		Week 52 (Day 308 to 420)		Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Gastrointestinal disorders													1						1	
Tooth infection													1						1	
General disorders and administration site conditions								1												1
Soft tissue inflammation								1												1
Infections and infestations	1		6	3	1	3	2	3	5	3	3	4	3	1	5	4	3	2	29	23
Bronchitis										1					1	2			1	3
Cellulitis			1					1	1										2	1
Clostridium difficile colitis			1																1	
Cystitis				1																1
Ear infection									1										1	
Fungal skin infection													1						1	
Herpes zoster													1						1	
Infected skin ulcer														1						1
Infection			1	1			2			1					1				4	2
Kidney infection																1				1
Localised infection																		1		1
Nasopharyngitis									1										1	
Onychomycosis	1																		1	
Osteomyelitis												1								1
Postoperative wound infection				1				2				1								4
Sinusitis									2	1					1	1			3	2
Staphylococcal infection						1						1	1		1		1		3	2
Tooth abscess											1								1	
Upper respiratory tract infection												1								1
Urinary tract infection			2		1	1					1				1		2		7	1
Wound infection			1			1					1							1	2	2
Injury, poisoning and procedural complication				1		3					1								1	4

System Organic Class / Preferred Term	Visit																		Total	
	Rx Day		Week 3 (Day 1 to 31)		Week 6 (Day 32 to 52)		Week 9 (Day 53 to 73)		Week 12 (Day 74 to 97)		Week 16 (Day 98 to 139)		Week 24 (Day 140 to 209)		Week 36 (Day 210 to 307)		Week 52 (Day 308 to 420)		Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Device related infection						1														1
Graft infection				1																1
Post procedural cellulitis						1														1
Postoperative wound infection											1								1	
Wound infection						1														1
Musculoskeletal and connective tissue disorder								1												1
Joint swelling								1												1
Reproductive system and breast disorders											2								2	
Prostatitis											2								2	
Respiratory, thoracic and mediastinal disorde														1						1
Nasopharyngitis														1						1
Skin and subcutaneous tissue disorders			2					1				1							2	2
Cellulitis			2					1				1							2	2
Surgical and medical procedures			1																1	
Wound drainage			1																1	

I-Investigational (AUGMENT Injectable, n=132), C-Control (Autologous Bone Graft, n=167)

Secondary Surgical Interventions

A summary of the subsequent secondary surgical interventions recorded through the 52 week post-op follow-up period is presented in Table 9. The secondary interventions reported include surgeries at the treated joint and those in other portions of the body. It should be noted that secondary procedures reported in BMTI-2006-01 were generally limited to those procedures directly involving the treated joint. For BMTI-2009-01 and BMTI-2010-01, secondary procedures were included and reported in secondary analyses and were collected with additional focus regarding other procedures both distant and adjacent to the treated joint.

Table 9: Subsequent Secondary Surgical Interventions[1]

Reason for Secondary Surgery[2]	Total Subjects through Week 9		Total Subjects through Week 24		Total Subjects through Week 52	
	I	C	I	C	I	C
Non Union/Delayed Union	0(0%)	0(0%)	1(0.8%)	1(0.6%)	3(2.3%)	2(1.2%)

Secondary Trauma	0(0%)	0(0%)	0(0%)	0(0%)	1(0.8%)	0(0%)
Hardware complication	0(0%)	0(0%)	8(6.1%)	7(4.2%)	16(12.1%)	12(7.2%)
Other	0(0%)	2(1.2%)	4(3%)	7(4.2%)	14(10.6%)	11(6.6%)
Total Procedures	**0(0%)**	**2(1.2%)**	**12(9.1%)**	**14(8.4%)**	**30(22.7%)**	**21(12.6%)**

I-Investigational (AUGMENT Injectable, N=132), C-Control (Autologous Bone Graft, N=167)

[1] **The follow-up period for BMTI-2010-01 differed from that for the other studies - 24 months vs. 12 months, respectively. As a result, direct comparisons between the various studies are limited to a maximum of 52 weeks post-op. Day 420 was used as the cutoff because it corresponds to the 52 week post-op evaluation time point plus the two month visit window utilized in the 2010-01 study.**

[2] **More than one reason may be selected for procedure and patients may have multiple procedures.**

Secondary surgical procedures for non-union occurred in 2.3% of AUGMENT® Injectable subjects compared with 1.2% of autograft subjects. Procedures for non-union are indicative of graft failure. Hardware removal following successful fusion can only be accomplished with success of the graft material to encourage bony fusion.

The secondary surgeries and procedures of greatest concern are those related to non-union of the joint. In order to better understand the types and rates of secondary surgeries, e.g., those related to non-union vs. those related to other events, the secondary procedures were sub-divided into the following categories:

- Surgeries at treated joint(s), with these surgeries further sub-divided for:
  - Removal: non-union/delayed union, with or without hardware removal or revision
  - Revision: hardware removal, without any procedure to address non-union/delayed union
  - Reoperation: Any other surgery at the treated joint that is not classified as a removal or revision, such as irrigation/debridement for infection or secondary trauma
- Other local: Surgeries at the treated foot/ankle, but not at the treated joint(s), and
- Other distant: Surgeries elsewhere in the body.

A breakdown of the secondary surgeries in this manner is included in Table 10.

Table 10: Categorized Subsequent Secondary Surgical Interventions

Type*	Total Procedures through Week 24		Total Subjects through Week 24		Total Procedures through Week 52		Total Subjects through Week 52	
	I	C	I	C	I	C	I	C
Revision and Hardware removal	8	10	8(6.1%)	10(6%)	15	16	15(11.4%)	16(9.6%)
Reoperation	0	1	0(0%)	1(0.6%)	1	1	1(0.8%)	1(0.6%)
Removal	1	1	1(0.8%)	1(0.6%)	3	2	3(2.3%)	2(1.2%)
Other-local	2	0	2(1.5%)	0(0%)	6	1	6(4.5%)	1(0.6%)
Other-distant	2	3	2(1.5%)	2(1.2%)	9	5	8(6.1%)	3(1.8%)

Total Procedures	**13**	**15**	**12(9.1%)**	**14(8.4%)**	**34**	**25**	**30(22.7%)**	**21(12.6%)**

I-Investigational (AUGMENT Injectable, N=132), C-Control (Autologous Bone Graft, N=167)

* More than one reason may be selected for procedure and patients may have multiple procedures.

Revision and Hardware Removal, Reoperation, and Removal occurred at a similar rate for AUGMENT® Injectable compared with autograft, with the majority of these events consisting of removal of hardware (e.g., screws) following joint fusion.

Surgeries at other locations within the foot and other locations in the body accounted for the difference in the overall number of secondary surgical procedures reported for AUGMENT® Injectable, due to the differences in secondary surgery reporting in the 2010-01 study compared to the 2006-01 and 2009-01 studies.

Graft Harvest Site Pain (Autograft Subjects)

Autograft was harvested from a number of anatomic sites in the control subjects. For each of these surgical sites, a separate incision and surgery was required to harvest the autograft material for the joint fusion. Because the AUGMENT® Injectable subjects did not receive this procedure, a comparison of graft site pain would not be appropriate.

Cancer Events

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

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® Injectable. A human pharmacokinetic study that included seven patients receiving AUGMENT® Bone Graft (a similar product containing rhPDGF-BB) 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® Injectable or similar products containing rhPDGF-BB and β-TCP.

In the combined studies, potential subjects who were being treated for cancer or had been treated for cancer were not eligible for inclusion. None of the AUGMENT® Injectable subjects in the combined studies were diagnosed with cancer. Four autograft

subjects were diagnosed with cancer - endometrial cancer (1), renal cell carcinoma (1) and unspecified benign/malignant neoplasm (2).

In a previous study for AUGMENT® Bone Graft (which also contains rhPDGF-BB), 1.8% of AUGMENT® Bone Graft patients developed neoplastic events when compared to 1.4% of autograft patients. In the AUGMENT® Bone Graft group, there were five cancer events: prostate (2), breast (1), hyperplastic colon polyp (1), and plantar fibroma (1). In the autograft group, there were two cancer events: renal cell carcinoma (1) and endometrial carcinoma (1). These findings should be interpreted in conjunction with the cancer information for REGRANEX®, which is described in more detail in the next section. The Investigational Device Exemption (IDE) protocol did not have an exclusion criterion for pre-existing cancers, but only for those untreated malignant neoplasms at the surgical site, or those patients currently undergoing radio- or chemotherapy. No potential safety concerns related to cancer or cancer mortality have been identified through routine post-marketing pharmacovigilance; however, it is important to recognize that the pharmacovigilance mechanism is a voluntary system in which patient outcomes are not actively researched.

This information is being supplied to permit the attending surgeon to evaluate all known aspects of the use of AUGMENT® Injectable in his/her intended patients. Interpretation of the results of these and all studies should be made with caution. Use of the product should be evaluated with this precautionary information in mind.

Summary of the Three REGRANEX® Post-Approval Studies' Findings Regarding Cancer [1, 2]

First, in a retrospective study 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 (rhPDGF-BB) 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® Injectable in bone grafting procedures of the ankle and hindfoot due to:

- higher doses of rhPDGF-BB with REGRANEX® Gel compared to AUGMENT® Injectable;
- 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.

Antibody Data

Serum samples were collected from subjects that received treatment in clinical trials BMTI-2006-01, BMTI-2009-01, and BMTI-2010-01, both pre-treatment and at pre-determined post-treatment intervals, and tested for the presence of anti-rhPDGF-BB antibodies using a tiered approach based upon a validated ELISA. A cell-based assay was used to determine the neutralizing properties of patient serum samples having positive anti-rhPDGF-BB antibody responses by measurement of the inhibition of rhPDGF-BB stimulated PDGF receptor phosphorylation activity in a human cell line.

A total of 4 subjects out of 132 subjects treated with AUGMENT® Injectable (3%) had detectable non-neutralizing anti-rhPDGF-BB antibodies in pre-treatment serum samples, suggesting that a low rate of pre-existing anti-rhPDGF-BB antibodies occurred across the clinical subject population. Alternatively, these may be accounted for as false positives in the assay or a combination of these two factors.

Overall, there were no apparent correlations between the reporting of TEAEs in any of the categories and the detection of either non-neutralizing or neutralizing anti-rhPDGF-BB antibodies in serum samples across subjects and treatments in any of the 3 clinical studies.

Deaths
There were no deaths in either the AUGMENT® Injectable or the autograft groups.

Safety Discussion
The key safety conclusions from the trial are that subjects treated with AUGMENT® Injectable had overall similar rates of treatment- emergent adverse events (TEAEs), serious TEAEs, treatment-related TEAEs, complications, and infections compared to subjects treated with autograft, when controlling for differences in adverse event reporting across different clinical studies.

Overall, there were no apparent correlations between the reporting of TEAEs in any of the categories and the detection of either non-neutralizing or neutralizing anti-rhPDGF-BB antibodies in serum samples across subjects and treatments. There was no impact on the clinical success rates for subjects that were serum positive for anti-rhPDGF-BB antibodies at any point in the AUGMENT® Injectable clinical studies.

The elimination of pain and morbidity resulting from the surgical approach in harvesting autograft may provide a benefit to patients receiving AUGMENT® Injectable.

2. Effectiveness Results

Clinical Endpoints
As outlined above, there were five clinical endpoints used to evaluate the effectiveness of AUGMENT® Injectable 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).

Graft volume
There was a difference seen in the distribution of the estimated amount of graft material used per subject, as the amount of graft material used was not employed in the propensity score matching process.

VAS Pain on Weight Bearing

In all 3 studies, pain on weight bearing was measured at baseline and all postoperative time points using a 100mm VAS scale. Success in the form of relief from pain on weight bearing (measured via VAS) was based on the clinically meaningful difference (20mm) with lower VAS scores indicating a decrease in pain. Table 11 presents pain on weight bearing data combined for the three studies.

Table 11: Weight bearing pain*

	AUGMENT Injectable			Autograft				
Week	**n**	**mean**	**std erro**	**n**	**mean**	**std error**	**diff**	**95% UB**
Baseline	132	71.0	2.0	164	70.7	1.8	0.3	5.1
9	108	29.5	2.9	136	28.2	2.5	1.3	8.0
12	124	26.8	2.5	154	24.6	2.2	2.2	7.9
16	129	26.4	2.4	159	24.4	2.1	2.0	7.6
24	128	25.1	2.4	160	18.3	2.1	6.8	12.5
36	124	18.7	2.3	156	15.8	2.0	2.9	8.2
52	124	16.6	2.4	157	15.9	2.1	0.7	6.2

*Results are based on generalized linear model with factors: baseline value, treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles. For baseline score analysis, baseline value is not included as a factor.

Both treatments provided a significant decrease in weight bearing pain from baseline to Week 9 that continued to decline throughout the 52 weeks of follow up. Subjects receiving AUGMENT® Injectable performed similarly to autograft subjects at all time points, with the exception of a difference at week 24. While this 6mm difference was statistically significant (based on the 95% confidence intervals), it was below the defined 20mm minimally clinically important difference (MCID) for this measurement.

Table 12 describes the percentage of subjects achieving a ≥ 20mm decrease in VAS pain on weight bearing from baseline. A 20mm decrease from baseline is considered a clinically meaningful reduction in pain.

Table 12: Significant Weight Bearing Pain Reduction Rate Estimates (score ≥ 20mm) - Propensity Score Adjusted*

	AUGMENT Injectable (n_{max}=132)			**Autograft (n_{max}=167)**				
Week	x	n	%*	x	n	%*	**95% CI LB**	**odds ratio**
9	82	108	76.1	97	136	71.4	0.74	1.27
12	99	124	78.0	115	154	77.1	0.62	1.05
16	106	129	80.6	119	159	77.4	0.70	1.21

24	105	128	80.5	125	160	81.4	0.53	0.94
36	106	124	84.0	135	156	90.7	0.28	0.54
52	110	124	87.2	128	157	86.3	0.56	1.08

* The values of x and n represent the observed data without adjustment. Actual success rates are computed based on a logistic regression with factors treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles to adjust for possible confounding by covariates. Therefore, estimated success rates at each time point cannot be determined by simply computing the value of *x/n*.

The proportion of subjects experiencing pain reduction of at least 20mm grows over time for each treatment group with the odds ratio near the equality value of 1.00. At all time points, with the exception of 36 weeks, the lower confidence bound exceeded the margin of 0.50, demonstrating non-inferiority of AUGMENT® Injectable relative to autograft.

Foot Function Index

The foot function index (FFI) was utilized to measure pain and function in the foot. A clinically important difference in the FFI total score was considered to be 10 points, with lower FFI scores indicating an increase in function.

Table 13 presents FFI data combined for the three studies. AUGMENT® Injectable subjects experienced a decrease in FFI from baseline (indicative of improvement in overall function) at week 9 that continued to decrease through 52 weeks. The upper bound of the 95% confidence interval indicates that the AUGMENT® Injectable group is non-inferior to autograft groups at all postoperative time points, save week 24, relative to a margin of 10 points.

Table 13: Foot Function Index*

Week	AUGMENT Injectable			Autograft				
	n	mean	std error	n	mean	std error	diff	95% UB
Baseline	132	50.6	1.6	167	50.0	1.4	0.6	4.2
9	126	41.8	1.7	157	45.0	1.5	-3.2	0.7
12	126	33.3	1.8	161	34.5	1.6	-1.2	3.1
16	127	29.7	2.0	162	28.0	1.7	1.7	6.2
24	129	26.3	1.8	164	19.8	1.6	6.5	10.7
36	124	21.8	1.8	159	16.7	1.6	5.1	9.3
52	123	19.6	1.9	160	16.9	1.6	2.7	7.1

*Results are based on generalized linear model with factors: baseline value, treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles. For baseline score analysis, baseline value is not included as a factor.

Table 14 presents the percentage of subjects achieving a ≥10 point decrease in FFI from baseline. A 10 point decrease from baseline is considered a clinically meaningful reduction in pain and increase in function. The proportion of subjects experiencing FFI improvement of at least 10 points grows over time for each treatment group. Functional improvement was observed in 74.4% of AUGMENT® Injectable subjects at week 24, with that percentage increasing to 84.6% by week 52.

Table 14: Significant FFI Improvement Rate Estimates (score ≥ 10 point decrease) Propensity Score Adjusted*

	AUGMENT Injectable (n_{max}=132)			Autograft (n_{max}=167)				
Week	x	n	%*	x	n	%*	**95% CI LB**	**odds ratio**
9	57	126	44.3	64	157	41.2	0.73	1.14
12	75	126	58.8	99	161	62.2	0.55	0.87
16	86	127	67.6	114	162	72.1	0.50	0.81
24	96	129	71.1	134	164	85.9	0.23	0.41
36	102	124	82.1	133	159	86.0	0.40	0.75
52	104	123	84.3	138	160	88.9	0.34	0.67

* The values of x and n represent the observed data without adjustment. Actual success rates are computed based on a logistic regression with factors treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles to adjust for possible confounding by covariates. Therefore, estimated success rates at each time point cannot be determined by simply computing the value of *x/n*.

AOFAS Ankle-Hindfoot Score

The AOFAS Ankle-Hindfoot Score ("AOFAS score") is a patient reported outcome that measures function of the ankle and hindfoot. This outcome measurement has a clinically meaningful difference of 20 points, with higher AOFAS scores indicating an increase in function. Table 15 presents the AOFAS Ankle-Hindfoot scores over time for the three treatment groups.

Table 15: AOFAS Total Score*

	AUGMENT Injectable			Autograft				
Week	**n**	**mean**	**std error**	n	**mean**	**std error**	**95% LB**	**diff**
Baseline	132	43.3	1.5	167	43.6	1.3	-3.8	-0.3
9	126	61.5	1.1	155	61.5	1.0	-2.6	0.0
12	124	66.9	1.3	162	66.6	1.1	-2.7	0.3
16	129	69.9	1.3	163	71.2	1.1	-4.2	-1.2
24	129	73.4	1.5	164	75.5	1.3	-5.6	-2.1
36	124	77.5	1.5	160	78.9	1.3	-4.7	-1.4
52	125	79.5	1.6	160	79.3	1.4	-3.4	0.2

*Results are based on generalized linear model with factors: baseline value, treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles. For baseline score analysis, baseline value is not included as a factor.

Table 16 presents the percentage of subjects achieving a ≥ 20 point increase in AOFAS Ankle-Hindfoot score over time.

Table 16: Significant AOFAS Improvement Rate Estimates (score ≥ 20) Propensity Score Adjusted*

	AUGMENT Injectable (n_{max}=132)			Autograft (n_{max}=167)				
Week	x	n	%*	x	n	%*	**95% CI LB**	**odds ratio**
9	50	126	41.4	67	154	42.2	0.62	0.97
12	66	124	56.9	90	162	53.0	0.75	1.17
16	75	128	62.5	105	163	62.0	0.65	1.02
24	85	129	70.2	117	164	69.5	0.64	1.03
36	92	124	77.2	125	160	76.6	0.61	1.04
52	96	123	80.2	124	160	76.6	0.72	1.24

* The values of x and n represent the observed data without adjustment. Actual success rates are computed based on a logistic regression with factors treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles to adjust for possible confounding by covariates. Therefore, estimated success rates at each time point cannot be determined by simply computing the value of *x/n*.

The proportion of subjects experiencing AOFAS improvement of at least 20 points increased over time for each treatment group with the odds ratio consistently near the value of 1.00 or greater. The lower confidence bound exceeded the margin value of 0.50 at all time points, which is indicative of non-inferiority of AUGMENT® Injectable relative to autograft.

Fusion Site Pain

In all 3 studies, fusion site pain was measured at baseline and all postoperative time points using a 100mm VAS scale. Success was based on a clinically meaningful difference of 20mm, with lower VAS scores indicative of a decrease in pain. Table 17 presents fusion site pain data combined for the three studies.

Table 17: Fusion Site Pain*

	AUGMENT Injectable			Autograft				
Week	n	**mean**	**std error**	n	**mean**	**std erro**	**diff**	**95% UB**
Baseline	132	51.4	2.4	167	50.4	2.1	1.0	6.6
9	126	20.5	2.1	158	15.4	1.8	5.0	9.8
12	126	18.9	2.1	162	17.8	1.8	1.1	5.9
16	129	21.7	2.2	162	18.9	2.0	2.8	8.0
24	129	20.9	2.2	164	15.3	1.9	5.7	10.7
36	124	17.4	2.1	159	12.4	1.8	5.0	9.8
52	125	15.8	2.2	160	12.6	1.9	3.2	8.3

*Results are based on generalized linear model with factors: baseline value, treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles. For baseline score analysis, baseline value is not included as a factor.

Both treatment groups show improvement during the study with improvement of over 30mm at study end. Fusion site pain at week 52 shows non-inferiority of AUGMENT® Injectable relative to autograft at all time points, except at Week 24.

Both treatments provided a dramatic decrease in fusion site pain from baseline to Week 12 that continued to decline throughout the 52 weeks of follow up. Subjects with AUGMENT® Injectable performed similarly to autograft subjects at all time points except at Week 24.

Table 18 presents the percentage of subjects achieving a ≥20mm decrease in VAS fusion site pain from baseline. A 20mm decrease from baseline is considered a clinically meaningful reduction in pain.

Table 18: Significant Fusion Site Pain Reduction Rate Estimates (score ≥ 20mm) Propensity Score Adjusted*

	AUGMENT Injectable			**Autograft (n_{max}=167)**				
Week	x	n	%*	x	n	%*	**95% CI LB**	**odds ratio**
9	79	126	64.1	107	158	66.9	0.56	0.89
12	77	126	63.6	108	162	65.0	0.60	0.94
16	79	129	61.9	102	162	62.7	0.62	0.97
24	80	129	61.8	108	164	66.3	0.52	0.82
36	82	124	66.7	113	159	71.1	0.50	0.81
52	85	125	68.5	109	160	68.5	0.61	1.00

* The values of x and n represent the observed data without adjustment. Actual success rates are computed based on a logistic regression with factors treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles to adjust for possible confounding by covariates. Therefore, estimated success rates at each time point cannot be determined by simply computing the value of *x/n*.

The proportion of subjects experiencing pain reduction of at least 20mm was relatively constant over time for each treatment group with the odds ratio near the equality value of 1.00. At all time points, the lower confidence bound exceeded the margin of 0.50, demonstrating non-inferiority of AUGMENT® Injectable relative to autograft.

SF-12 Physical Function (SF-12 PCS)

SF-12 Physical Function (SF-12 PCS) is a measure of overall quality of life and was collected at baseline and all follow up time points except for week 9 in the three studies. SF-12 PCS provides a global assessment of patient quality of life and is not specific to the foot and ankle. Table 19 presents the timecourse of SF-12 physical function scores.

Table 19: SF-12 PCS Total Score*

Week	AUGMENT Injectable			Autograft				
	n	mean	std error	n	mean	std error	95% LB	diff
Baseline	132	30.8	0.8	167	30.8	0.7	-1.7	0.0
12	126	36.9	0.8	158	36.3	0.7	-1.4	0.5
16	128	37.9	0.8	162	39.0	0.7	-3.1	-1.1
24	129	40.3	0.9	164	42.2	0.7	-3.9	-1.9
36	124	42.1	0.9	159	44.5	0.8	-4.4	-2.4
52	123	42.9	0.9	160	45.5	0.8	-4.6	-2.5

Note: SF-12 is not evaluated at Week 9
*Results are based on generalized linear model with factors: baseline value, treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles. For baseline score analysis, baseline value is not included as a factor.

Both treatment groups show improvement over the course of the study with improvement of at least 12 points. SF-12 PCS shows non-inferiority of AIBG relative to autograft at all time points.

On average, AUGMENT® Injectable subjects achieved an increase in overall quality of life that was evident at week 12 and more pronounced by week 36 and week 52. The AUGMENT® Injectable and autograft groups performed similarly on the mean SF-12 PCS at all postoperative time points. Furthermore, the lower bound of the 95% confidence interval indicates that AUGMENT® Injectable is non-inferior to autograft at all postoperative time points, relative to a margin of 5 points.

Table 20 presents the percentage of subjects having a > 5 point increase in SF-12 PCS from baseline scores over time.

Table 20: SF-12 PCS Improved (score > 5 points) - Propensity Score Adjusted*

	AUGMENT Injectable (n_{max}=132)			Autograft (n_{max}=167)				
Week	x	n	%*	x	n	%*	95% CI LB	odds ratio
12	64	126	48.3	87	158	52.2	0.56	0.85
16	79	128	56.0	97	162	61.5	0.51	0.80
24	90	129	65.4	115	164	72.8	0.44	0.71
36	94	124	67.5	121	159	76.1	0.40	0.65
52	95	123	69.3	122	160	76.3	0.43	0.70

* The values of x and n represent the observed data without adjustment. Actual success rates are computed based on a logistic regression with factors treatment (AUGMENT® Injectable vs autograft) and propensity score quintiles to adjust for possible confounding by covariates. Therefore, estimated success rates at each time point cannot be determined by simply computing the value of *x/n*.

The proportion of subjects experiencing SF-12 PCS improvement increased over time for each treatment group.

Across the different time points, the AUGMENT® Injectable subjects responded similarly to autograft subjects with respect to the percentage of subjects with clinically significant improvements.

Effectiveness Discussion

The effectiveness of AUGMENT® Injectable was evaluated using clinical and functional measures of each subject's outcomes. The following outcome measures demonstrated non-inferiority of AUGMENT® Injectable and autograft at 52 weeks post-operatively when measuring changes from baseline score:

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

A summary of the effectiveness measurements for AUGMENT® Injectable and autograft through 52 weeks follow-up is presented in Table 21.

Table 21: Summary of Effectiveness Measurements for AUGMENT® Injectable and Autograft at 52 weeks

Effectiveness Measurement	AUGMENT® Injectable	Autograft	95% confidence limit for non-inferiority determination*
Pain Reduction (via VAS)			
Average change in weight bearing pain (mm)	-54.3	-55.0	7.3
Average change in fusion site pain (mm)	-34.4	-37.6	9.2
Functional Improvement			
Average change in Foot Function Index	-30.5	-33.3	7.9
Average change in AOFAS Total Score	35.9	35.7	-4.1
Quality of Life Maintenance/Improvement			
Average change in SF-12 PCS	12.0	14.6	-5.0

* Confidence limits are presented as either upper- or lower-confidence limits, depending on the nature of the measure. For pain measurements and Foot Function Index, smaller values are beneficial to the patient; thus, these are upper confidence limits: the difference (AUGMENT® Injectable minus autograft) between the means and the confidence limit should be less than the desired delta. For AOFAS and SF-12 PCS, larger values are beneficial to the patient; thus, these are lower confidence limits: the difference (AUGMENT® Injectable minus autograft) between the means and the confidence limit should be greater than the negative of the desired delta. In all cases, the differences between the two treatments can be interpreted to be "no worse than" the value of the confidence limit.

The confidence limits should be compared to the non-inferiority margins, which were no more than 10mm for weight bearing pain, 10mm for fusion site pain, 10 pts for FFI, -10 pts for AOFAS and -5 pts for the SF-12.

Any benefits of AUGMENT® Injectable are achieved without the pain and morbidity associated with harvesting autograft bone.

3. Subgroup Analyses

There were no subgroup analyses.

4. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

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 39 Principle Investigators and 43 Co-investigators investigators of which none were full-time or part-time employees of the sponsor and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Advisory Committee, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical data demonstrate that AUGMENT® Injectable is effective in:

- Pain Reduction: At 52 weeks, AUGMENT® Injectable subjects had an average improvement of 54mm in their weight bearing pain compared with autograft subjects having an average improvement of 55mm. Similar changes in fusion site pain were seen as well.

- Functional and Quality of Life Improvement: AUGMENT® Injectable subjects saw an improvement in foot and ankle function, as demonstrated by the mean changes in FFI and AOFAS scores. An overall increase in physical quality of life was also noted by increases in SF-12 through 52 weeks.

In all of the clinical and functional outcome measurements described above, AUGMENT® Injectable was non-inferior to autograft.

B. Safety Conclusions

Adverse event reporting was utilized as a major element of the safety evaluation of AUGMENT® Injectable. There were key differences in AE reporting which should be noted when comparing AE rates among the studies consolidated in this report, although they do not adversely impact the ability to draw comparisons between treatments.

Of greater importance in the interpretation of the safety of AUGMENT® Injectable compared to autograft is the method by which the AEs were evaluated. As described above, there were concerns related to differences in how events were recorded (physical exam observations vs. AEs). The CEC that was implemented to address these concerns was not designed in a manner whereby its adjudication of AEs would eliminate bias. It is important to keep this in mind when comparing adverse event rates between the investigational and control subjects. A slightly higher rate of overall AEs and surgical complications was reported in the AUGMENT® Injectable group compared with the autograft group. This finding may be partially attributed to the differences in AE reporting described above.

A low rate of treatment-related AEs was present in all groups, with 2.3% in the AUGMENT® Injectable group and 3.6% in the autograft group. Subjects treated with AUGMENT® Injectable had overall similar rates of serious AEs and treatment-related AEs compared to subjects treated with autograft. The rates of overall AEs, complications, and infections were also similar when taking into account the differences in the reporting of these AE types across studies.

Anti-rhPDGF-BB antibodies in serum were seen in 20% (27/132) of subjects treated with AUGMENT® Injectable, compared with 4% (7/189) of subjects treated with autograft. Development of neutralizing anti-rhPDGF-BB antibodies (NAb) was found to be rare and transient, occurring in 1.5% (2/132) of AUGMENT® Injectable subjects, with the NAb positive sample at one time point only for each of these subjects and considered a transient immune response. Overall, there was no impact on AE type or rate, as well as success rates for subjects that were serum positive for anti-rhPDGF-BB antibodies at any point in the 3 clinical studies.

Significant graft harvest site pain was reported in 40.4% of the autograft subjects at the 1-3 week time point, with this amount decreasing to 10.1% at one year and 6.5% at two years postoperatively. Graft harvesting was also associated with other AEs, e.g., infection and nerve injury. As there was no graft harvest required in the AUGMENT® Injectable group, this finding provides additional benefit to patients receiving AUGMENT® Injectable.

Within the limits of the AE interpretation described above, AUGMENT® Injectable may be safe, as demonstrated by the adverse event, secondary surgery, and immunogenicity data.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical studies conducted to support PMA approval as described above. AUGMENT® Injectable and autograft control subjects achieved comparable clinical and functional improvements in outcomes (pain on weight bearing, Foot Function Index (FFI), and AOFAS Score).

AUGMENT® Injectable patients did not require the need for autograft thereby avoiding pain and morbidity at a secondary harvest site. Based on the literature (Baumhauer, 2013, August and November [3,4]), morbidities associated with the harvest of the bone graft include increased operative time and hospital stay (resulting in increased costs); increased blood loss; post-operative and chronic pain; risk of nerve injury, and increased infection and/or fracture rates. Other limitations associated with the use of autograft include, limited tissue supply, and variability in cellular activity of the bone graft. As fusion surgery with AUGMENT® Injectable does not require autograft, these risks are eliminated with the use of AUGMENT® Injectable as an alternative to autograft.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that 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, the probable benefits of AUGMENT® Injectable outweigh its probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The analysis of the

clinical outcome from the combined dataset described above supports the safety and effectiveness of AUGMENT® Injectable used in fusion procedures of the ankle and hindfoot stabilized by screw, staple or pin fixation. When compared to foot and ankle fusions performed using autograft bone, the same procedure incorporating AUGMENT® Injectable is not associated with the morbidity resulting from autograft harvesting.

XIII. CDRH DECISION

CDRH issued an approval order on June 12, 2018. The final conditions of approval cited in the approval order are described below.

The applicant proposes a continued follow-up of the premarket PMA cohort study. A prospective, controlled study within the US and Canada comparing AUGMENT® Injectable to autograft in hindfoot and ankle arthrodesis at 5 or more years posttreatment is proposed. The study will address the following objectives:

(1) Can it be assessed and confirmed that bridging bone occurs in the long-term after AUGMENT® Injectable has been resorbed?

(2) Are the improvements in clinical outcomes associated with the use of AUGMENT® Injectable 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® Injectable exceed the expected rate of promotion in patients not treated with AUGMENT® Injectable or other growth factors used to promote fusion?

The primary effectiveness endpoints will consist of the following:

- Pain on Weight Bearing (via VAS) (≥ 60 months post-op).

The secondary effectiveness endpoints will consist of the following:

- Confirmation of bridging bone via CT (≥ 60 months post-op); and
- Patient Function (≥ 60 months post-op) as determined by AOFAS Score and Foot Function Index (FFI).

The primary safety endpoints will consist of the following:

- Presence of all treatment related 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);
- 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; and
  - Neoplasms benign, malignant and unspecified (including cysts and polyps) [all lower level terms associated with neoplasms]; and

- rhPDGF-BB antibody status.

At evaluation, subjects will be interviewed regarding significant medical conditions, including incidence of cancer.

Secondary evaluations will include subgroup analyses based on comparison of subject subtypes and graft material kits used.

Target enrollment is proposed to be a minimum of eighty-eight (88) subjects (44 in each of the two treatment groups) who are 5 or more years post treatment with AUGMENT® Injectable or autograft, to be evaluated at a single investigative site visit. Those autograft subjects who agree to participate will undergo propensity score matching with the AUGMENT® Injectable subjects who agree to participate, in a manner consistent with what was done in the propensity score matching exercise for AUGMENT® Injectable.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Seeger, et al. "A Cohort Study of the Risk of Cancer in Regranex (Becaplermin) Users and Matched Comparators" Pharmacoepidemiology and Drug Safety, 2007.

2. Ziyadeh, et al. "A Matched Cohort Study of the Risk of Cancer in Users of Becaplermin" Advances in Skin and Wound Care, 2011.

3. Baumhauer JF, Pinzur MS, Daniels TR, Lin SS, Beasley W, Donahue RM, DiGiovanni CW. Survey on the need for bone graft in foot and ankle fusion surgery. Foot Ankle Int. 2013 Dec;34(12):1629-33. doi: 10.1177/1071100713503815. Epub 2013 Aug 28. PubMed PMID: 23986324.

4. Baumhauer J, Pinzur MS, Donahue R, Beasley W, DiGiovanni C. Site Selection and Pain Outcome After Autologous Bone Graft Harvest. Foot Ankle Int. 2013 Nov 13. doi: 10.1177/1071100713511434. [Epub ahead of print] PMID: 24227683.