PROPOSED SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Bone grafting material containing a therapeutic biologic

Device Trade Name: Augment™ Bone Graft

Applicant's Name and Address: BioMimetic Therapeutic

389 Nichol Mill Lane

Franklin, TN 37067

Date of Panel Recommendation: Not Applicable at this time

Premarket Approval Application (PMA) Number: P100006

Date of FDA Notice of Approval: Not Applicable at this time

II. INDICATIONS FOR USE

Augment™ Bone Graft is indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions.

III. CONTRAINDICATIONS

Augment Bone Graft **should not**:

• be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products.

• be used in patients with active cancer.

• be used in patients who are skeletally immature (‹18 years of age or no radiographic evidence of closure of epiphyses).

• be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.

• be implanted in patients with an active infection at the operative site.

• be used in situations where soft tissue coverage is not achievable.

• be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes.

• be used as a substitute for structural graft.

IV. WARNINGS AND PRECAUTIONS

- Women of childbearing potential should be advised that antibody formation to rhPDGF-BB or its influence on fetal development have not been assessed. In two pilot clinical studies to support the safety and effectiveness of Augment, 74 patients were evaluated for the presence of antibodies to rhPDGF-BB. Antibodies were detected in 9 out of 74 (12%) patients. However, none of the antibodies were found to be neutralizing. The clinical significance of these non-neutralizing antibodies is not known.
- The safety and effectiveness of Augment in nursing mothers has not been established. It is not known if rhPDGF-BB is excreted in human milk.
- Women of childbearing potential should be advised to avoid becoming pregnant for one year following treatment with Augment.
- The safety and effectiveness of Augment has not been established in anatomical locations other than the foot or ankle, used in surgical techniques other than open surgical approaches, or combined with autogenous bone or other bone grafting materials.
- Augment does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.
- Augment should only be used by surgeons who are familiar with bone grafting techniques used in foot and ankle surgery.
- In order to enhance the formation of new bone, Augment should be placed in direct contact with well-vascularized bone. Cortical bone may be perforated prior to placement of the material. In order to optimize bony fusion, Augment should be implanted such that it does not prevent bony apposition of the articular surfaces intended for fusion.
- The β-TCP component is radiopaque, which must be considered when evaluating radiographs as it may mask underlying pathological conditions.
- The safety and effectiveness of repeat applications of Augment have not been established.
- Careful consideration should be given to alternative therapies prior to performing bone grafting in patients who have severe endocrine-induced bone diseases (e.g. hyper-parathyroidism); who are receiving immunosuppressive therapy; or who have known conditions that may lead to bleeding complications (e.g. hemophilia).

- The safety and effectiveness of Augment in pediatric patients below the age of 18 years has not been established.
- Augment is supplied as a single use only kit. Discard any unused material. The individual components of this product should not be used separately. Use a new device for subsequent applications.
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, do not use the product. Retain the packaging and contact a representative of BioMimetic Therapeutics, Inc.
- **Immunogenicity**: As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of Augment. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal study for foot and ankle fusions. In this study population, anti-rhPDGF-BB antibodies were detected in 13.9% of Augment-treated patients However, there were no antibodies that were found to be neutralizing antibodies. The clinical significance of these binding non-neutralizing antibodies is not known. All of the patients antibody levels returned to baseline at follow-up visits. The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Augment with the incidence of antibodies to other products may be misleading.

V. DEVICE DESCRIPTION

Augment is a combination device/drug product being developed for use in bone repair and regenerative procedures. Augment is indicated for the treatment of foot and ankle fusions. The product eliminates the need for a second surgery to harvest autologous bone, therefore there is no donor site morbidity (e.g. pain, infection, etc.).

Augment combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable synthetic bone matrix (beta-tricalcium phosphate or β-TCP). *Augment* can only achieve its intended use when the two functional components are combined. These two components are packaged together and sold as a system. They are physically combined immediately prior to use.

Augment is comprised of the following subassembly components:

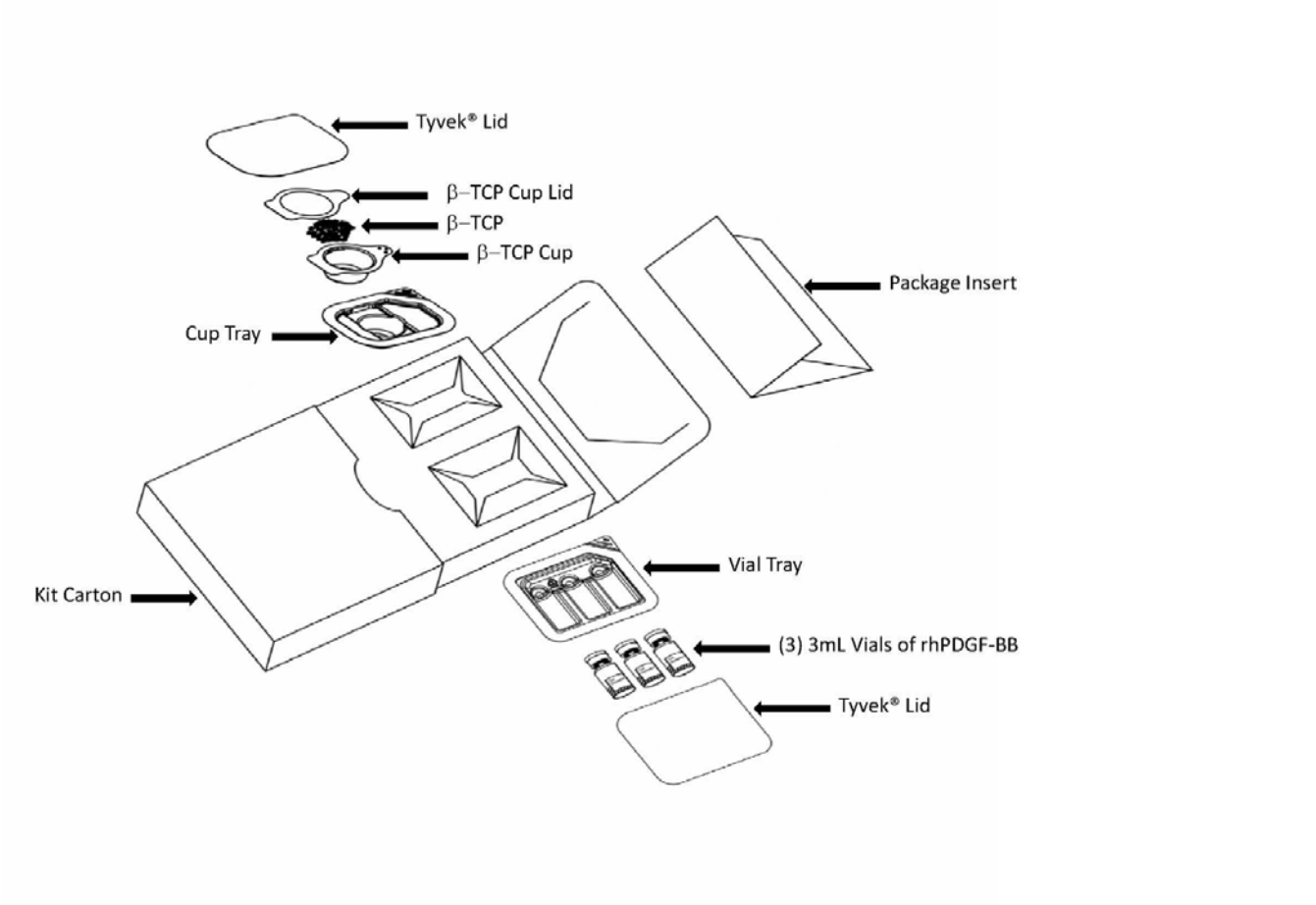
1.5, 3, 6, or 9 cc of synthetic β-TCP in granule form (nominal particle size 1000 to 2000 µm) provided in a 44 mm PETG/PE laminate cup closed with a heat-sealed PET/PE/Foil laminate lid. The β-TCP cup is packaged into a PETG tray closed with a heat-sealed coated *Tyvek*® lid. The finished component (cup/tray subassembly) is terminally sterilized by gamma irradiation; and

1.5, 3, 6, or 9 mL of rhPDGF-BB (0.3 mg/mL in 20mM USP sodium acetate buffer, pH 6.0) aseptically filled into a single or multiple 3 mL USP Type I borosilicate glass vial(s) (Kimble or Schott) with a 13 mm stopper (West Pharma S2-F451 4432/50 Gray Butyl Rubber with B2-40 Coating) and a flip-off tear cap. The rhPDGF-BB vial is packaged into a PETG tray closed with a heat-sealed coated *Tyvek*® lid. The finished component (vial/tray subassembly) is terminally sterilized by ethylene oxide gas.

Equal volumes of β-TCP and rhPDGF-BB are mixed in a surgical bowl. On administration, the surgeon estimates the volume of graft material required, which is dependent on the size of the void to be filled and selects the appropriate kit for the surgery. Any remaining material is discarded.

The two sub-assemblies of equal size are included in each kit, along with the package insert and are packed together in an SBS carton as the final product (Figure 1-1).

Figure 1-1. Augment Bone Graft final kit (finished product) showing the assembly of the β-TCP device component (filled cup in a tray) and the rhPDGF-BB drug component (filled vial in a tray). The package insert is placed in the flipside of the carton when pulled open.



VI. ALTERNATIVE PRACTICES AND PROCEDURES

Currently, there are no generally accepted alternatives to autograft for fusion procedures of the foot or ankle. Hindfoot and ankle fusion procedures, such as triple (three hindfoot articulations), subtalar fusions, and ankle fusions involve the same treatment principles of creating a peri-articular osteotomy, stabilizing the joint with rigid fixation, placing autograft bone harvested locally, and following standard post-operative regimen of physical therapy and gradually increasing load on the fusion.

One of the most widely used options for bone graft is autologous bone due to the fact that there is no risk of cross contamination with autologous bone in contrast to allografts or xenografts; however, clinical difficulties have been associated with autograft. Most of these difficulties

result from the harvest of the bone graft, including increased operative time, hospital stay and cost, increased blood loss, post-operative pain, risk of infection and/or fracture. Other reported complications associated with autograft include a potential nidus for infection associated with avascular bone, limited tissue supply, and variability in cellular activity of the bone graft (Younger *et al.,* 1989). In addition to these complications, limitation exists in the amount of bone graft that may be harvested. The morbidity associated with autograft and its limited amount available to be harvested has directed surgeons to look for a better alternative for a chemotactic, mitogenic, and angiogenic bone graft substitute as an alternative to accelerate healing (St. John *et al.,* 2003).

VII. MARKETING HISTORY

On November 3, 2009, BioMimetic received approval from Health Canada to begin marketing Augment™ Bone Graft in Canada for midfoot, hindfoot and ankle fusion indications. The components of Augment (rhPDGF-BB and β-TCP) have been independently marketed in the United States, Canada, and internationally. Neither Augment or any of its components have ever been withdrawn from a market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No serious adverse events (SAE's) directly attributable to Augment™ Bone Graft have been reported in clinical studies with the product, however 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.

IX. SUMMARY OF PRE CLINICAL STUDIES

Pre-clinical studies were conducted to assess the safety and effectiveness of the individual and combined components contained in *Augment*. BioMimetic Therapeutics conducted an extensive preclinical evaluation of rhPDGF-BB in combination with β-TCP matrices to provide sufficient data supporting its safe and effective use in treating orthopedic indications.

The structure, biology, and function of the rhPDGF-BB protein have been extensively characterized and reported in the scientific literature. rhPDGF-BB functions to stimulate wound

healing by attracting healing cells to wound sites, induces them to proliferate, and supports neovascularization to help establish an adequate blood supply. There is no evidence of systemic toxicity, acute or chronic, associated with rhPDGF-BB, and its weak immunogenic potential following injection provides a strong assurance of safety.

The efficacy of rhPDGF-BB combined with β-TCP for stimulating bone wound healing and regeneration was evaluated in a variety of animal preclinical studies. Several animal models of bone healing demonstrated the local pharmacological activity and safety of rhPDGF-BB in combination with β-TCP and other matrix materials. The data from these studies demonstrate the safety and efficacy of rhPDGF-BB for stimulating the healing of fractures, fusions and defects lending support for the intended clinical use of *Augment* for enhancing bone healing following a foot and ankle fusion procedure.

To evaluate the biocompatibility, toxicology and ADME/pharmacokinetics of rhPDGF-BB alone or in combination with β-TCP, a series of studies were perfomed. The Company conducted a panel of medical device biocompatibility/toxicology studies in compliance with ISO 10993 and USP guidelines. These studies evaluated β-TCP alone or in combination with rhPDGF-BB and on β-TCP from several sources with or without rhPDGF-BB. An abbreviated panel of tests was conducted on rhPDGF-BB samples stored under non-standard storage conditions for 12 months at 30°C and 5°C. The sum of the data from the biocompatibility studies demonstrated that rhPDGF-BB combined with β-TCP is non-toxic and biocompatible, which supports the safety profile for the *Augment* product. In addition, the results from 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 thus providing additional data supporting the safety of rhPDGF-BB administered either locally or intravenously in animal models.

Two studies were presented that provide data characterizing the 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 minimal systemic exposure to the protein following intramuscular implantation of ^{125}I-rhPDGF-BB combined with *Augment* β-TCP and clearance is again mainly in the urine. Overall, the toxicology and pharmacokinetic data demonstrated that rhPDGF-BB combined with *Augment* 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 minimal systemic exposure.

The characterization of the release kinetics, biological potency and biochemical integrity of rhPDGF-BB combined with β-TCP from different sources was also studied. Both *in vivo* and *in vitro* preclinical data demonstrated that rhPDGF-BB is released rapidly from *Augment* β-TCP

and other sources of β-TCP in a similar fashion. The protein retains its biological potency and is biochemically intact following release from β-TCP matrices. Thus, the data support *Augment* β-TCP as an appropriate matrix as the device component of this combination product.

Additional safety testing to address potential concerns related to reproductive/developmental toxicity and carcinogenicity of rhPDGF-BB are in progress. These types of studies are typically not performed on a locally administered single dose product such as *Augment* because there is minimal systemic exposure to the protein following administration. However, BioMimetic chose to perform these studies to address the potential concerns arising from the FDA's Early Communication on *Regranex*. The studies are intended to assess the potential for rhPDGF-BB to induce developmental toxicity, long-term carcinogenicity and enhance tumor progression. These studies are being completed as part of a Post-Approval Requirement.

In summary, taken together, the safety, toxicology, pharmacokinetic, and pharmacodynamic data provide strong evidence of non-clinical safety and efficacy in support of *Augment* in the proposed clinical indication.

X. SUMMARY OF PRIMARY CLINICAL STUDY

April 2007 (first patient enrolled) to
January 2010 (last patient completed 52 weeks)

Phase of Development:
Pivotal study under an approved Investigational Device Exemptions Application

Objectives:
The study objective is to demonstrate equivalent clinical, radiologic and safety outcomes for Augment and the "gold standard" (autologous bone graft) in a representative clinical model (foot and ankle fusions).

Methodology:
This prospective, randomized, controlled, non-inferiority, multi-center clinical trial was undertaken to evaluate the safety and effectiveness of Augment Bone Graft compared to autologous bone graft as a bone regeneration device. The study intent was to enroll patients requiring fusion in either the hindfoot or ankle (tibiotalar) requiring the use of bone graft. Each patient was to have a physical exam of the anatomical region to be treated, incorporating medical history and injury/disease etiology. Upon confirmation of eligibility, patients were randomized into one of two treatment groups: standard rigid fixation plus autologous bone graft, or standard rigid fixation plus Augment Bone Graft. Randomization was conducted at a 2:1 ratio of Augment Bone Graft Augment Bone Graft to autologous

bone graft. The patients then underwent a hindfoot/ankle fusion procedure using open surgical technique with supplemental bone graft or substitute, according to the randomization assignment. The fusion construct required adequate reduction and stabilization with rigid fixation intra-operatively in order to meet final study eligibility. Both treatment groups were immobilized according to standardized operative and post-operative protocols.

The investigators, who were fellowship trained and board certified foot and ankle surgeons, performed clinical and radiographic assessments (as required by protocol) to monitor healing/union status. A masked independent radiographic assessment was performed by a designated fellowship trained and board certified musculoskeletal radiologist who assessed radiographic parameters for fusion. All enrolled patients were to be monitored over a 12-month period to evaluate for clinical and safety outcomes, including incidence of loss of reduction, infection, non-union, need for revision fusion surgery, and associated complications with hindfoot and ankle fusion procedures, in addition to the occurrence of other adverse device effects.

Number of Patients (Planned and Analyzed):
396 patients were planned; 435 patients were randomized (331 in US and 104 in Canada); 434 patients were analyzed. Patient population totals for the analyses are:
Intent-to-treat (ITT): 434
Safety (or Treated Population): 414
Modified intent-to-treat (mITT): 397

Diagnosis and Main Criteria for Inclusion:
Male and female patients over the age of 18 years of age requiring a hindfoot/ankle fusion procedure involving a bone grafting procedure.

Test Therapy:
Standard rigid fixation + Augment Bone Graft, containing β-TCP and 0.3 mg/mL rhPDGF-BB in sodium acetate buffer

Reference Therapy:
Standard rigid fixation + Autologous Bone Graft

Randomization Scheme:
2:1 ratio of Standard rigid fixation + Augment Bone Graft (Test therapy) to Standard rigid fixation + Autologous Bone Graft (Reference therapy)

Duration of Follow-up:
12 months (primary endpoint at 6 months)

Summary of Results

Effectiveness:

The results from the statistical analyses revealed both statistically significant and clinically relevant benefits for the Augment Bone Graft, compared to the gold standard of autograft. In addition, the results from both study groups are comparable to available historical literature for union rates associated with autograft, particularly considering the relatively compromised patient population. The results from the effectiveness analysis are presented based upon the mITT patient population which is defined as all randomized patients who were eligible, properly randomized, and received treatment according to the study protocol.

Primary Endpoint (mITT Population):

At 24 weeks post-surgery, a statistically significant CT fusion rate (defined as at least 50% osseous bridging) was demonstrated for non-inferiority of Augment versus autograft for the full complement analysis (p=0.038) indicating that the fusion rates (61.2% for Augment and 62.0% for autograft) are equivalent between the two groups, as analyzed by the most rigorous methodology (CT scan).

Secondary Endpoints (mITT Population):

At week 24, Augment demonstrated non-inferiority versus autograft for the all joints analyses (p<0.001) indicating that the fusion rates (66.5% for Augment and 62.6% for autograft) are equivalent between the two groups.

Augment Bone Graft demonstrated 30.8% and 38.3% of patients achieving union via three (3) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 32.8% (p=0.054) and 37.9% (p=0.007) of patients achieving radiographic union on three (3) radiographic aspects for full complement and all joints, respectively. Augment Bone Graft demonstrated 60.8% and 67.5% achieving union on two (2) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 66.4% (p=0.194) and 70.9% (p=0.049) of patients achieving radiographic union on two (2) radiographic aspects for full complement and all joints, respectively.

The clinical healing status at the joint level demonstrated statistical significance for non-inferiority based on the full complement and all joints treated. At week 24, Augment patients achieved 82.3% clinical union for the full complement and 83.5% for all joints compared to autograft which achieved 83.2% (p=0.011) for the full complement and 83.3% (<0.001) for all joints.

A composite success endpoint, which comprised clinical, functional, and radiologic endpoints, demonstrated statistical significance for non-inferiority at week 24, with Augment achieving 70.8% success compared to 69.3% success in the autograft treatment group (p=0.009). In addition, rates of clinical success (defined by improved pain with weight-bearing and lack of requirement for secondary therapeutic intervention) at week 24 were 74.6% and 78.1% for Augment and autograft, respectively (p=0.071).

The therapeutic failure rate was calculated, based upon a determination of either delayed union or non-union, or if the patient required a therapeutic intervention or a secondary procedure to address delayed union or non-union. At week 24, 9.2% of Augment Bone Graft patients were declared therapeutic failures, compared with 10.9% of autologous bone graft patients, supporting non-inferiority ($p<0.001$).

Quality-of-life and functional outcomes scores included SF-12, FFI, and AOFAS Ankle-Hindfoot questionnaires. At week 24, the Augment Bone Graft patients reported a mean SF-12 Physical Component Score (PCS) of 39.9 (improvement from 31.0 at screening), compared with 41.4 in the autologous bone graft group (improvement from 31.6 at screening); a mean FFI total score of 27.4 (improvement from 51.6 at screening), compared with 22.3 in the autologous bone graft group (improvement from 48.6 at screening); and a mean AOFAS Ankle-Hindfoot total of 71.7 (improvement from 40.4 at screening), compared to 75.9 in the autologous bone graft group (improvement from 40.5 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

Pain assessments were made on a visual analog scale (VAS) regarding overall fusion site pain and pain on weight-bearing. At week 24, Augment Bone Graft patients reported a mean overall fusion site pain assessment of 18.9 mm (mean improvement of 32.6 from screening), versus a mean pain assessment of 16.5 mm (mean improvement of 33.0) in autologous bone graft patients overall (p=0.001).

For weight-bearing pain at week 24, Augment Bone Graft patients reported a mean assessment of 23.5 mm on weight-bearing (mean improvement of 43.4 from screening) versus a mean assessment of 19.3 mm when weight-bearing (mean improvement of 45.4 from screening) in autologous bone graft patients overall) (p=0.016). These results demonstrated statistical significance for non-inferiority of Augment Bone Graft versus autologous bone graft.

For subjects who were treated with autologous bone graft, pain at the bone graft harvest site was recorded. Almost all patients (95.6%) noted some degree of pain associated with the autograft harvest site. Notably, 12.4% of subjects reported clinically significant pain at 24 weeks post-operatively (pain ≥ 20mm on a 100mm VAS scale). All subjects in the Augment group were spared the additional surgery of bone graft harvest and therefore did not report any pain for bone graft harvest.

A summary of the key effectiveness results at week 24 for the mITT population is presented below:

Week 24 Results Summary

	Augment™ Bone Graft	Autologous Bone Graft	Non-inferioriy test p-value
Subjects (N=397)	**(N=260)**	**(N=137)**	
Individual joints [All Joints] (N=597)	**(N=394)**	**(N=203)**	
CT Fusion Rates			
Full Complement of Joints:	61.2%	62.0%	**0.038**
All Joints (assessed individually):	66.5%	62.6%	**<0.001**
Plain Film Radiographic Union Rates (3 Aspects)			
Full Complement of Joints:	30.8%	32.8%	0.054
All Joints (assessed individually):	38.3%	37.9%	**0.007**
Plain Film Radiographic Union Rates (2 Aspects)			
Full Complement of Joints:	60.8%	66.4%	0.194
All Joints (assessed individually):	67.5%	70.9%	**0.049**
Clinical Healing Status at the Patient Level:	83.1%	83.9%	**0.010**
Clinical Healing Status by Joint			
Full Complement of Joints:	82.3%	83.2%	**0.011**
All Joints (assessed individually):	83.5%	83.3%	**<0.001**
Composite Success Rate:	70.8%	69.3%	**0.009**
Clinical Success Rate:	74.6%	78.1%	0.071
Therapeutic Failure Rate*:	9.2%	10.9%	**<0.001**
SF-12 Mean PCS:	39.9	41.4	**<0.001**
FFI Mean Total Score:	27.4	22.3	**0.012**
AOFAS Mean Total Score:	73.9	75.9	**<0.001**
Fusion Site Pain:	18.9	16.5	**0.001**
Weight-bearing Pain:	23.5	19.3	**0.016**
Graft Harvest Site Pain:	n/a	8.1	**<0.001**

*Therapeutic failures are patients who were assessed as having non-union or delayed union, or required secondary therapeutic intervention for non-union or delayed union

Results after 24 Weeks

Week 36 Results

At the Week 36 assessment, fusion rates continued to increase for all patients, though the increase from the previous assessment was greater for the autologous bone graft patients than for the Augment Bone Graft patients. The week 36 fusion rate results for the full complement of joints were 63.5% for Augment and 69.3% for autograft. This increased difference in rates did not continue to support non-inferiority at week 36 for either the full complement of joints (p=0.202) or all joints (p= 0.103) for this secondary endpoint.

Augment Bone Graft demonstrated 30.0% and 39.1% of patients achieving union via three (3) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 35.8% (p=0.198) and 42.9% (p=0.072) of patients achieving radiographic union on three (3) radiographic aspects for full complement and all joints, respectively. Augment Bone Graft demonstrated 62.7% and 70.3% achieving union on two (2) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 69.3% (p=0.249) and 72.4% (p=0.021) of patients achieving radiographic union on two (2) radiographic aspects for full complement and all joints, respectively.

The clinical healing status at the joint level demonstrated statistical significance for non-inferiority based on the full complement and all joints treated. At week 36, Augment patients achieved 84.2% clinical union for the full complement and 86.8% for all joints compared to autograft which achieved 86.9% (p=0.022) for the full complement and 85.7% (<0.001) for all joints.

A composite success endpoint, which comprised clinical, functional, and radiologic endpoints, demonstrated Augment achieving 71.5% success compared to 77.4% success in the autograft treatment group (p=0.179). In addition, rates of clinical success (defined by improved pain with weight-bearing and lack of requirement for secondary therapeutic intervention) at week 36 were 73.8% and 75.9% for Augment and autograft, respectively (p=0.041).

The therapeutic failure rate was calculated, based upon a determination of either delayed union or non-union, or if the patient required a therapeutic intervention or a secondary procedure to address delayed union or non-union. At week 36, 7.7% of Augment Bone Graft patients were declared therapeutic failures, compared with 9.5% of autologous bone graft patients, supporting non-inferiority (p<0.001).

Quality-of-life and functional outcomes scores included SF-12, FFI, and AOFAS Ankle-Hindfoot questionnaires. At week 36, the Augment Bone Graft patients reported a mean SF-12 Physical Component Score (PCS) of 41.4 (improvement from 31.0 at screening), compared with 44.2 in the autologous bone graft group (improvement from 31.6 at screening); a mean FFI total score of 22.0 (improvement from 51.6 at screening), compared with 18.2 in the autologous bone

graft group (improvement from 48.6 at screening); and a mean AOFAS Ankle-Hindfoot total of 75.0 (improvement from 40.4 at screening), compared to 77.3 in the autologous bone graft group (improvement from 40.8 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

Pain assessments were made on a visual analog scale (VAS) regarding overall fusion site pain and pain on weight-bearing. At week 36, Augment Bone Graft patients reported a mean overall fusion site pain assessment of 16.2 mm, versus a mean pain assessment of 13.9 mm in autologous bone graft patients overall ($p < 0.001$). For weight-bearing pain at week 36, Augment Bone Graft patients reported a mean assessment of 18.8 mm on weight-bearing versus a mean assessment of 15.7 mm when weight-bearing in autologous bone graft patients overall ($p=0.005$). These results demonstrated statistical significance for non-inferiority of Augment Bone Graft versus autologous bone graft. For subjects who were treated with autologous bone graft, pain at the bone graft harvest site was recorded. Notably, 7.3% of subjects in the autograft treatment group reported clinically significant pain at 36 weeks post-operatively.

A summary of results at Week 36 is presented below:

Week 36 Results Summary

	Augment™ Bone Graft	Autologous Bone Graft	Noninferiority test p-value
Subjects (N=397)	**(N=260)**	**(N=137)**	
Individual joints [All Joints] (N=597)	**(N=394)**	**(N=203)**	
CT Fusion Rates			
Full Complement of Joints:	63.5%	69.3%	0.202
All Joints (assessed individually):	68.8%	73.9%	0.103
Plain Film Radiographic Union Rates (3 Aspects)			
Full Complement of Joints:	30.0%	35.8%	0.198
All Joints (assessed individually):	39.1%	42.9%	0.072
Plain Film Radiographic Union Rates (2 Aspects)			
Full Complement of Joints:	62.7%	69.3%	0.249
All Joints (assessed individually):	70.3%	72.4%	**0.021**
Clinical Healing Status at the Patient Level:	84.6%	88.3%	**0.038**
Clinical Healing Status by Joint			
Full Complement of Joints:	84.2%	86.9%	**0.022**
All Joints (assessed individually):	86.8%	85.7%	**<0.001**
Composite Success Rate:	71.5%	77.4%	0.179
Clinical Success Rate:	73.8%	75.9%	**0.041**
Therapeutic Failure Rate*:	7.7%	9.5%	**<0.001**

SF-12 Mean PCS:	41.4	44.2	**0.020**
FFI Mean Total Score:	22.0	18.2	**0.001**
AOFAS Mean Total Score:	75.0	77.3	**<0.001**
Fusion Site Pain:	16.2	13.9	**<0.001**
Weight-bearing Pain:	18.8	15.7	**0.005**
Graft Harvest Site Pain:	n/a	6.1	**<0.001**

*Therapeutic failures are patients who were assessed as having non-union or delayed union, or required secondary therapeutic intervention for non-union or delayed union

Week 52 Results

Results measured at 52 weeks also continued to show improvement. Fusion via CT scan was not measured at 52-weeks. Clinical healing status results for the full complement of joints were 86.2% for Augment and 87.6% for autograft for the full complement of joints; supporting non-inferiority at week 52 (p= 0.008). Clinical healing status results for all joints were 88.3% for Augment and 87.2% for autograft for the full complement of joints; also supporting non-inferiority at week 52 (p < 0.001).

Augment Bone Graft demonstrated 36.9% and 48.5% of patients achieving union via three (3) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 36.5% (p=0.020) and 44.3% (p < 0.001) of patients achieving radiographic union on three (3) radiographic aspects for full complement and all joints, respectively. Augment Bone Graft demonstrated 70.8% and 77.2% achieving union on two (2) radiographic aspects for full complement and all joints analyses, respectively. Autograft demonstrated 75.2% (p=0.115) and 77.8% (p=0.005) of patients achieving radiographic union on two (2) radiographic aspects for full complement and all joints, respectively.

Rates of clinical success (defined by improved pain with weight-bearing and lack of requirement for secondary therapeutic intervention) at week 52 were 76.9% and 78.1% for Augment and autograft, respectively (p=0.022).

The therapeutic failure rate was calculated, based upon a determination of either delayed union or non-union, or if the patient required a therapeutic intervention or a secondary procedure to address delayed union or non-union. At week 52, 7.3% of Augment Bone Graft patients were declared therapeutic failures, compared with 8.0% of autologous bone graft patients, supporting non-inferiority (p<0.001).

Quality-of-life and functional outcomes scores included SF-12, FFI, and AOFAS Ankle-Hindfoot questionnaires. At week 52, the Augment Bone Graft patients reported a mean SF-12 Physical Component Score (PCS) of 42.4 (improvement from 31.0 at screening), compared with 45.0 in the autologous bone graft group (improvement from 31.6 at screening); a mean FFI total

score of 20.1 (improvement from 51.6 at screening), compared with 17.5 in the autologous bone graft group (improvement from 48.6 at screening); and a mean AOFAS Ankle-Hindfoot total of 77.8 (improvement from 40.4 at screening), compared to 78.2 in the autologous bone graft group (improvement from 40.8 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

Pain assessments were made on a visual analog scale (VAS) regarding overall fusion site pain and pain on weight-bearing. At week 52, Augment Bone Graft patients reported a mean overall fusion site pain assessment of 13.2 mm, versus a mean pain assessment of 12.9 mm in autologous bone graft patients overall ($p < 0.001$). For weight-bearing pain at week 52, Augment Bone Graft patients reported a mean assessment of 15.6 mm on weight-bearing versus a mean assessment of 15.8 mm when weight-bearing in autologous bone graft patients overall ($p < 0.001$). These results demonstrated statistical significance for non-inferiority of Augment Bone Graft versus autologous bone graft. For subjects who were treated with autologous bone graft, pain at the bone graft harvest site was recorded. Notably, 8.8% of subjects in the autograft treatment group reported clinically significant pain at 52 weeks post-operatively.

A summary of results at Week 52 is presented below:

Week 52 Results Summary

	Augment™ Bone Graft	Autologous Bone Graft	Non-inferiority test p-value
Subjects (N=397)	**(N=260)**	**(N=137)**	
Individual joints [All Joints] (N=597)	**(N=394)**	**(N=203)**	
Plain Film Radiographic Union Rates (3 Aspects)			
Full Complement ofJoints:	36.9%	36.5%	**0.020**
All Joints (assessed individually):	48.5%	44.3%	**<0.001**
Plain Film Radiographic Union Rates (2 Aspects)			
Full Complement of Joints:	70.8%	75.2%	0.115
All Joints (assessed individually):	77.2%	77.8%	**0.005**
Clinical Healing Status at the Patient Level:	87.7%	88.3%	**0.003**
Clinical Healing Status by Joint			
Full Complement of Joints:	86.2%	87.6%	**0.008**
All Joints (assessed individually):	88.3%	87.2%	**<0.001**
Clinical Success Rate:	76.9%	78.1%	**0.022**

Therapeutic Failure Rate*:	7.3%	8.0%	**<0.001**
SF-12 Mean PCS:	42.4	45.0	**0.015**
FFI Mean Total Score:	20.1	17.5	**<0.001**
AOFAS Mean Total Score:	77.8	78.2	**<0.001**
Fusion Site Pain:	13.2	12.9	**<0.001**
Weight-bearing Pain:	15.6	15.8	**<0.001**
Graft Harvest Site Pain:	n/a	6.1	**<0.001**

*Therapeutic failures are patients who were assessed as having non-union or delayed union, or required secondary therapeutic intervention for non-union or delayed union

Safety:

Of 973 reported treatment-emergent adverse events (TEAEs), there were no remarkable differences in incidence between treatment groups. Of note, there were fewer related TEAEs in the Augment Bone Graft group (2.2% versus 4.2%). There were also fewer serious TEAEs in the Augment Bone Graft group (10.3% versus 14.8%) and analysis of coding revealed fewer surgical complications noted as infections for Augment Bone Graft (6.6% versus 7.7%). In the effectiveness evaluation, the surgical wound infection rate was also lower for Augment in the mITT population (8.8% versus 9.5%). Total TEAEs were similar between groups with an overall rate of 77.9% for Augment Bone Graft (212 of 272 patients) and 73.9% for autologous bone graft (105 of 142 patients).

Nine surgical wound infections met the criteria for serious TEAEs; of these serious surgical wound infections, 4 were in the Augment Bone Graft treatment group (in 3 patients; 1.1%) and 5 were in the autologous bone graft treatment group (3.5%). Notably, there was also a single incidence of deep wound infection at an autograft harvest site requiring medical/ surgical intervention, which is illustrative of the types of complications potentially related to the harvest of autologous graft.

Patients in the autologous bone graft group also continued to report clinically significant pain at the graft harvest site (≥ 20 mm) on VAS at and after the week 24 visit: 12.4% of autologous bone graft patients at week 24, 7.3% at week 36, and 8.8% at week 52.

In the week 24 analysis, 65 serious adverse events (SAEs) were reported for this study. However, 8 SAE cases were downgraded to non-serious AEs after further review by the primary investigator at the investigational site, resulting in a total of 57 SAEs reported within this study. In the safety population, 30 of the 272 Augment Bone Graft patients reported 32 SAEs, while 24 of the 142 autologous bone graft patients reported 25 SAEs. In a review of causality, all SAEs in the Augment Bone Graft group were assessed as “not related” to the study device.

A low percentage of patients tested positive for non-neutralizing binding antibodies to rhPDGF-BB (13.9% of Augment Bone Graft patients and 3.6% of autologous bone graft patients). At the 24 week follow up, 14 patients had a titer of binding antibodies and were asked to submit at least 2 additional serum samples three months apart. One patient at visit 6 who had a titer of binding antibodies, but did not give a sample at visit 8, was also asked to submit additional serum samples. Following subsequent serum analyses, all patients tested negative for anti-drug antibody (ADA), i.e. antibody level returned to baseline.

Importantly, none of the binding ADAs in the follow up patients have shown neutralizing activity.

A summary of the key safety results for the safety population is presented below. The p-values signify the difference between treatments, rather than non-inferiority testing.

	Augment™ Bone Graft (N=272)	Autologous Bone Graft (N=142)	Fisher Exact Test p-value
Pre-Treatment Signs and Symptoms	2.6%	2.8%	>0.999
Treatment Emergent Adverse Events (TEAEs)	77.9%	73.9%	0.393
Serious TEAEs	10.3%	14.8%	0.201
Related TEAEs	2.2%	4.2%	NA
Overall complications	35.3%	38.7%	0.519
Complications associated with surgical procedure	23.9%	30.3%	NA
Serious complications	5.1%	6.3%	0.654
Infections	8.5%	11.3%	0.378

CONCLUSIONS

Effectiveness Conclusions:

The results from the statistical analyses revealed statistically significant and clinically relevant benefits for the Augment Bone Graft, compared to the gold standard of autograft. In addition, the results from both study groups, which include patients with substantial co-morbidities, are comparable to available historical literature for union rates associated with autograft. The results from the effectiveness analysis are presented based upon the mITT patient population which is defined as all randomized patients who were eligible, properly randomized, and received treatment according to the study protocol.

At the primary endpoint 24 weeks post-surgery, a statistically significant CT fusion rate (defined as at least 50% osseous bridging) was demonstrated for non-inferiority of Augment Bone Graft to autograft for the full complement as well as individual joints analyses ($p=0.038$ and $p<0.001$, respectively) indicating that the full complement fusion rates (61.2% for Augment and 62.0% for autograft) are equivalent between the two groups, as analyzed by the most rigorous methodology (CT scan).

Other effectiveness data support statistical significance for non-inferiority across a range of secondary endpoints via multiple outcome measures (radiologic, clinical, functional and patient-reported measures of success), forming a robust comparison to the current clinical standard of autologous bone graft. In addition to the primary endpoint, the following non-inferiority tests are also significant at week 24 in the mITT population:

- Plain film radiographic union rate (at 3 aspects) for all individual joints
- Plain film radiographic union rate (at 2 aspects) for all individual joints
- Clinical healing status for the full complement of joints, all individual joints

- Therapeutic failure rate (non-union, delayed union or requiring secondary therapeutic intervention
- Composite Success Rate
- SF-12 mean PCS
- FFI mean total score
- AOFAS mean total score

Data after 24 Weeks

Success rates for Augment Bone Graft patients continued to improve for radiographic and clinical endpoints after week 24, consistent with success rates for autograft.

The clinical study results demonstrated that Augment Bone Graft provided for osseous fusion equivalent (i.e. non-inferior) to autograft. Furthermore, Augment Bone Graft demonstrated non-inferiority to autograft for radiologic, clinical, functional, and quality of life assessments. Notably, examination of the 20 measurements composing the primary and secondary endpoints (encompassing radiographic fusion, clinical observation, subject pain and subject function) shows that all but one measurement achieved statistical significance for non-inferiority for at least one timepoint assessed at 24, 36 or 52 weeks post-operatively.

Safety Conclusions:

The key safety conclusions from the trial are that patients treated with Augment Bone Graft had fewer serious TEAEs, fewer overall complications, fewer complications associated with the surgical procedure, fewer serious complications, fewer serious surgical complications and fewer infections than patients treated with autologous bone graft, although these analyses were not statistically superior. Further, the elimination of pain and morbidity resulting from the surgical approach in harvesting autologous graft provides additional benefit to patients receiving Augment Bone Graft. Graft harvest site pain is significant by its absence in Augment Bone Graft patients. Given that the primary 24-week effectiveness endpoint is equivalent (i.e. non-inferior) to autograft, the reduction of complications and elimination of harvest site pain and morbidity are substantial benefits of Augment Bone Graft.

In conclusion, the data demonstrate that use of Augment Bone Graft stimulated equivalent clinical and radiologic healing to autograft as determined by the patients, the surgeons and a masked independent radiologist, with fewer complications and without the additional patient pain and morbidity associated with a separate surgical site to harvest autologous bone. Consequently, the benefits of the device outweighed any potential risks.

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Primary Endpoint:					
CT fusion (%)	Full Complement of Joints	Week 24	61.2	62.0	0.038
Secondary Endpoints:					
Radiographic :					
CT fusion (%)	All Joints	Week 24	66.5	62.6	<0.001
	All Joints	Week 36	68.8	73.9	0.103
	Full Complement of Joints	Week 36	63.5	69.3	0.202
Radiographic Union (3 Aspects) (%)	Full Complement of Joints	Week 24	30.8	32.8	0.054
	Full Complement of Joints	Week 36	30.0	35.8	0.198
	Full Complement of Joints	Week 52	36.9	36.5	0.020
Radiographic Union (3 Aspects) (%)	All Joints	Week 24	38.3	37.9	0.007
	All Joints	Week 36	39.1	42.9	0.072
	All Joints	Week 52	48.5	44.3	<0.001
Radiographic Union (2 Aspects) (%)	Full Complement of Joints	Week 24	60.8	66.4	0.194
	Full Complement of Joints	Week 36	62.7	69.3	0.249
	Full Complement of Joints	Week 52	70.8	75.2	0.115
Radiographic Union (2 Aspects) (%)	All Joints	Week 24	67.5	70.9	0.049
	All Joints	Week 36	70.3	72.4	0.021
	All Joints	Week 52	77.2	77.8	0.005
Clinical Union:					

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Clinical Healing (%)	Patient	Week 24	83.1	83.9	0.010
	Patient	Week 36	84.6	88.3	0.038
	Patient	Week 52	87.7	88.3	0.003
Clinical Healing (%)	Full Complement of Joints	Week 24	82.3	83.2	0.011
	Full Complement of Joints	Week 36	84.2	86.9	0.022
	Full Complement of Joints	Week 52	86.2	87.6	0.008
Clinical Healing (%)	All Joints	Week 24	83.5	83.3	<0.001
	All Joints	Week 36	86.8	85.7	<0.001
	All Joints	Week 52	88.3	87.2	<0.001
Delayed/Non-Union (%)	Patient Level	Week 24	8.8	10.2	<0.001
		Week 36	6.5	8.0	<0.001
		Week 52	4.2	5.8	<0.001
Therapeutic Failure Rate (%)	Patient Level	Week 24	9.2	10.9	<0.001
		Week 36	7.7	9.5	<0.001
		Week 52	7.3	8.0	<0.001
Composite Success (%)	Patient Level	Week 24	70.8	69.3	0.009
		Week 36	71.5	77.4	0.179

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Clinical Success (%)	Patient Level	Week 24	74.6	78.1	0.071
		Week 36	73.8	75.9	0.041
		Week 52	76.9	78.1	0.022
Functional:					
SF-12 (Mean PCS)	Patient Level	Week 24	39.9	41.4	<0.001
		Week 36	41.4	44.2	0.020
		Week 52	42.4	45.0	0.015
FFI (Mean Total Score)	Patient Level	Week 24	27.38	22.30	0.012
		Week 36	21.96	18.19	0.001
		Week 52	20.08	17.52	<0.001
AOFAS (Mean Total Score)	Patient Level	Week 24	71.7	73.9	<0.001
		Week 36	75.0	77.3	<0.001
		Week 52	77.8	78.2	<0.001
Pain:					
Fusion Site Pain (Mean)	Patient Level	Week 24	18.9	16.5	0.001
		Week 36	16.2	13.9	
		Week 52	13.2	12.9	<0.001
Weight-Bearing Pain (Mean)	Patient Level	Week 24	23.5	19.3	0.016
		Week 36	18.8	15.7	0.005
		Week 52	15.6	15.8	<0.001

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Significant Graft Site Pain (%)	Patient Level	Week 24	0	12.4	<0.001
		Week 36	0	7.3	<0.001
		Week 52	0	8.8	<0.001
Graft Harvest Site Pain	Patient Level	Week 24	0	8.1	<0.001
		Week 36	0	6.1	<0.001
		Week 52	0	6.1	<0.001
Safety Endpoints:					
Serious TEAE (%)	All Patients	Week 24	7.7	14.1	0.055
Surgical Complications (%)	All Patients	Week 24	23.5	29.6	0.193
Serious Complications (%)	All Patients	Week 24	4.4	6.3	0.480
Infections (%)	All Patients	Week 24	7.7	9.9	0.462
Serious TEAE (%)	All Patients	Week 52	10.3	14.8	0.201
Surgical Complications (%)	All Patients	Week 52	23.9	30.3	0.195
Serious Complications (%)	All Patients	Week 52	5.1	5.3	0.654
Infections (%)	All Patients	Week 52	8.5	11.3	0.378

XI. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics

Patients randomized to Augment Bone Graft tended to be female (52.3%), while patients randomized to autologous bone graft tended to be male (56.4%). The mean age of all patients in the study was 56.6 years, with the mean and median ages in the autologous bone graft group about 1 year older than the mean and median ages for all patients in the study. Any other differences in demographic characteristics between the treatment groups were minor.

A post-traumatic injury/deformity was the most common reason for study surgery, reported in 48.2% of all patients (comparable between groups), with primary arthritis reported in 34.3% of patients (about 5% higher in autologous bone graft patients). The incidence of baseline rheumatoid arthritis was about 5% higher in the Augment Bone Graft group.

The most common risk factor noted was obesity, reported in 48.4% of patients (6% higher in the autologous bone graft patients). There were a notable number of patients (23.3%) with a previous history of non-fusion surgery at the fusion site(s). A significant number of patients in both treatment groups reported a history of smoking within 5 years of study entry (24.9% Augment Bone Graft and 22.8% of autologous bone graft patients). As noted in the table below (Demographics and Clinical Characteristics), 40/285 (14%) of Augment Bone Graft subjects reported current smoking (mean of 9.3 cigarettes/day). Conversely, it is noted that only 12/149 (8.1%) of autograft patients reported current smoking (mean of 14.0 cigarettes/day). Thus, the Augment treatment group had a higher percentage of current smokers than the autograft group.

Demographics and clinical characteristics are summarized for all patients in the ITT population in the table below. Five patients who were randomized but did not have study surgery represented the only missing demographic data.

Demographic & Clinical Characteristics at Baseline - ITT Population

	All Patients (N=434)	Augment Bone Graft (N=285)	Autologous Bone Graft (N=149)
Gender			
Male	216 (49.8%)	132 (46.3%)	84 (56.40%)
Female	213 (49.1%)	149 (52.3%)	64 (43.00%)
Missing	5 (1.20%)	4 (1.40%)	1 (0.70%)
Age (years)			
N	429	281	148
Mean	56.6	56.2	57.5
Standard deviation	14.09	14.56	13.15
Median	58.7	58.6	59.7

Min-Max	19.8 - 86.2	19.8 - 86.2	20.3 - 82.2
BMI (kg/m^2)			
N	433	285	149
Mean	30.8	30.7	31.1
Standard deviation	5.69	5.63	5.82
Median	30	30	31
Min-Max	19 - 45	19 - 45	20 - 44
Affected Foot/Ankle			
Right	222 (51.2%)	142 (49.8%)	80 (53.70%)
Left	189 (43.5%)	130 (45.6%)	59 (39.60%)
Bilateral	18 (4.10%)	9 (3.20%)	9 (6.00%)
Missing	5 (1.20%)	4 (1.40%)	1 (0.70%)
Foot/Ankle to be treated			
Right	230 (53.0%)	147 (51.6%)	83 (55.70%)
Left	199 (45.9%)	134 (47.0%)	65 (43.60%)
Missing	5 (1.20%)	4 (1.40%)	1 (0.70%)
Age of Injury/Deformity at Baseline (Weeks)			
N	270	177	93
Mean	279.6	261.1	314.8
Standard deviation	458.78	460.62	455.66
Median	115.2	96.4	132.9
Min-Max	1.1 - 2591	1.1 - 2591	3.1 - 2116.4
Description of Injury/Deformity			

Primary Arthritis	149 (34.3%)	93 (32.60%)	56 (37.60%)
Rheumatoid Arthritis	29 (6.70%)	24 (8.40%)	5 (3.40%)
Post-traumatic injury/deformity	209 (48.2%)	139 (48.8%)	70 (47.00%)
Ankylosing spondylitis	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	42 (9.70%)	25 (8.80%)	17 (11.40%)
Missing	5 (1.20%)	4 (1.40%)	1 (0.70%)
Risk factors			
Smoking history within last five years	105 (24.2%)	71 (24.90%)	34 (22.80%)
Obesity (BMI >= 30 kg/m2)	210 (48.4%)	132 (46.3%)	78 (52.30%)
Previous revision surgery*	101 (23.3%)	65 (22.80%)	36 (24.20%)
Diabetes history (type 1 or 2)	52 (12.00%)	32 (11.20%)	20 (13.40%)

Note: Percents are based on the number of patients in the ITT population.
* This includes any surgery at the revision site(s).

XII. ADVERSE EFFECTS THAT OCCURRED IN THE PMA CLINICAL STUDY:

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

Additionally, per protocol all treated subjects were immobilized through week 12.

Per the SAE listing, there were a total of 9 subject reported with DVT/PE (5 Augment and 4 Autograft).

There were no trends noted in occurrence or recurrence of cancers. There were five (5) SAEs related to cancer (3 Augment and 2 Autograft).

The total numbers of SAEs is given in the table below.

SAE's

	Augment Bone Graft	Autologous Bone Graft
Number of SAE's Reported	39	26
Causality:		
Related	0	0
Not related	39	25
Unlikely	0	1
Event Outcome:		
Recovered/resolved	30	20
Not recovered/not resolved	4	3
Recovered/resolved with sequelae	4	3
Death	1	0

Augment Bone Graft was shown to be safe and effective as a bone graft substitute in a large, randomized clinical trial involving 434 patients. These conclusions are based upon radiologic, clinical, and functional measurements. Further, these assessments include masked independent radiologic measurements, investigator assessments, and patient-initiated measurements; thereby establishing a highly robust dataset by which to assess safety and effectiveness.

The data quality in this randomized, controlled clinical study was assured through: 1) the use of a masked independent assessment for the primary endpoint (CT fusion rate); 2) the use of an independent CRO which analyzed the study data in accordance with GCPs; 3) the integration of independent, physician, and patient-initiated outcomes assessments. Moreover, the kappa analysis demonstrated a high degree of reliability (κ=0.70 for intra-examiner reliability) in the CT analysis by the independent radiologist.

Consistent with the extensive biocompatibility profile on the combination product and the historical safe use of each individual component, the study revealed no evidence of either local or systemic adverse effects. There were no adverse outcomes attributable to the study device and the device was found to be safe. Further it is clinically important to surgeons and patients that, that, with use of Augment, there was no pain or morbidity associated with bone graft harvest.

Augment Bone Graft was found to be as effective a treatment as autograft for hindfoot and ankle fusion procedures, as shown by:

- CT fusion rate (full complement of joints and all joints analyses);
- Plain film radiographic union rate (at 3 aspects) for all joints
- Plain film radiographic union rate (at 2 aspects) for all joints
- Clinical healing status for the full complement of joints and all joints
- Therapeutic failure rate
- SF-12 mean PCS
- AOFAS mean score
- FFI mean scores

XIII. CONCLUSIONS

Three additional trials in foot and ankle fusions were also performed. Both a controlled pilot (n=20) and two open-label trials (n=60 and n=108) demonstrated comparable results to the primary trial. Therefore, the results of the primary trial together with extensive and confirmatory data from *in vitro*, animal and human studies demonstrate that Augment Bone Graft stimulates bone healing and fusion in musculoskeletal applications.

As a fully synthetic product, the risk-to-benefit assessment establishes the Augment Bone Graft device to have a sound and compelling clinically significant beneficial effect as measured by standard and accepted outcomes with minimal or no risks. Further, using the most rigorous and cutting edge imaging methodologies available, Augment Bone Graft has demonstrated equivalent fusion outcomes as autograft.

In summary, Augment Bone Graft achieved statistically non-inferior results for CT fusion rate at six (6) months, compared to the autograft control group. The durability of these results was confirmed by the clinical outcomes, including clinical healing status at both the 6 and 12 month timepoints. The clinical significance of these results was further underscored by the relative high risk patient populations and are confirmed by a comparison to historical literature. Additionally, 8.8% of Autograft patients had clinically significant graft harvest site pain at 12 months and the absence of this pain in Augment patients is a significant benefit. Therefore, it is concluded that

Augment Bone Graft was shown to achieve clinical and radiographic effectiveness for the use as a bone graft substitute in hindfoot and ankle fusion procedures with a superior safety profile.

XIV. PANEL RECOMMENDATION

TBD

XV. CDRH DECISION

TBD

XVI. APPROVAL SPECIFICATIONS

Directions for Use: See labeling.

Hazards to health from use of the device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling

Post approval requirements and restrictions: See approval order.