

# AUGMENT<sup>®</sup> INJECTABLE PACKAGE INSERT

## I. PRODUCT DESCRIPTION

AUGMENT<sup>®</sup> 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 - beta tricalcium phosphate ( $\beta$ -TCP) granules and a collagen matrix.

The  $\beta$ -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 100-300 $\mu$ m.

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  $\beta$ -TCP granules to form a composite matrix that is 80%  $\beta$ -TCP and 20% bovine Type I collagen. The matrix is then lyophilized, mechanically shredded and sieved. The shredded  $\beta$ -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 rhPDGF-BB component of AUGMENT<sup>®</sup> Injectable is identical to the rhPDGF-BB contained in AUGMENT<sup>®</sup> Bone Graft (P100006).

Recombinant human platelet-derived growth factor B homodimer (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<sub>43</sub> and Cys<sub>52</sub> 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<sup>®</sup> 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  $\beta$ -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<sup>®</sup> Injectable**

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

## **II. STORAGE CONDITIONS**

AUGMENT<sup>®</sup> Injectable must be stored at refrigerated temperature (2-8°C, 36-46°F). Do not

freeze.

### **III. INDICATIONS FOR USE**

AUGMENT<sup>®</sup> 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.

### **IV. CONTRAINDICATIONS**

AUGMENT<sup>®</sup> 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 or bovine collagen-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.

### **V. WARNINGS AND PRECAUTIONS**

#### Warnings:

- As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of AUGMENT<sup>®</sup> Injectable. The immune response to rhPDGF-BB was evaluated for AUGMENT<sup>®</sup> Injectable in two studies, in two pilot and one pivotal study for ankle and hindfoot arthrodesis procedures. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AUGMENT<sup>®</sup> Injectable with the incidence of antibodies to other products may be misleading.
- Women of childbearing potential should avoid becoming pregnant for one year following treatment with AUGMENT<sup>®</sup> Injectable. The implantation of rhPDGF-BB in women and the influence of their development of anti-PDGF-BB antibodies, with or without neutralizing activity, on human fetal development are not known.

- The safety and effectiveness of AUGMENT<sup>®</sup> Injectable in nursing mothers has not been established. It is not known if rhPDGF-BB is excreted in human milk.
- The safety and effectiveness of AUGMENT<sup>®</sup> Injectable has not been established in anatomical locations other than the ankle or hindfoot, or when combined with autologous bone or other bone grafting materials.
- The safety and effectiveness of repeat applications of AUGMENT<sup>®</sup> Injectable have not been established.
- The safety and effectiveness of AUGMENT<sup>®</sup> Injectable in pediatric patients below the age of 18 years have not been established.
- AUGMENT<sup>®</sup> Injectable does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.
- The  $\beta$ -TCP component is radiopaque, which must be considered when evaluating radiographs for the assessment of bridging bone. The radiopacity may also mask underlying pathological conditions. Over time, the  $\beta$ -TCP is intended to be resorbed at the fusion site and replaced by new bone. Under such circumstances, it would typically be indistinguishable from surrounding bone.

Precautions:

- It is not known if some routine ankle arthrodesis subjects requiring less than 3cc of graft material substantially benefit from any type of graft material or if their results would be as good even if no graft material was used. Further study of these subjects would be required to make this determination. Therefore, physicians should use their clinical judgment in determining if subjects with these criteria would benefit from the addition of any graft material.
- In order to enhance the formation of new bone, AUGMENT<sup>®</sup> Injectable 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<sup>®</sup> Injectable should be implanted to fill all osseous defects and gaps, while ensuring that it does not prevent direct bony apposition of the articular surfaces intended for fusion.
- Careful consideration should be given to alternative therapies prior to performing bone grafting in patients who have severe endocrine-induced bone diseases (e.g., hyperparathyroidism); who are receiving immunosuppressive therapy; or who have known conditions that may lead to bleeding complications (e.g., hemophilia).
- AUGMENT<sup>®</sup> Injectable should only be used by surgeons who are familiar with bone grafting techniques used in ankle and hindfoot surgery.

- AUGMENT<sup>®</sup> 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. See cancer events under safety and effectiveness results section below.
- AUGMENT<sup>®</sup> Injectable 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 for visible damage. If damage is visible, do not use the product. Do not use if the safety seal is broken. Retain the packaging and contact a representative of Wright Medical.
- Do not use after the expiration date located on the product carton. The product expires on the last day of the month indicated on the carton label.

## **VI. SUMMARY OF 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<sup>®</sup> Bone Graft which consists of  $\beta$ -TCP granules and rhPDGF-BB. The investigational graft material in the other two studies (BMTI-2009-01 and BMTI-2010-01) was AUGMENT<sup>®</sup> Injectable, consisting of different  $\beta$ -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<sup>®</sup> Bone Graft and AUGMENT<sup>®</sup> 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:

### **1<sup>st</sup> data source - BMTI-2006-01 (AUGMENT<sup>®</sup> Bone Graft clinical study performed in the US under IDE G050118)**

The data from the control population of this study was used to supplement the control population data from the clinical study that evaluated AUGMENT<sup>®</sup> 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<sup>2</sup>
- 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  $\pm$  7 days, 9 weeks  $\pm$  7 days, 12 weeks  $\pm$  7 days, 16 weeks  $\pm$  7 days, 24 weeks  $\pm$  14 days, 36 weeks  $\pm$  14 days and 52 weeks  $\pm$  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 ( $\leq$  6 months), delayed union ( $\leq$  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.

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 AP, lateral and oblique views of the ankle and AP, lateral, 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 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 ( $\geq$  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 is 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.

**2<sup>nd</sup> data source - BMTI-2009-01 (AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 tibiototalcalcaneal (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<sup>2</sup>
- 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 -)
- 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, 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 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  $\beta$ -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 (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 ( $\geq 50\%$  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  $\geq 6$  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.

### **3<sup>rd</sup> 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 this, 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), 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 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<sup>2</sup>
- 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 -)
- neuro 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 ( $\geq 36$  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 endpoints 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  $\leq 20$ mm 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  $\geq 20$ mm reduction on VAS pain assessment of fusion site (performed prior to all other functional assessments and rehabilitation procedures at each visit)
- assessment of  $\beta$ -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*

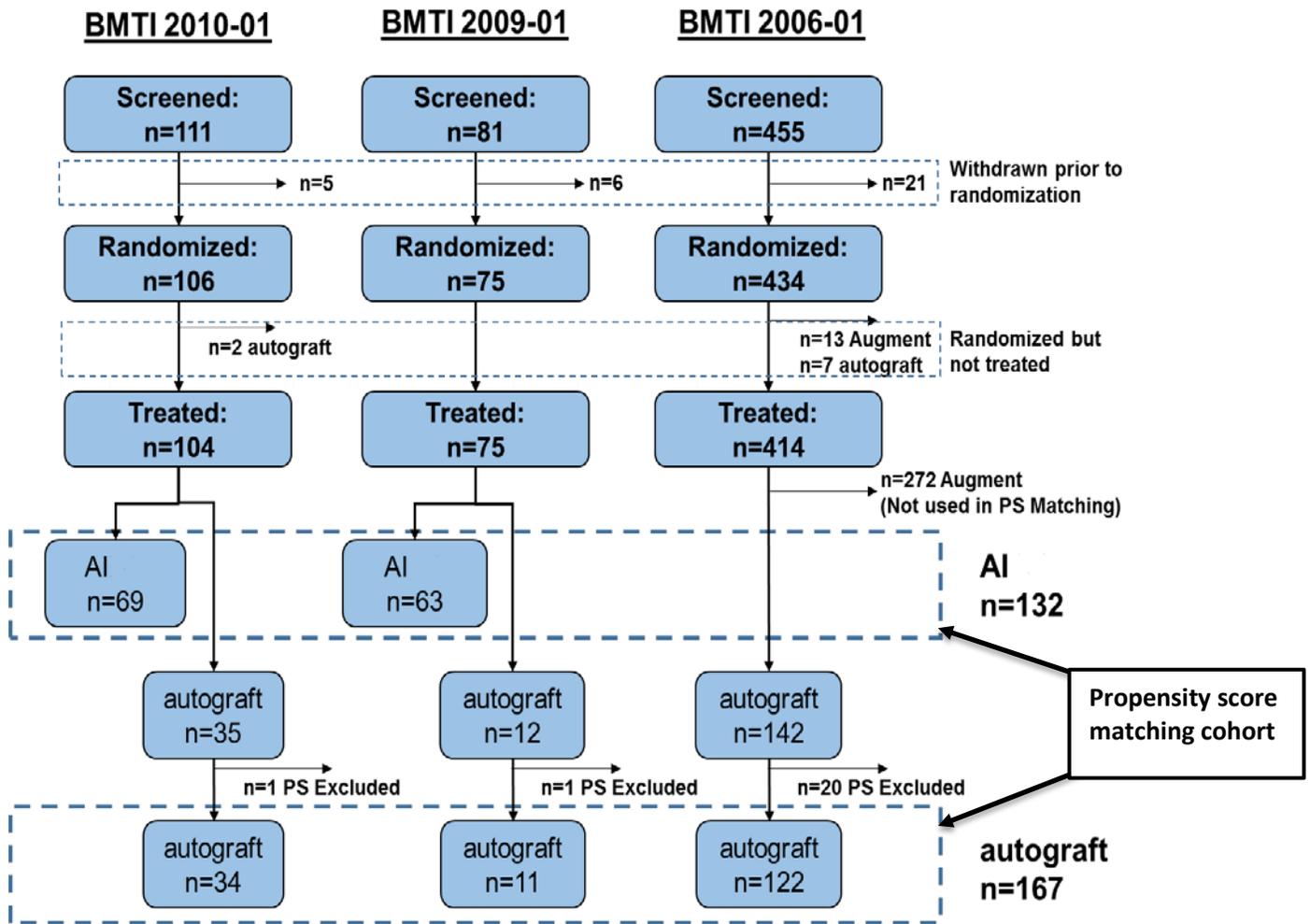
- operative time
- wound infection rate
- pain scores at any secondary surgical site
- overall AEs
- pain at graft harvest site (assessed prior to collection of other functional assessments and rehab)

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.

**Combined dataset – subject accounting and demographics**

Because each of the three datasets described above incorporated different inclusion/exclusion criteria and endpoints, e.g., foot fusion alone vs. 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<sup>®</sup> 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 1** presents the number of subjects who withdrew prior to randomization for each study.

**Table 1: Study Withdrawals Pre-randomization**

Pre-randomization withdrawal	Subjects
BMTI 2009-01	6
BMTI 2010-01	5
BMTI 2006-01	21
<b>Total subjects withdrawn prior to randomization</b>	<b>32</b>

Randomized but not treated

**Table 2** presents the number of subjects in each study who withdrew following randomization but prior to treatment.

**Table 2: Study withdrawals post-randomization/pre-treatment**

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

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

Subject demographics

The baseline demographic factors for the treated subjects in the combined dataset are presented in **Table 3**. Overall, the baseline subject demographics in the investigational and control groups were similar, a consequence of the propensity score matching algorithm.

**Table 3: Demographics & Clinical Factors**

	AUGMENT Injectable (AI) N=132	Autograft N=167	AI vs Autograft P-value*
<b>Sex</b>			0.816
Male	70 (53.03%)	86 (51.5%)	
Female	62 (46.97%)	81 (48.5%)	
<b>Affected Foot/Ankle</b>			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 <sup>1</sup>	21 (15.91%)	17 (10.18%)	
Triple arthodesis <sup>2</sup>	19 (14.39%)	36 (21.56%)	
Ankle-Hindfoot fusion	0 (0.0%)	0 (0.0%)	
<b>Ever smoked</b>			0.562
No	61 (46.21%)	83 (49.7%)	
Yes	71 (53.79%)	84 (50.3%)	
<b>Obese (BMI &gt;= 30)</b>			0.061
No	68 (51.52%)	68 (40.72%)	
Yes	63 (47.73%)	99 (59.28%)	
<b>Older (&gt;= 65 yo)</b>			0.133
No	97 (73.48%)	109 (65.27%)	
Yes	35 (26.52%)	58 (34.73%)	
<b>Baseline Weight Bearing Pain &gt; 40mm</b>			0.569
No	12 (9.09%)	19 (11.38%)	
Yes	120 (90.91%)	145 (86.83%)	
<b>Graft Material Used<sup>3</sup></b>			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

<sup>1</sup> Combination of any two of the joints: subtalar, talonavicular and calcaneocuboid joint

<sup>2</sup> Subtalar, talonavicular, and calcaneocuboid joints

<sup>3</sup> 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.

### 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

## Safety and Effectiveness Results

### 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 Event Summary***

A summary of the AEs by MedDRA class through 52 weeks follow-up is presented in **Table 4**. 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 4: Summary of Treatment Emergent Adverse Events through 52 weeks post-treatment**

	<b>AUGMENT Injectable (n=132)</b>		<b>Autograft (n=167)</b>	
	<b>Events</b>	<b>Subjects</b>	<b>Events</b>	<b>Subjects</b>
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<sup>®</sup> 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<sup>®</sup> 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 5**.

**Table 5: Timecourse Distribution of Serious Treatment Emergent Adverse Events by SOC and PT through 52 weeks post-treatment**

System Organic Class Preferred Term	Visit																Total Events		
	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)				
	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 con				1															1
Impaired healing				1															1
Hepatobiliary disorders														1					1
Gallbladder pain														1					1
Immune system disorders	1																		1
Hypersensitivity	1																		1
Infections and infestations	1	1									3		1	1		1	1	3	6

System Organic Class Preferred Term	Visit																Total Events	
	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)			
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Clostridium difficile colitis												1						1
Infection		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
Arthralgia	1																	1
Osteoarthritis													1			1		1
Osteoporosis													1					1
Pain in extremity																1	1	1
Neoplasms benign, malignant and unspecified (		1													1			2
Endometrial cancer															1			1
Renal cell carcinoma stage unspecified		1																1
Pregnancy, puerperium and perinatal condition															1			1
Pregnancy															1			1
Psychiatric disorders					1						1							1
Alcohol withdrawal syndrome											1							1
Suicidal ideation					1													1
Renal and urinary disorders	1														1			1
Ureteric injury															1			1
Urinary tract infection	1																	1

	Visit																Total Events	
	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)			
System Organic Class Preferred Term	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
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<sup>®</sup> Injectable subjects (I) and autograft control subjects (C) through 52 weeks follow up is presented in **Table 6**. The infection types and rates were similar between the two treatment groups.

**Table 6: 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 con								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

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
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
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 disorder														1						1
Nasopharyngitis														1						1
Skin and subcutaneous tissue disorders			2					1			1								2	2

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	
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 7**. 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 7. Subsequent Secondary Surgical Interventions<sup>1</sup>**

Reason for Secondary Surgery <sup>2</sup>	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%)
<b>Total Procedures</b>	<b>0(0%)</b>	<b>2(1.2%)</b>	<b>12(9.1%)</b>	<b>14(8.4%)</b>	<b>30(22.7%)</b>	<b>21(12.6%)</b>

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

<sup>1</sup> 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.

<sup>2</sup> 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<sup>®</sup> 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 8**.

**Table 8. 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 & 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%)
<b>Total Procedures</b>	<b>13</b>	<b>15</b>	<b>12(9.1%)</b>	<b>14(8.4%)</b>	<b>34</b>	<b>25</b>	<b>30(22.7%)</b>	<b>21(12.6%)</b>

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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable subjects did not receive this procedure, a comparison of graft site pain would not be appropriate.

#### ***Cancer Events***

AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable. A human pharmacokinetic study that included seven patients receiving AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable or similar products containing rhPDGF-BB and  $\beta$ -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<sup>®</sup> 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<sup>®</sup> Bone Graft (which also contains rhPDGF-BB), 1.8% of AUGMENT<sup>®</sup> Bone Graft patients developed neoplastic events when compared to 1.4% of autograft patients. In the AUGMENT<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> Post-Approval Studies' Findings Regarding Cancer<sup>1,2</sup>

First, in a retrospective study of a medical claims database, cancer rates and overall cancer mortality were compared between 1622 patients who used REGRANEX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Gel did not have a greater incidence of post-treatment cancer, but patients treated with 3 or more tubes of REGRANEX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable in bone grafting procedures of the ankle and hindfoot due to:

- higher doses of rhPDGF-BB with REGRANEX<sup>®</sup> Gel compared to AUGMENT<sup>®</sup> 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 enzyme-linked immunosorbent assay (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<sup>®</sup> 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<sup>®</sup> Injectable or the autograft groups.

### **Safety Discussion**

The key safety conclusions from the trial are that subjects treated with AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable.

### **Effectiveness Results**

#### **Clinical Endpoints**

As outlined above, there were five clinical endpoints used to evaluate the effectiveness of AUGMENT<sup>®</sup> 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 9** presents pain on weight bearing data combined for the three studies.

**Table 9: Weight bearing pain\***

Week	AUGMENT Injectable			Autograft			diff	95% UB
	n	mean	std error	n	mean	std error		
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 10** describes the percentage of subjects achieving a  $\geq 20$ mm decrease in VAS pain on weight bearing from baseline. A 20mm decrease from baseline is considered a clinically meaningful reduction in pain.

**Table 10: Significant Weight Bearing Pain Reduction Rate Estimates (score  $\geq 20$ mm) Propensity Score Adjusted\***

AUGMENT Injectable (n <sub>max</sub> =132)	Autograft (n <sub>max</sub> =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 11** 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 11: Foot Function Index\***

Week	AUGMENT Injectable			Autograft			diff	95% UB
	n	mean	std error	n	mean	std error		
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 12** presents the percentage of subjects achieving a  $\geq 10$  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 12: Significant FFI Improvement Rate Estimates (score ≥ 10 point decrease) Propensity Score Adjusted\***

Week	AUGMENT Injectable (n <sub>max</sub> =132)			Autograft (n <sub>max</sub> =167)			95% CI LB	odds ratio
	x	n	%*	x	n	%*		
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 13** presents the AOFAS Ankle-Hindfoot scores over time for the three treatment groups.

**Table 13: AOFAS Total Score\***

Week	AUGMENT Injectable			Autograft			95% LB	diff
	n	mean	std error	n	mean	std error		
Baseline	132	43.3	1.5	16	43.6	1.3	-3.8	-0.3
9	126	61.5	1.1	15	61.5	1.0	-2.6	0.0
12	124	66.9	1.3	16	66.6	1.1	-2.7	0.3
16	129	69.9	1.3	16	71.2	1.1	-4.2	-1.2
24	129	73.4	1.5	16	75.5	1.3	-5.6	-2.1
36	124	77.5	1.5	16	78.9	1.3	-4.7	-1.4
52	125	79.5	1.6	16	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 14** presents the percentage of subjects achieving a  $\geq 20$  point increase in AOFAS Ankle-Hindfoot score over time.

**Table 14: Significant AOFAS Improvement Rate Estimates (score  $\geq 20$ )  
Propensity Score Adjusted\***

Week	AUGMENT Injectable (n <sub>max</sub> =132)			Autograft (n <sub>max</sub> =167)			95% CI LB	odds ratio
	x	n	%*	x	n	%*		
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 15** presents fusion site pain data combined for the three studies.

**Table 15: Fusion Site Pain\***

Week	AUGMENT Injectable			Autograft			diff	95% UB
	n	mean	std error	n	mean	std error		
Baseline	132	51.4	2.4	16	50.4	2.1	1.0	6.6
9	126	20.5	2.1	15	15.4	1.8	5.0	9.8
12	126	18.9	2.1	16	17.8	1.8	1.1	5.9
16	129	21.7	2.2	16	18.9	2.0	2.8	8.0
24	129	20.9	2.2	16	15.3	1.9	5.7	10.7
36	124	17.4	2.1	15	12.4	1.8	5.0	9.8
52	125	15.8	2.2	16	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 16** presents the percentage of subjects achieving a  $\geq 20$ mm decrease in VAS fusion site pain from baseline. A 20mm decrease from baseline is considered a clinically meaningful reduction in pain.

**Table 16: Significant Fusion Site Pain Reduction Rate Estimates (score  $\geq 20$ mm) Propensity Score Adjusted\***

Week	AUGMENT Injectable (n <sub>max</sub> =132)			Autograft (n <sub>max</sub> =167)			95% CI LB	odds ratio
	x	n	%*	x	n	%*		
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 AIBG 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 17** presents the timecourse of SF-12 physical function scores.

**Table 17: SF-12 PCS Total Score\***

Week	AUGMENT Injectable			Autograft			95% LB	diff
	n	mean	std error	n	mean	std error		

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

**Table 18: SF-12 PCS Improved (score > 5 points)  
Propensity Score Adjusted\***

Week	AUGMENT Injectable (n <sub>max</sub> =132)			Autograft (n <sub>max</sub> =167)			95% CI LB	odds ratio
	x	n	%*	x	n	%*		
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 19.

**Table 19: Summary of Effectiveness Measurements for AUGMENT® Injectable and Autograft at 52 weeks**

<b>Effectiveness Measurement</b>	<b>AUGMENT® Injectable</b>	<b>Autograft</b>	<b>95% confidence limit for non-inferiority determination*</b>
<b><i>Pain Reduction (via VAS)<sup>1</sup></i></b>			
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
<b><i>Functional Improvement</i></b>			
Average change in Foot Function Index	-30.5	-33.3	7.9
Average change in AOFAS Total Score	35.9	35.7	-4.1
<b><i>Quality of Life Maintenance/Improvement</i></b>			
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<sup>®</sup> Injectable are achieved without the pain and morbidity associated with harvesting autograft bone.

## VII. CONCLUSIONS DRAWN FROM CLINICAL STUDIES

### Effectiveness Conclusions

The clinical data demonstrate that AUGMENT<sup>®</sup> Injectable is effective in:

- ***Pain Reduction:*** At 52 weeks, AUGMENT<sup>®</sup> 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 & Quality of Life Improvement:*** AUGMENT<sup>®</sup> 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<sup>®</sup> Injectable was non-inferior to autograft.

### Safety Conclusions

Adverse event reporting was utilized as a major element of the safety evaluation of AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable group and 3.6% in the autograft group. Subjects treated with AUGMENT<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injectable group, this finding provides additional benefit to patients receiving AUGMENT<sup>®</sup> Injectable.

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

### **Benefit-Risk Conclusions**

The probable benefits of AUGMENT<sup>®</sup> Injectable are based on data collected in the clinical trials as described above. AUGMENT<sup>®</sup> 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<sup>®</sup> Injectable patients did not require the need for autograft thereby avoiding pain and morbidity at a secondary harvest site. Based on the literature (<sup>3,4</sup> Baumhauer, 2013, Aug. & Nov.), 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<sup>®</sup> Injectable does not require autograft, these risks are eliminated with the use of AUGMENT<sup>®</sup> Injectable as an alternative to autograft.

### **Overall Conclusions**

The analysis of the clinical outcome from the combined dataset described above supports the safety and effectiveness of AUGMENT<sup>®</sup> 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<sup>®</sup> Injectable is not associated with the morbidity resulting from autograft harvesting.

## **VIII. PREPARATION FOR USE**

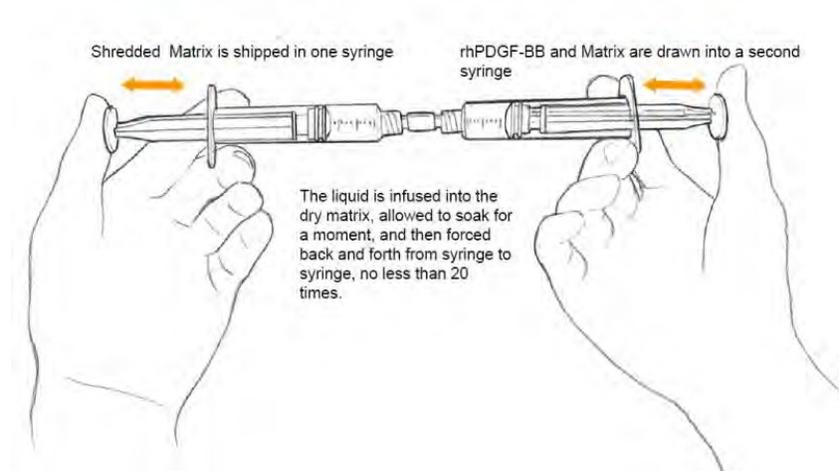
1. Completely withdraw the contents of the vial containing the rhPDGF-BB solution using

the empty syringe and the 18 gauge needle. After all of the fluid has been extracted from the vial, remove the needle and displace any air remaining in the syringe.

2. Remove the cap from the syringe containing the  $\beta$ -TCP/collagen matrix. Pull the plunger to the 10ml mark and tap the syringe to loosen the matrix.
3. Connect the syringe containing the rhPDGF-BB solution with the syringe containing the matrix using the female-to-female luer-lock connector.
4. Transfer the rhPDGF-BB solution into the syringe containing the matrix. After transferring all of the rhPDGF-BB solution, pull the plunger on the syringe containing the hydrated matrix past the 10ml mark.
  - a. Note: For the 1.5 cc kit, pull the plunger to the 5.5 ml mark.
5. Release the plunger of the syringe containing the hydrated matrix.

**Let the syringes sit undisturbed for a minimum of 90 seconds.**

6. AUGMENT<sup>®</sup> Injectable is then prepared by completely saturating the  $\beta$ -TCP/collagen matrix with the rhPDGF-BB solution, as shown in the following diagram:



7. After hydrating the matrix, transfer the contents back and forth between the two syringes for no less than (20) twenty cycles. Note: A cycle is defined as passing the matrix to the empty syringe and back. Upon completion, the matrix should form a homogenous paste.
8. Transfer all of the paste to one of the syringes, and relieve any pressure built up during the mixing process by gently pulling the plunger containing the matrix.
9. Disconnect the empty syringe and female-to-female luer-lock connector from the syringe that contains the paste. Displace any air remaining in the syringe and connect the 14 gauge needle. The syringe is now ready to dispense the hydrated matrix into the surgical void.

## **IX. RECOMMENDED SURGICAL TECHNIQUE**

For recommended surgical technique, refer to the enclosed Surgical Technique Insert.

## X. REFERENCES

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

## XI. SYMBOLS:

	Consult instructions for use
	Caution
	Do not re-use
	Use-by date
	Prescription only
	Temperature limit
	Manufacturer
	Do not use if package is damaged
	Keep dry
	Catalogue number
	Batch code
	Sterilized using irradiation

**STERILE EO** Sterilized using ethylene oxide

**STERILE A** Sterilized using aseptic processing techniques

 Peel Here

### Catalog (REF) Numbers

REF	Product
K300-015-10	AUGMENT <sup>®</sup> Injectable 1.5 cc Kit
K300-030-10	AUGMENT <sup>®</sup> Injectable 3.0 cc Kit

Patent: [www.wright.com/patent](http://www.wright.com/patent)

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LBS164-00  
May, 2018

## AUGMENT® Injectable Surgical Technique Guide

AUGMENT® Injectable is a device/drug combination product for use in bone fusion of the foot/ankle.

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.

AUGMENT® Injectable combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable composite matrix comprised of 80% beta tricalcium phosphate ( $\beta$ -TCP) in granule particulate form (nominal particle size 100-300 $\mu$ m) and 20% bovine Type I collagen. The rhPDGF- BB functions as a chemo-attractant and mitogen for cells involved in wound healing and through its promotion of angiogenesis at the site of healing. The  $\beta$ - TCP acts as a bone void filler and as a scaffold for new bone growth. When mixed at the time of surgery, the three components combine to create a flowable gel-like consistency that allows the surgeon to place the product at the fusion site, using a 14 gauge blunt needle attached to a 10 ml syringe (included).

### **KIT COMPONENTS**

---

- 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  $\beta$ -TCP/bovine Type I collagen (ratio=4:1) matrix. Also included are an empty polypropylene syringe, one 14 gauge blunt tip needle for administration of the combination product, one 18 gauge needle (to draw up the PDGF from the vial), and female/female luer connector for mixing of the two components. The tray is sterilized by gamma irradiation.
  - The vial tray contains one vial, dependent on the kit configuration, of 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.

### **STERILITY**

---

- The contents within each kit are supplied sterile and are **for single use only**
- The contents of the kit are sterile until the expiration date printed on the package and must be used before this date
- The kit is not to be used in the event that any of kit seals are breached. Notify your sales representative or BioMimetic Therapeutics LLC directly
- The sterile  $\beta$ -TCP/collagen syringe is contained within a sterile tray
- The rhPDGF-BB vial is contained in a sterile tray
- Both the sterile  $\beta$ -TCP/collagen syringe and the rhPDGF-BB vial can be handled

in the sterile field

- AUGMENT® Injectable cannot be reused, and components of AUGMENT® Injectable must not be re-sterilized by any method

### **PREPARATION NOTES**

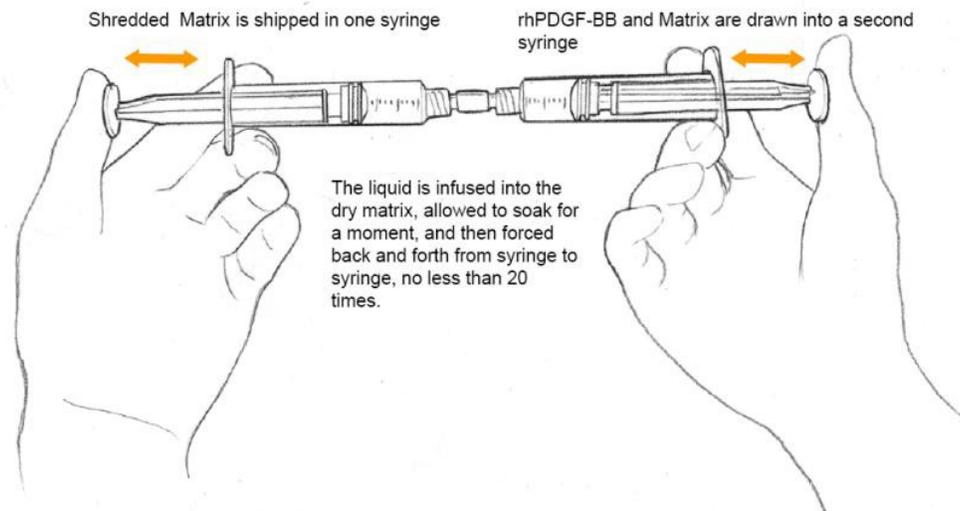
- Familiarization with the device and its handling properties, proper sterile surgical grafting techniques, and thorough surgical preparation of the host bone surfaces intended for arthrodesis and all associated bony defects are extremely important when using AUGMENT® Injectable.

### **AUGMENT® INJECTABLE PREPARATION**

1. Completely withdraw the contents of the vial containing the rhPDGF-BB solution using the empty syringe and the 18 gauge needle. After all of the fluid has been extracted from the vial, remove the needle and displace any air remaining in the syringe.
2. Remove the cap from the syringe containing the  $\beta$ -TCP/collagen matrix.
3. Pull the plunger to the 10ml mark and tap the syringe to loosen the matrix.
4. Connect the syringe containing the rhPDGF-BB solution with the syringe containing the matrix using the female-to-female luer-lock connector.
5. Transfer the rhPDGF-BB solution into the syringe containing the matrix. After transferring all of the rhPDGF-BB solution, pull the plunger on the syringe containing the hydrated matrix past the 10ml mark.

Note: For the 1.5 cc kit, pull the plunger to the 5.5 ml mark.

6. Release the plunger of the syringe containing the hydrated matrix. Let the syringes sit undisturbed for a minimum of 90 seconds.
7. AUGMENT® Injectable is then prepared by completely saturating the  $\beta$ -TCP/collagen matrix with the rhPDGF-BB solution, as shown in the following diagram:



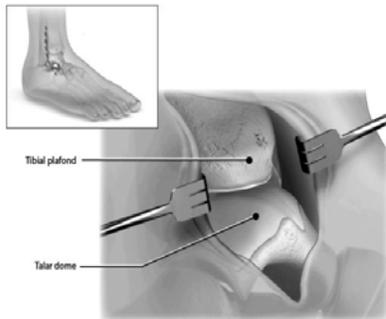
8. After hydrating the matrix, transfer the contents back and forth between the two syringes for no less than (20) twenty cycles. Note: A cycle is defined as passing the matrix to the empty syringe and back. Upon completion, the matrix should form a homogenous paste.
9. Transfer all of the paste to one of the syringes, and relieve any pressure built up during the mixing process by gently pulling the plunger containing the matrix.
10. Disconnect the empty syringe and female-to-female luer-lock connector from the syringe that contains the paste. Displace any air remaining in the syringe and connect the 14 gauge blunt needle. The syringe is now ready to dispense the hydrated matrix into the surgical void as described below in the “Recommended Surgical Technique” section.

## **RECOMMENDED SURGICAL TECHNIQUE**

**NOTE:** Always complete proper surgical preparation of all host articular surfaces intended for arthrodesis prior to implanting any graft material to these sites.

### **Preparation of the Joint**

1. In *standard fashion for arthrodesis surgery*, debride and denude all articular surfaces by exposing viable host bone and decorticating these surfaces. This will maximize an osseous healing response. Following exposure of the joint(s) intended for arthrodesis, all remaining cartilage should be removed. The opposing bony surfaces should be adequately prepared to optimize the osseous healing response and allow apposition of healthy, vascularized bone.



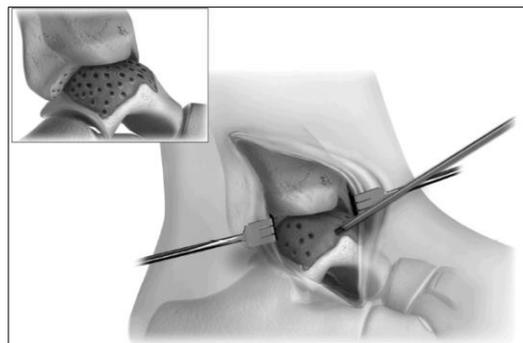
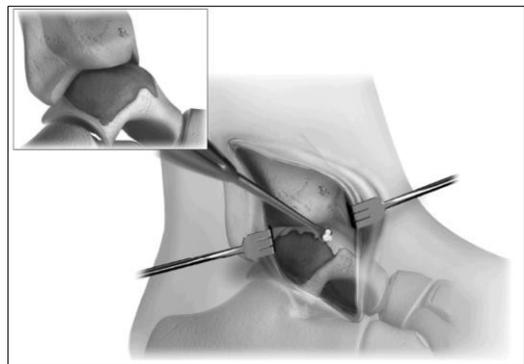
### **Preparation of the Bone Interface**

#### **2. Debridement**

Debridement should be performed by feathering and/or perforating the subchondral plate of all exposed articular surfaces intended for arthrodesis. This can be accomplished by using any standard technique and preferred combination of curettes, burrs, drill bits, and/or osteotomes as a means of maximizing the surface area of exposed bleeding bone (see below 2a and b).

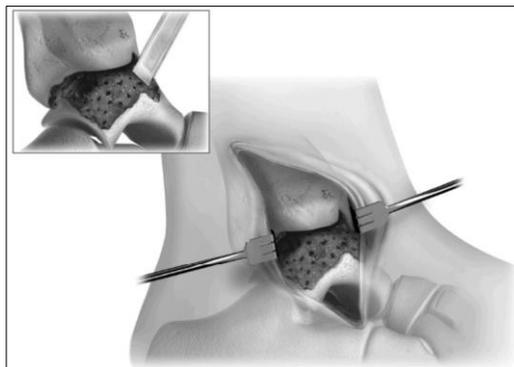
#### **2A. Perforation**

Some surgeons may prefer to perforate the cortical bone with drilling prior to placement of the AUGMENT® Injectable material. Drilling of the bone surface helps to create a bleeding bone environment to promote fusion.



## 2B. Feathering

Alternatively, other surgeons may choose to create subchondral exposure by using a burr, osteotome and/or curette to roughen and “feather” the joint surface to maximize the surface area of bleeding bone. **It does not matter which method is chosen (2A or 2B), as long as one of these two joint preparation techniques is employed subsequent to denuding all remaining joint cartilage and prior to implantation of any AUGMENT® Injectable.**



***Tip: In more severe deformities, portions of the talar head may need to be resected to reduce the deformity and create a good bone-on-bone interface.***

## Application of the Graft to the Implant Site

3. Using the prepared syringe (see AUGMENT® Injectable Preparation section, above), dispense the hydrated matrix into the void. Note: It may require an initial force to get the paste to flow through the 14 gauge needle. However, once the paste starts to flow, the force required to maintain a flow will be reduced.
4. Carefully apply the hydrated matrix to the surgical site (i.e. the subchondral voids, and surface irregularities visualized throughout the entire joint) such that the graft material is in contact with the entire osseous surfaces to be fused/repaired while allowing rigid fixation and primary bone contact to occur between the osseous surfaces. Immediately after joint reduction and hardware fixation of the fusion site, any remaining (unused) AUGMENT® Injectable should be applied around the external perimeter of the fusion construct.
  - *Because AUGMENT® Injectable does not harden or “set”, standard hardware implantation to ensure rigid fixation is necessary.*
  - In order to enhance the formation of new bone, AUGMENT® Injectable should be placed in direct contact with well-vascularized bone. Cortical bone may be perforated prior to placement of the AUGMENT® Injectable material.

***Remember: It is important to ensure that all bony defects are grafted. Adequate graft fill is needed to optimize results with any grafting material.***

5. Once AUGMENT® Injectable has been applied to the defect site, carefully layer periosteal and overlying soft tissue to enclose and contain the graft material.

6. Care should be taken not to irrigate the graft site following implantation of AUGMENT® Injectable.
  - *To guard against ectopic bone formation, take care to prevent AUGMENT® Injectable extrusion beyond the desired fusion regions, especially during hardware placement and joint reduction.*
7. Any remaining graft material should be discarded.

### **Fixation of the Joint**

8. Reduce the joint and apply rigid fixation.



### **Closure of the Site**

9. Following reduction and fixation, perform a carefully layered periosteal and capsular closure with the overlying soft tissues to enclose and contain all graft material in its intended joint spaces(s). Employ standard surgical technique to complete any remaining portion of the procedure.
10. Apply the self-adhesive labels that indicate the lot number of each device to the patient's permanent records and discard any remaining AUGMENT® Injectable.



**Please see the AUGMENT® Injectable Package Insert for information regarding contraindications, warnings, precautions and storage instructions.**

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LBS165-00  
May, 2018