AUGMENT® BONE GRAFT

℞ only

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I. DEVICE DESCRIPTION

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

Augment® Bone Graft combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable synthetic bone matrix (beta-tricalcium phosphate or β-TCP). The rhPDGF-BB functions as a chemo-attractant and mitogen for cells involved in wound healing and through its promotion of angiogenesis at the site of healing. The β-TCP acts as bone void filler to prevent soft tissue from collapsing into the void. When the β-TCP is placed near a viable host bone, it acts as a scaffold for new bone growth (osteoconductive).

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

- β-TCP: 1.5, 3, 6, or 9cc (particle size 1 to 2 mm)
- rhPDGF-BB: 1.5, 3, 6, or 9 mL (0.3 mg/mL in 20mM USP sodium acetate buffer)

Note: The finished component (vial/tray subassembly) is terminally sterilized

II. STORAGE CONDITIONS

Augment® Bone Graft must be stored at refrigerated temperature (2-8°C, 36-46°F). Do not freeze.

Figure 1: Augment® Bone Graft

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

III. INDICATIONS FOR USE

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

IV. CONTRAINDICATIONS

Augment® Bone Graft **should not**:

- be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products
- be used in patients with active cancer
- be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses)
- be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated
- be implanted in patients with an active infection at the operative site
- be used in situations where soft tissue coverage is not achievable
- be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes
- be used as a substitute for structural graft

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® Bone Graft. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal studies 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® Bone Graft 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® Bone Graft. 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® Bone Graft 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® Bone Graft 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® Bone Graft have not been established.
- The safety and effectiveness of Augment® Bone Graft in pediatric patients below the age of 18 years have not been established.
- Augment® Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.
- The β-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 β-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® Bone Graft 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® Bone Graft 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® Bone Graft should only be used by surgeons who are familiar with bone grafting techniques used in ankle and hindfoot surgery.
- Augment® Bone Graft contains becaplermin (rhPDGF-BB), which promotes cellular chemotaxis, proliferation and angiogenesis. rhPDGF-BB is also the active ingredient of two FDA approved products: 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® Bone Graft is supplied as a single use only kit. Discard any unused material. The individual components of this product should not be used separately. Use a new device for subsequent applications.
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, do not use the product. Do not use if the safety seal is broken. Retain the packaging and contact a representative of BioMimetic/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 STUDY

Study Design:

The Augment® Bone Graft pivotal study was a randomized, controlled study conducted under IDE at 37 centers in the U.S. and Canada to evaluate the safety and effectiveness of Augment® Bone Graft compared to autograft in hindfoot and ankle arthrodesis. A total of 414 patients were treated. Patients were randomized in a 2:1 ratio to either Augment® Bone Graft or autograft.

Study Population:

The patients enrolled in the study were at least 18 years of age and had a bone defect (surgically created osseous defects or osseous defects resulting from pathology or traumatic injury to the bone) in the ankle or hindfoot requiring fusion surgery using an open surgical technique with supplemental bone graft. There were three patient populations separately accounted for: Intent to Treat (ITT), modified Intent to Treat (mITT), and Safety or "All Treated." The ITT population consisted of 434 patients. Of these, 285 were implanted with Augment® Bone Graft and 149 received autograft. The mITT population, submitted as the primary effectiveness analysis for the radiographic evaluation of bridging bone, consisted of 397 patients (414 patients in the Safety, or "All Treated", group minus an additional 17 subjects excluded post-operatively) divided into 260 with Augment® Bone Graft and 137 with autograft. Table 1 summarizes the baseline and patient demographic characteristics for the "All Treated" population.

Table 1: Demographic & Clinical Characteristics at Baseline – "All Treated" Population

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

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

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

Baseline radiographs were assessed for the presence of parameters, which physicians would use to enroll patients based on the absence or presence of a bony defect, to indicate the need for bone graft in ankle and hindfoot arthrodesis surgery as described in a survey article by Baumhauer, et al.[3] The results of this review are included in Table 2.

Table 2: Radiographic Assessment of the Need for Graft Material

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

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

Safety and Effectiveness Results

Safety was evaluated based on the nature and frequency of adverse events which occurred in the Augment® Bone Graft group, as compared to those that occurred in the autograft group. Safety was also assessed by evaluating graft harvest site pain scores as the primary safety endpoint. Antibody test results were not considered as part of the safety evaluation.

Adverse Events

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

All Adverse Events

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

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

Table 3 – Adverse Events Summary by MedDRA SOC and PT

System Organ Class Preferred Term	All Patients (N=414)		Augment® Bone Graft (N=272)		Autologous Bone Graft (N=142)	
	Subjects	Events	Subjects	Events	Subjects	Events
Any Adverse Event	317 (76.6%)	973	212 (77.9%)	657	105 (73.9%)	316
Blood and lymphatic system disorders	2 (0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Cardiac disorders	9 (2.2%)	10	3 (1.1%)	3	6 (4.2%)	7
Congenital, familial and genetic disorders	2 (0.5%)	2	1 (0.4%)	1	1 (0.7%)	1
Ear and labyrinth disorders	3 (0.7%)	3	1 (0.4%)	1	2 (1.4%)	2
Endocrine disorders	2 (0.5%)	3	2 (0.7%)	3	0 (0.0%)	0
Eye disorders	5 (1.2%)	6	2 (0.7%)	3	3 (2.1%)	3
Gastrointestinal disorders	52 (12.6%)	66	35 (12.9%)	45	17 (12.0%)	21
General disorders and administration site conditions	56 (13.5%)	61	37 (13.6%)	40	19 (13.4%)	21
Hepatobiliary disorders	1 (0.2%)	1	1 (0.4%)	1	0 (0.0%)	0
Immune system disorders	12 (2.9%)	13	10 (3.7%)	11	2 (1.4%)	2
Infections and infestations	89 (21.5%)	121	61 (22.4%)	86	28 (19.7%)	35
Injury, poisoning and procedural complications	104 (25.1%)	125	67 (24.6%)	82	37 (26.1%)	43
Medical device pain	21 (5.1%)	21	14 (5.1%)	14	7 (4.9%)	7
Investigations	9 (2.2%)	9	6 (2.2%)	6	3 (2.1%)	3
Metabolism and nutrition disorders	8 (1.9%)	9	4 (1.5%)	5	4 (2.8%)	4
Musculoskeletal and connective tissue disorders	166 (40.1%)	276	117 (43.0%)	193	49 (34.5%)	83
Arthralgia	53 (12.8%)	63	38 (14.0%)	46	15 (10.6%)	17
Pain in extremity	69 (16.7%)	80	48 (17.6%)	56	21 (14.8%)	24
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.7%)	7	5 (1.8%)	5	2 (1.4%)	2
Nervous system disorders	58 (14.0%)	65	43 (15.8%)	49	15 (10.6%)	16
Psychiatric disorders	16 (3.9%)	18	11 (4.0%)	13	5 (3.5%)	5
Renal and urinary disorders	28 (6.8%)	29	17 (6.3%)	17	11 (7.7%)	12
Reproductive system and breast disorders	3 (0.7%)	3	1 (0.4%)	1	2 (1.4%)	2
Respiratory, thoracic and mediastinal disorders	25 (6.0%)	30	14 (5.1%)	15	11 (7.7%)	15
Skin and subcutaneous tissue disorders	61 (14.7%)	69	41 (15.1%)	47	20 (14.1%)	22
Surgical and medical procedures	14 (3.4%)	16	9 (3.3%)	9	5 (3.5%)	7
Vascular disorders	27 (6.5%)	29	18 (6.6%)	20	9 (6.3%)	9

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

There are five categories of adverse events in which the Augment® Bone Graft group is greater than or equal to two percentage points higher than the autograft control group: immune system disorders (3.7% vs 1.4%); musculoskeletal and connective tissue disorders (43.0% vs 34.5%); arthralgia (14.0% vs 10.6%); pain in extremity (17.6% vs 14.8%); and nervous system disorders (15.8% vs 10.6%). There are two categories of adverse events in which the autograft control group had a higher rate by two percentage points or more than the Augment® Bone Graft group: cardiac disorders (4.2% vs. 1.1%); and respiratory, thoracic and mediastinal disorders (7.7% vs. 5.1%). The correlation of high rates of pain measured as adverse events with secondary outcome measures for product effectiveness is unclear. Infection and infestation rates between the two groups were similar (Augment® Bone Graft, 20.2% and autograft control, 18.3%). An overall number rate of infections that approach 20% is clinically concerning for both groups. No inferential statistical comparison of adverse events between investigational and autograft control groups was performed.

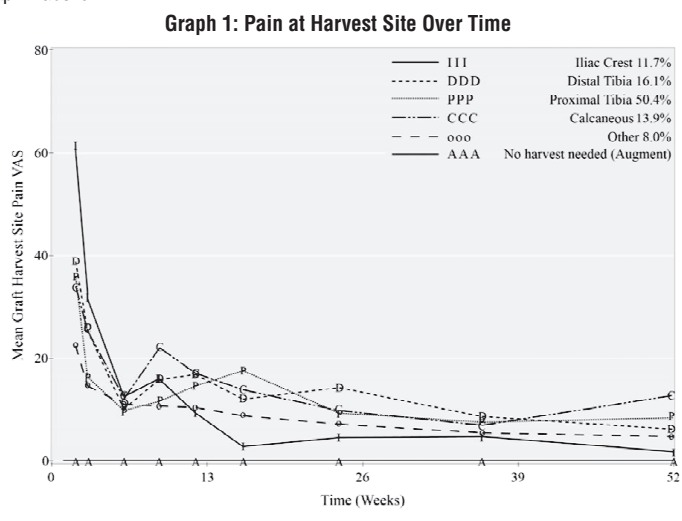
Detailed Information on Specific Adverse Event Categories

Graft Harvest Site Pain

Augment® Bone Graft subjects were spared the additional pain and morbidity associated with graft harvest and therefore experienced no graft harvest site pain. Subjects in the autologous bone graft group reported clinically significant pain at the graft harvest site (≥20 mm) on VAS at and after the week 24 visit: 12.4% of autologous bone graft subjects at week 24 and 8.8% at week 52.

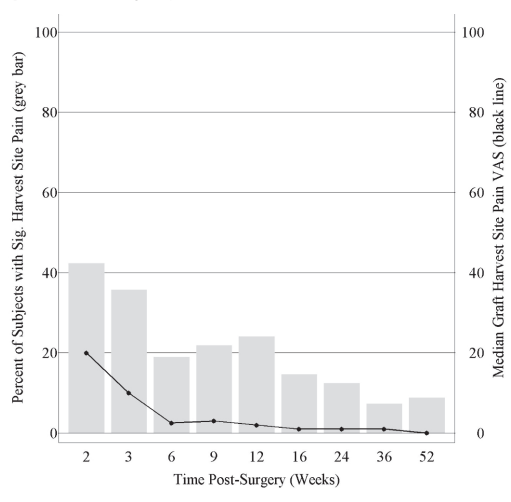
A breakdown of the different anatomical areas from which graft material was obtained showed that iliac crest constituted only 11.7% of all site materials used whereas approximately 50% of all autograft subjects received graft material harvested at the proximal tibia. Distal tibia (16.1%) and calcaneous (13.9%) were also used. The remaining autograft subjects utilized some other autograft source location. (These percentages can be found in the legend of Graph 1.) As shown in Graph 1, only patients with Iliac Crest Bone Graft (ICBG) achieved a VAS score greater than 40 mm and this was in the post-operative period (approximately 3 weeks) as presented in Graph 1 above.

Graph 1: Pain at Harvest Site Over Time



Immediately after surgery, average graft harvest site pain exceeded 60 mm for iliac crest and exceeded 20 mm for all the other graft harvest sites. Iliac crest mean pain was the lowest of the autograft sites at and after week 12; overall distal tibia presented mean scores between 10 and 20 mm at and after week 12.

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



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

Infection Rates

Infection and infestation rates between the two groups were similar (Augment® Bone Graft, 20.2% and autograft control, 18.3%). However, this is a clinically concerning overall number of infections. No inferential statistical comparison of adverse events between investigational and autograft control groups was performed.

Vascular Events

As with any lower extremity surgery, ankle and hindfoot surgery carries an increased risk of subjects developing deep vein thrombosis (DVT) or pulmonary embolism (PE). The incidence of serious "complications" coded as vascular disorders was reported as 13 events for 12 patients, or by treatment group of 2.9% Augment® Bone Graft and 2.8% for autograft controls (DVT: 2.2% Augment® Bone Graft versus 2.1% autograft control; Pulmonary Embolus: 0.7% Augment® Bone Graft versus 0.7% autograft control; and Thrombosis: 0.4% Augment® Bone Graft and 0% autograft control).

One patient in the Augment® Bone Graft group died of a pulmonary embolism 14 days after surgery. This event was assessed as being "not related" to the study device. This event, however, was likely related to the surgical procedure.

Cancer Events

Augment® Bone Graft contains becaplermin (rhPDGF-BB) which promotes cellular chemotaxis, proliferation and angiogenesis. rhPDGF-BB is also the active ingredient of two FDA approved products: a topical gel formulation indicated for the treatment of lower extremity diabetic neuropathic ulcers; and a synthetic grafting system for bone and periodontal regeneration. The product label of REGRANEX® Gel contains a warning identifying an increased rate of mortality secondary to malignancy in patients treated with three or more tubes of this product based on the results of the first of three post-approval studies of REGRANEX® Gel.

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

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

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

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

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

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

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

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

Third, a study evaluating cancer risk associated with the use of Becaplermin (rhPDGF-BB) for the treatment of diabetic foot ulcers was conducted by the Veterans Administration. This study compared cancer rates and overall cancer mortality between 6429 patients who used REGRANEX® Gel and 6429 matched comparators followed over 11 years (1998 through 2009). The hazard ratio for cancer mortality among those who received 3 or more tubes of REGRANEX® Gel relative to those who received none was 1.04 (95% confidence interval 0.73-1.48). This study provided no evidence of a cancer risk among becaplermin users, and did not indicate an elevated risk of cancer mortality.

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

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

Immunogenicity

As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of Augment® Bone Graft. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal study for foot and ankle fusions. In this study population of a total of 356 patients treated with Augment® Bone Graft, all randomized and treated subjects were tested for anti-rhPDGF-BB antibodies before implantation and at 2, 6, 12, and 24 weeks after implantation. In accordance with the protocol, additional serum samples were not obtained from subjects that tested negative for anti-rhPDGF-BB antibodies at 6 months. Anti-rhPDGF-BB antibodies were detected in 14.5% (41 out of 282) of patients receiving Augment® Bone Graft and in 3.5% (5 out of 141) in those that received an autograft. Anti-rhPDGF-BB antibodies persisted for up to six months with no data available beyond that time. Neutralizing activity was observed in 6 out of the 41 patients that confirmed positive for anti-rhPDGF-BB antibodies (6 out of 282 ~ 2.12%). No neutralizing antibodies were detected in patients that received an autograft. The clinical significance of the anti-rhPDGF-BB antibodies or any neutralizing activity is not known.

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

Effectiveness Results

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

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

Clinical Endpoints

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

Pain on Weight Bearing

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

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

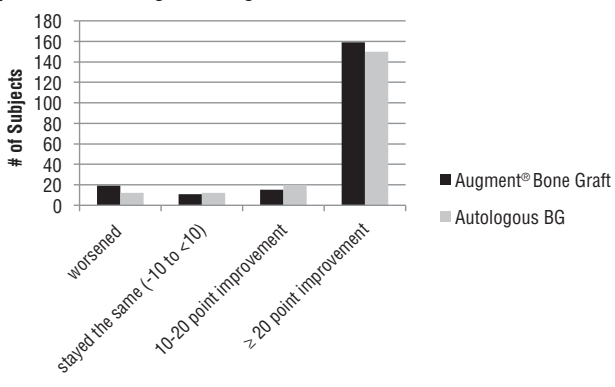


Table 4: Reduction in Pain on Weight Bearing at 24 and 52 weeks – "Per Protocol" Population

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

[1] Clinically significant improvement: ≥20 mm decrease from baseline
[2] Detectable improvement: 10-20 mm decrease from baseline
[3] Maintained: <10 mm decrease from baseline and <10 mm increase from baseline
[4] Deteriorated: >10 mm increase from baseline

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

Pain at Fusion Site

Table 5 displays pain at fusion site (measured by VAS) at week 24 and week 52. In the data presentations, the "clinically significant improvement" group was defined by a greater than 20 mm decrease in VAS score compared to baseline, the "improved" group was defined by a 10-20 mm decrease in VAS score compared to baseline, and the maintained group was defined by a change in VAS of -10 to 10 mm as compared to baseline.

Table 5 Fusion Site Pain at 24 and 52 Weeks – "Per Protocol" Population

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

[1] Clinically significant improvement: ≥20 mm decrease from baseline
[2] Detectable improvement: 10-20 mm decrease from baseline
[3] Maintained: <10 mm decrease from baseline and <10 mm increase from baseline
[4] Deteriorated: >10 mm increase from baseline

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

Foot Function Index (FFI)

Graph 4 displays data on functional improvement measured by the Foot Function Index (FFI) at week 24, as assessed in the cohort used to determine individual success and taking into account the 2:1 randomization. Table 6 presents data in the "Per Protocol" population. In the data presentations, the "clinically significant improvement" group was defined by a greater than 10 point decrease in FFI score compared to baseline, the "improved" group was defined by a 5-10 point decrease in FFI score compared to baseline, and the "maintained" group was defined by a change in FFI of -5 to 5 points as compared to baseline.

Graph 4 - FFI Assessed for Individual Success at 24 Weeks

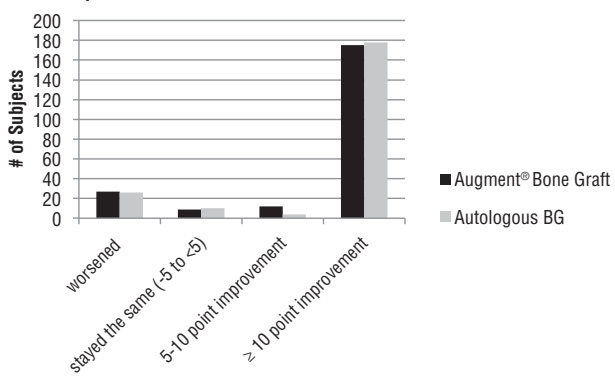


Table 6: Foot Function Index at 24 and 52 Weeks – "Per Protocol" Population

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

[1] Clinically significant improvement: ≥10 point decrease from baseline
[2] Improved: 5-10 point decrease from baseline
[3] Maintained: <5 point decrease from baseline and <5 point increase from baseline
[4] Deteriorated: >5 point increase from baseline

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

AOFAS Hindfoot and Ankle Score

Graph 5 displays data on functional improvement measured by AOFAS Hindfoot and Ankle Score at week 24, as assessed in the cohort used to determine individual success and taking into account the 2:1 randomization. Table 7 presents data in the "Per Protocol" population. In the data presentations, the "clinically significant improvement" group was defined by a greater than 20 point increase in AOFAS score compared to baseline, the "improved" group was defined by a 10-20 point increase in AOFAS score compared to baseline, and the "maintained" group was defined by a change in AOFAS of 10 to -10 points as compared to baseline.

Graph 5 - AOFAS Assessed for Individual Success at 24 Weeks

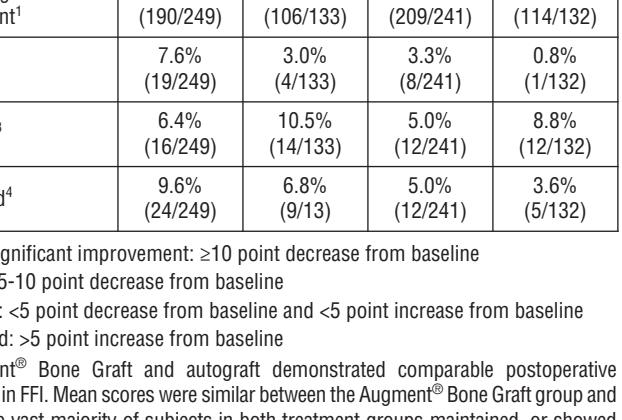


Table 7: AOFAS Hindfoot and Ankle Score at 24 and 52 Weeks – "Per Protocol" Population

Category	24 Weeks		52 Weeks	
	Augment® Bone Graft	Autograft	Augment® Bone Graft	Autograft
Clinically Significant Improvement[1]	72.6% (180/248)	70.1% (94/133)	80.9% (195/241)	80.3% (106/132)
Improved[2]	10.9% (27/248)	14.3% (19/133)	9.1% (22/241)	7.6% (10/132)
Maintained[3]	13.3% (35/248)	10.5% (14/133)	7.9% (19/249)	8.3% (11/132)
Deteriorated[4]	3.2% (8/248)	4.5% (6/133)	2.1% (5/249)	3.8% (5/132)

[1] Clinically significant improvement: ≥20 point increase from baseline
[2] Improved: 10-20 point increase from baseline
[3] Maintained: <10 point increase from baseline and <10 point decrease from baseline
[4] Deteriorated: >10 point decrease from baseline

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

SF-12 Physical Component Score

Table 8 presents data on overall quality of life measured by SF-12 Physical Component Score (PCS) at weeks 24 and 52. In the data presentations, the "maintenance or improvement" group was defined by an increase in SF-12 PCS as compared to baseline.

Table 8: SF-12 Physical Component Score (PCS) at 24 and 52 Weeks – "Per Protocol" Population

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

[1] Maintenance or improvement: ≥0 point increase from baseline
[2] Slight Decline: 0-10 point decrease from baseline
[3] Deteriorated: >10 point decrease from baseline

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

Of these assessments, FDA chose to analyze VAS on weight bearing, FFI, and AOFAS in a post-hoc manner. The analysis demonstrated equivalent improvements in outcomes for both Augment® Bone Graft and autograft at weeks 24 and 52, postoperatively.

VII. CONCLUSIONS DRAWN FROM CLINICAL STUDIES

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

Effectiveness Conclusions

The following outcome measures demonstrated comparable postoperative outcomes of Augment® Bone Graft and autograft at 24 and 52 weeks post-operatively:

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

The elimination of pain and morbidity resulting from the surgical approach in harvesting autograft provides additional benefit to patients receiving Augment® Bone Graft.

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

Safety Conclusions

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

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

Overall Conclusions

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

VIII. PREPARATION FOR USE

1. Using sterile technique, transfer the cup (containing the β-TCP granules) and the vial(s) (containing the rhPDGF-BB solution) to the sterile field.
2. Open the cup and transfer the β-TCP granules to a sterile surgical bowl.
3. Using a syringe and needle, draw up the contents of the vial(s) in entirety and transfer all of the fluid to the surgical bowl containing the β-TCP granules. If multiple kits are used, the contents may be combined.
4. Gently stir the two components together for approximately 30 seconds using a spatula, curette or similar instrument.
5. The mixture should be left undisturbed for 10 minutes before being implanted to ensure optimal saturation of the β-TCP particles.
6. The product should be implanted within one (1) hour after mixing the two components using the Recommended Surgical Technique.

IX. RECOMMENDED SURGICAL TECHNIQUE

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

X. REFERENCES

1. Younger EM, Chapman MW. "Morbidity at Bone Graft Donor Sites" Journal of Orthopaedic Trauma. 1989; 3(3):192-195.
2. St John TA, Vaccaro AR, Sah AP, Schaefer M, Berta SC, Albert T, Hilibrand A. "Physical and Monetary Costs Associated with Autogenous Bone Graft Harvesting" Am J Orthop (Belle Mead NJ). 2003 Jan; 32(1):18-23.
3. Baumhauer, et al. "Survey on the Need for Bone Graft in Foot and Ankle Fusion Surgery" Foot and Ankle International 34(12): 1629-1633.
4. Seeger, et al. "A Cohort Study of the Risk of Cancer in Regranex (Becaplermin) Users and Matched Comparators" Pharmacoepidemiology and Drug Safety, 2007.
5. Ziyadeh, et al. "A Matched Cohort Study of the Risk of Cancer in Users of Becaplermin" Advances in Skin and Wound Care, 2011.

X. SYMBOLS:

⚠	Attention, See Instructions for Use
2	Single Use Only
	Expiration Date
Rx	Prescription Only
+8°C +2°C	Store at Refrigerated Temperature
	Manufacturer
	Do Not Use If Package Is Open Or Damaged
REF	Reorder Number
LOT	Lot Number
STERILE R	Sterilized by Irradiation
STERILE EO	Sterilized by Ethylene Oxide
STERILE A	Sterilized by Aseptic Techniques
	Peel Here

Catalog (REF) Numbers

REF	Product
K200-015-00	Augment® Bone Graft 1.5 cc Kit
K200-030-00	Augment® Bone Graft 3.0 cc Kit
K200-060-00	Augment® Bone Graft 6.0 cc Kit
K200-090-00	Augment® Bone Graft 9.0 cc Kit

This product is covered by US patent No. 7,473,678. Other patents pending.

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WRIGHT

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