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Prospective, Randomized, Multi-Center Feasibility Trial of rhPDGF-BB Versus Autologous Bone Graft in a Foot and Ankle Fusion Model

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ABSTRACT

Background: **The increased morbidity and surgical time associated with harvesting autologous bone graft (ABG) have encouraged surgeons to develop synthetic orthobiologic alternatives. The recombinant form of platelet-derived growth factor (rhPDGF-BB), an angiogenic, mitogenic, and chemotactic cytokine, has been shown to significantly enhance bone formation in human periodontal osseous defects when combined with a tricalcium phosphate carrier (β-TCP). The purpose of this prospective, controlled, randomized, multi-center feasibility clinical trial was to compare the safety and efficacy of this biosynthetic bone graft substitute (Augment™ Bone Graft) to ABG during ankle and hindfoot fusion.** ***Materials and Methods:*** **Twenty adult subjects requiring ankle or hindfoot fusion from three U.S. centers were enrolled and randomized in a 2:1 ratio to receive Augment™ or ABG, respectively. Surgical approach and fixation techniques were standardized, and minimum followup was 9 months. The primary endpoint was radiographic osseous union, evaluated by a blinded independent radiologist. Secondary endpoints included assessment of clinical success, union rate by serial computed tomography (CT) examination, time to full weightbearing, AOFAS Ankle-Hindfoot Score (AOFAS), Foot Function Index (FFI), Short Form-12 (SF-12), and Visual Analog pain assessment Scale (Pain VAS).** ***Results:*** **At 36 weeks, 77% (10/13) of the Augment™ and 50% (3/6) of the ABG patients were fused based on radiographic criteria. There were two nonunions in the Augment™ group (9%, 2/14). Healing rates based on 12 week CT scanning (50% osseous bridging) were 69% (9/13) in the Augment™ and 60% (3/5) in the ABG groups, respectively. All functional outcome measures (FFI, AOFAS, SF-12), as well as the VAS pain scores, improved in both groups over time. Surgical procedure times lasted an average 26 minutes longer for the ABG as compared to the Augment™ populations. There were no device related serious adverse events in this study.** ***Conclusion:*** **Based on the available data, the rate of radiographic union, time to full weightbearing, and outcomes scores between the Augment™ and ABG subjects appear comparable. Augment™ may represent a safe and efficacious treatment alternative to ABG during foot and ankle arthrodesis.**

Level of Evidence:

Key Words: Ankle and Hindfoot fusion; Autologous Bone Graft; Recombinant Platelet Derived Growth Factor; Biosynthetic Bone Graft Substitute

INTRODUCTION

Autologous bone graft (ABG) remains the gold standard in foot and ankle fusion procedures due to its osteoconductive, osteoinductive, and osteoproductive properties. Autograft, however, is not a panacea. Its shortcomings include limited quantity, variability in graft osteogenic (cellular) activity, and donor site morbidity.[10,27] The risk of a complication associated with autograft taken from the iliac crest during lumbar fusion, for example, can approach 25%.[26] The advent of orthobiologic technology has spurred interest in the possibility of eliminating donor-site morbidity via development of a synthetic bone graft substitute that yields union rates comparable to ABG.[25] Currently, the only FDA-approved bioactive synthetic bone graft substitutes available for orthopaedic applications remain recombinant bone morphogenetic proteins (rhBMP-2 and rhBMP-7), both of which have demonstrated union rates comparable to ABG in clinical trials.[2,9,11,14] Nonetheless, the on-label indications for these biosynthetic devices are still narrow, and neither have FDA approval for any foot or ankle application. Such therapeutic challenges are further exacerbated by the high-risk patient populations frequently encountered in foot and ankle surgery.[8]

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Platelet-derived growth factor (PDGF) is an angiogenic, mitogenic, and chemotactic growth factor that affects numerous cell types, including osteoblasts and chondroblasts.[15,23,23,24] Data suggest that the direct cellular response is probably partly mediated by the environment in which the PDGF is introduced.[16,20,21] When implanted in human and canine periodontal osseous defects, PDGF has been shown to promote bone formation.[13,16] Experimental data using a femur fracture model as well as a distraction osteogenesis model have highlighted the significant promise of rhPDGF in bone remodeling and healing.[1,12,17] A human clinical trial in periodontal osseous defects utilizing recombinant PDGF (rhPDGF-BB) and recombinant human insulin-like growth factor I (rhIGF-1) resulted in a significant improvement in bone generation compared to conventional surgery plus a buffer.[13] Additionally, a human clinical trial using rhPDGF-BB in combination with an FDA-approved β-tricalcium phosphate (β-TCP) in periodontal osseous defects resulted in statistically significant effectiveness of rhPDGF-BB/β-TCP as compared to β-TCP alone, without serious or unanticipated adverse events.[18] Given the promise of such recent data, the hypothesis of this prospective, controlled, randomized, multi-center feasibility clinical pilot study was that rhPDGF-BB in a β-TCP matrix (Augment™) would be a safe and effective bone graft substitute yielding union rates comparable to ABG in a human foot and ankle fusion model. This is clinically relevant because eliminating the need to harvest ABG would obviously diminish operative time and avoid donor-site morbidity, as well as potentially expedite postoperative rehabilitation and return to work status.

MATERIALS AND METHODS

Patient population

Between 2006 and 2007, 20 skeletally mature patients 18 years of age or older who required an ankle or hindfoot fusion were recruited prospectively for randomization into this study. Within each center, subjects were randomly assigned on the day of surgery and upon verification of entry criteria to one of the following groups in a 2:1 ratio respectively: Group I as standard rigid fixation plus Augment™ with sodium acetate buffer containing 0.3 mg/ml rhPDGF-BB, and Group II as standard rigid fixation plus autograft. In order to facilitate balance and promote randomness within each center, randomization was performed using institution balancing using a variable block size.[28] Treatment was administered through the orthopaedic clinics of three academic medical centers (five fellowship-trained and ankle surgeons) in the United States (The Warren Alpert School of Medicine at Brown University, The University of Rochester School of Medicine, and The University of Medicine and Dentistry of New Jersey). This study was conducted under an FDA-approved Investigational Device Exemption (IDE). Institutional review board approval and informed consent were obtained prior to any patient enrollment. All subjects were screened to ensure they met strict inclusion and exclusion criteria (Table 1). Patients were randomized two to one to receive rigid internal fixation plus Augment™ (14 patients) or rigid internal fixation plus ABG (six patients). Surgical approach was standardized for each hindfoot and ankle fusion procedure across all treatment centers. All joints were fused with a predefined maximum number of screws, although supplemental Kirschner wires and staples were permitted. The use of additional bony reconstructive procedures, plates, rods, or structural bone grafts was prohibited, as was a history of prior fusion surgery at the site.

Augment™ bone graft

Each Augment™ kit (BioMimetic Therapeutics, Franklin, TN) was prepared under sterile conditions, and contained a syringe with 3 cc (0.3 mg/mL in 20 mM sodium acetate buffer) of rhPDGF-BB and a separate container with 3 cc of β-TCP (a purified, multicrystalline, porous form of calcium phosphate with a Ca:PO4 ratio similar to human bone). The β-TCP provides an osteoconductive scaffold for new bone formation. The rhPDGF-BB component is a highly concentrated recombinant form of this human platelet-derived growth factor that promotes revascularization and cellular ingrowth into the β-TCP matrix. Once the liquid 3 cc of rhPDGF-BB are added to the porous β-TCP matrix, a mandatory incubation period of 10 minutes is required prior to implantation. This allows for absorption of the protein solution and does not substantially increase the total volume of the Augment™ graft material. Any excess fluid is thereafter administered in situ at the bone graft site(s). Investigators were permitted to use up to 9 cc (three kits) of Augment™ as a maximum per procedure, limited to one Augment™ kit (or 3 cc ABG) per each hindfoot joint fused or a total of 2 Augment™ kits (or 6 cc ABG) per ankle joint fused. Corresponding volumes of ABG were obtained for subjects randomized to the control arm group, in a manner that was meant to standardize between Augment™ and ABG during surgical procedures. The protocol permitted graft harvest from the site of surgeon preference, as long as it was not located proximate to the fusion area, to accommodate surgeon experience and expertise.

Intra- and postoperative protocol

The surgical procedures were performed under either regional or general anesthesia, at the discretion of the investigator and anesthesiologist. Preoperative antibiotics were administered. Randomization of each patient occurred perioperatively. Standard surgical approaches were employed to gain access to each fusion site. Each affected joint was denuded to subchondral bone prior to hardware placement, and the cortices were perforated and/or feathered to augment fusion potential. Additional soft tissue balancing procedures deemed necessary at the time of surgery to gain appropriate

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Table 1: Study Exclusion & Inclusion Criteria

Exclusion Criteria

1. Previous post-surgical infection of the proposed fusion site.
2. Fusion site plate fixation or more than 9 cc (3 kits) of graft material to fill the fusion space.
3. Detectable untreated cancer or ongoing radiation therapy or chemotherapy.
4. Metabolic disorders known to adversely affect the skeleton, other than primary osteoporosis or diabetes (e.g., renal osteodystrophy).
5. Chronic use of medications known to affect the skeleton (e.g., glucocorticoid usage >10 mg/day); NSAIDs are permitted.
6. Pre-existing sensory impairment (diabetic patients not sensitive to the 5.07 Semmes-Weinstein monofilament test we excluded).
7. Obesity (BMI $\geq$ 30 kg/m^2) or has a smoking history of more than 20 cigarettes/day within the last 6 months.
8. Physical or mental compromise (e.g., currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, etc.).
9. Allergy to yeast-derived products.
10. Patient received an investigational therapy or approved therapy for investigational use within 30 days of surgery or during the followup phase of the study.
11. Patient was a prisoner, known or suspected of being a transient, or had a history of drug/alcohol abuse within the 12 months prior to screening for the study.
12. Pregnancy, or a female intending on becoming pregnant during the study period; a urine pregnancy test was administered within 21 days of the surgical visit to all females unless she was post-menopausal or surgically sterile.

Inclusion Criteria

1. IRB-approved informed consent prior to enrollment.
2. A bone defect in the hindfoot/ankle requiring fusion (up to 3 joints included) with supplemental bone graft/substitute, including:
   a. Ankle joint fusion
   b. Subtalar fusion
   c. Triple arthrodesis
   d. Calcaneocuboid fusion
   e. Talonavicular fusion
3. Each fusion site was able to be rigidly stabilized with no more than three screws. Supplemental pins and staples could be used. Plate fixation is excluded.
4. The patient was independent, ambulatory, and could comply with all postoperative evaluations and visits.
5. The patient was at least 18 years of age and skeletally mature.

alignment were permitted, such as gastrocnemius recession or Achilles lengthening. Prior to applying rigid fixation, either ABG or Augment™ was packed into the fusion site such that the graft material was in contact with the entire perimeter of the joint to be fused, but not placed in a manner which precluded direct host bone-bone apposition. ABG patients underwent autogenous bone graft harvest from the distal tibia, Gerdy's tubercle, or iliac crest, as per investigator preference. Following reduction and fixation, additional respective graft material was placed around the fusion site(s) as necessary to fill any exposed voids or interstices, without exceeding the allowed limit. A layered periosteal and soft tissue closure was then meticulously performed to maximize graft containment, as well as to minimize the risk of graft resorption, heterotopic ossification, and ulceration at the surgical site. Upon completion of the procedure, the affected foot and ankle was placed in a posterior splint in neutral alignment. Postoperative anesthetic blockade was provided for pain relief prior to splint application.

The postoperative protocol for all patients was standardized. At the initial postoperative visit (Day 7 to 14), all splints were removed and, if possible, sutures were taken out in preparation for short leg cast application. Patients remained nonweightbearing in this cast until the Week 6 visit, at which time they were advanced to a CAM walker or walking cast and permitted to perform touch down weightbearing. Physical therapy was then initiated and patients were progressively advanced in their weightbearing status.

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Radiographic and clinical endpoints

Excepting the event of any patient withdrawal, all enrolled patients were meant to be followed for 36 weeks postoperatively. The primary endpoint for the study was time to osseous union, as determined radiographically by a blinded independent radiologist. Standard orthogonal radiographs appropriate to the foot and/or ankle were obtained prior to surgical management, immediately postoperatively, and at each defined followup visit thereafter (Day 7 to 14, Weeks 4, 6, 8, 10, 12, 24, and 36). Radiographic osseous union was stringently defined as osseous bridging across the subchondral surfaces of at least three of the four regions delineating each fused joint, namely the anterior/superior, posterior/inferior, medial, and lateral quadrants. Osseous bridging was defined as trabeculation or density crossing the former joint space with complete loss of distinctiveness of bone graft particles and particle density equalling that of adjacent subchondral trabeculation.

Although the primary endpoint of this study was radiographic evidence of osseous union, CT evidence of osseous union was included as a secondary endpoint to assess osseous union due to recent reports suggesting that CT examinations are superior to radiographs in establishing the presence of fusion.[3,5] An isotropic dataset was created by CT utilizing non-contrast multi-detector acquisition, (Lightspeed VCT and Lightspeed RT 16, GE Medical Systems; Brilliance CT, Philips) kvP 130 to 140, mAs 200, 0.5 to 0.7 mm collimation and 0.3 mm interval. This dataset was then reconstructed into direct axial, coronal, and sagittal planes with slice thicknesses of 2 mm at 2 mm intervals. The same definition of osseous bridging used for radiographic assessment was used for CT. A semi-quantitative assessment was used to determine the percentage of joint surface having developed osseous bridging as follows: absent (0% to 25% osseous bridging), minimal (26% to 50% osseous bridging), moderate (51% to 75% osseous bridging), and complete (76% to 100% osseous bridging). Osseous union was declared using CT criteria when osseous bridging fell into either of the latter two (51% to 100%) categories. Interval CT examinations were routinely obtained at Weeks 6 and 12, but also at Week 16 if delayed union was suspected.

Secondary, semi-quantitative, radiographic parameters for healing were also included, such as callus formation, presence of heterotopic ossification, evidence of abnormal bone resorption, assessment of β-TCP resorption, and hardware complications. Clinical success/union in this pilot study, when required of a patient with more than one joint fused (i.e., a triple arthrodesis), was defined by surgeon impression based on the status of overall patient progress rather than performance of any one individual joint. This definition thus was defined as the express clinical opinion of the patient's status at the given time points, and included as another requirement for clinical success the lack of any revision surgery.

Radiographic, clinical, and functional endpoints were monitored at fixed intervals throughout the 36-week followup period including operative time, 24-week union rate, time to full weightbearing, and outcomes measures and quality of life assessments. In the ABG group, postoperative donor site pain was monitored with the VAS. For the duration of the study, all subjects were monitored for adverse events, defined as any unfavorable or unintended sign, symptom, or disease temporally associated with use of the investigational product, regardless of whether or not the event was related to the investigational product. All events were collected and analyzed, including events considered to be normal sequelae to foot and ankle surgery (such as increased postoperative pain, swelling, and warmth at the fusion site). The severity of the adverse event was classified as either mild (symptom barely noticeable to the subject), moderate (symptom of sufficient severity to make subject uncomfortable), or severe (symptom causes incapacitation or significant impact on subject's daily life). A listing of the key clinical and functional assessments can be found in Table 2.

Anti-rhPDGF-BB antibody analysis

All patients enrolled in this study, including those who received Augment™ and those who received ABG, had blood drawn for Anti-rhPDGF-BB antibody, with two exceptions: one patient who was withdrawn from the study and another who refused the blood draw. Subjects who elected not to participate in the serum collection analysis were not excluded from the other safety and efficacy analyses. Blood was drawn to obtain up to 3 ml of serum in a sterile tube pre-operatively and at Week 12 and 24 visits. Samples were processed, stored, and shipped according to instructions provided by the central laboratory (AAI Development). These samples were analyzed for the presence of neutralizing and non-neutralizing antibody formation to rhPDGF-BB.

Table 2: Clinical and Functional Assessments

Clinical and Functional Assessments
1. Pain, as assessed by the visual analog scale (VAS)
2. Motion at the fusion site
3. Warmth at the fusion site
4. Swelling
5. Tenderness
6. Neurovascular status
7. Evidence of infection/ulceration
8. Evidence of non-union/malunion
9. Weightbearing status
10. Clinical assessment of healing based on radiographic assessment (surgeon's radiographic interpretation)

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Statistical analysis

Demographic, diagnostic, and surgery data were reported using means and percentages. Radiographic union, complete clinical union, and full weightbearing rates were presented at each visit along with the distribution of osseous bridging outcomes. Fusion site VAS pain assessments were reported with means, medians, standard deviations, and minima and maxima for both raw scores and changes from pre-surgery. AOFAS ankle-hindfoot scale, foot function index, and SF-12 physical and mental summaries were similarly presented. Adverse events and surgical complication rates were compared between the two groups with Fisher's exact test.

RESULTS

Demographics

Patient demographics are presented in Table 3. The Augment™ study group consisted of 14 patients, as compared to six in the ABG control group. All but one patient, who was withdrawn at Week 10 for revision surgery requirements (but still followed), completed the entire 36-week postoperative protocol. The ABG group had a slightly lower mean age than that of the Augment™ group and had fewer patients who smoked. Body mass indices (BMI) were comparable. The distal tibia was the most frequent site selected for autogenous graft harvest in the ABG group (3/6). Half (7/14) of the Augment™ patients received two kits and half (7/14) received three kits of the biosynthetic product. Fairly even distribution was noted between groups with regard to both arthritic etiology and anatomic fusion site, as outlined in Table 3.

Table 3: Patient Demographics

	Overall ($n = 20$)	Augment™ ($n = 14$)	ABG ($n = 6$)
Male	9 (45%)	4 (29%)	5 (83%)
Female	11 (55%)	10 (71%)	1 (17%)
Mean Age	51.8	55.2	43.7
BMI	30.0	29.8	30.5
Smoker/History	8 (40%)	7 (50%)	1 (17%)
Diagnosis			
Primary Arthritis	3 (15%)	2 (14%)	1 (17%)
Rheumatoid Arthritis	2 (10%)	2 (14%)	0
Post-traumatic Arthritis	14 (70%)	9 (65%)	5 (83%)
Other	2 (10%)	1 (7%)	0
Fusion Type			
Ankle	7 (35%)	5 (36%)	2 (33%)
Triple Arthrodesis	9 (45%)	6 (43%)	3 (50%)
Subtalar	4 (20%)	3 (21%)	1 (17%)
Autograft Harvest Site			
Iliac Crest	1 (5%)	N/A	1 (17%)
Distal Tibia	3 (15%)	N/A	3 (50%)
Proximal Tibia	2 (10%)	N/A	2 (33%)
Amount of Graft Material Used			
3–6 cc	9 (45%)	7 (50%)	2 (33%)
6–9 cc	10 (50%)	7 (50%)	3 (50%)
>9 cc	1 (25%)	0 (0%)	1 (17%)

Radiographic outcome: primary endpoint

Radiographic assessments of progressive union rates were similar for both groups (Table 4A). At Week 12, 42% of patients in the Augment™ treatment group and 33% of patients in the ABG group achieved osseous union using the primary radiographic endpoint criterion of three of four quandrants, which became 77% (10/13) and 50% (3/6), respectively, by Week 36. One Augment™ patient withdrew from the study at Week 12. Missing or uninterpretable radiographs and CT scans were found on five Augment™ patients (14 visits) and three autologous patients (15 visits) at varying time frames, sometimes limiting interpretation of union at those intervals. Almost every one of these patients was ultimately found to be healed by these criteria by the final endpoint (Table 4A).

Table 4A: Fusion by Imaging (X-Ray and CT)

	Overall ($n = 20$)	Augment ($n = 14$)	ABG ($n = 6$)
Visit 5 (Week 6)			
X-ray Fusion (>3/4)	0/15 (0%)	0/11 (0%)	0/4 (0%)
CT Fusion (>50%)	7/18 (39%)	5/13 (38%)	2/5 (40%)
Visit 8 (Week 12)			
X-ray Fusion (>3/4)	6/15 (40%)	5/12 (42%)	1/3 (33%)
CT Fusion (>50%)	12/18 (67%)	9/13 (69%)	3/5 (60%)
Visit 11 (Week 36)			
X-ray Fusion (>3/4)	13/18 (72%)	10/13 (77%)	3/6 (50%)

Numbers and percents are based on observed data at each visit. Subject 25-01 (Augment) did not have any CT scans taken; subject 27-05 (ABG) missed the Week 12 visit. Union is defined as greater than 50% healing and it is noted that seven of 18 are healed by CT at Week 6 and 12 of 18 are healed by CT at Week 12. One did not have a CT scan (27 to 05) and one withdrew; thus having complete data for CT on 18 patients.

Radiographic outcome: secondary endpoints

Osseous bridging was best visualized and most easily quantified on the CT examinations. (Table 4A). Only those patients whose osseous union remained in question by Week 12 received a Week 16 CT study (6 patients). This data is not included, however, since none of those who remained unfused by Week 12 CT criteria were found fused by Week 16 CT assessment and thus the Week 16 data was ultimately determined to be of limited comparative value. CT examination demonstrated moderate to complete (greater

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Table 4B: Complete Clinical Union by Visit

	Overall ($n = 20$)	Augment™ ($n = 14$)	ABG ($n = 6$)
Visit 3 (Day 7–14)	0/20 (0.0%)	0/14 (0.0%)	0/6 (0.0%)
Visit 5 (Week 6)	0/20 (0.0%)	0/14 (0.0%)	0/6 (0.0%)
Visit 6 (Week 8)	1/20 (5.0%)	0/14 (0.0%)	1/6 (16.7%)
Visit 7 (Week 10)	6/20 (30.0%)	3/14 (21.4%)	3/6 (50.0%)
Visit 8 (Week 12)	12/19 (63.2%)	7/14 (50.0%)	5/5 (100.0%)
Visit 10 (Week 24)	17/19 (89.5%)	11/13 (84.6%)	6/6 (100.0%)
Visit 11 (Week 36)	18/20 (90.0%)	12/14 (85.7%)	6/6 (100.0%)

Numbers and percents are based on observed data at each visit. Subject 27-06 (Augment™) withdrew prior to study completion; subject 27-05 (ABG) missed the Week 12 visit.

than 50%) osseous bridging in nine of 13 of the Augment™ versus three of five of the ABG patients by Week 12. The remaining secondary radiographic endpoints were effectively analogous between groups. Neither group had evidence of bone resorption or excess callus formation. One ABG patient had evidence of heterotopic ossification, which was not observed in the Augment™ group.

Other clinical parameters

Mean procedure time was 144 minutes for the ABG group and 118 for the Augment™ group. The interpretive differences between the surgeon's assessment of clinical union rates (termed 'clinical success') and the radiologist's assessment of radiographic union rates can be interpolated by viewing Tables 4, A and B. Although statistical differences could not be calculated, it is evident that these data do not precisely correlate. By Week 36, 12 of 14 Augment™ patients were considered by the clinician to have achieved complete "clinical union" (clinical success), compared to six of six in the ABG. The two failures (2/14) in the Augment™ group were the result of delayed/non-union, and both patients underwent reoperation with ABG. One of these subsequent ABG revisions also failed to unite after the second surgery. Time to full weightbearing was found to be comparable between the two groups.

Outcomes measures

The pre- and postoperative VAS pain scores for both the midpoint (Week 12) and final week (Week 36) time points (mean and standard deviation (SD)) are reported in Table 5.

Table 5: Fusion Site VAS Pain Assessment

	Overall ($n = 20$)	Augment™ ($n = 14$)	ABG ($n = 6$)
Visit 2 (Pre-surgery)	$n = 19$	$n = 13$	$n = 6$
Mean (SD)	33.3 (33.80)	32.0 (32.66)	36.3 (39.20)
Median	27.0	27.0	24.5
Min, Max	0.0, 85.0	0.0, 84.0	0.0, 85.0
Visit 8 (Week 12)	$n = 19$	$n = 14$	$n = 5$
Mean (SD)	18.6 (25.00)	17.3 (24.24)	22.2 (29.66)
Median	8.0	8.3	6.5
Min, Max	0.0, 85.0	0.0, 85.0	0.0, 70.5
Change from Pre-Surgery to Visit 8	$n = 18$	$n = 13$	$n = 5$
Mean (SD)	−13.9 (27.01)	−14.7 (22.99)	−14.1 (38.92)
Median	−6.3	−3.0	−9.5
Min, Max	−76.5, 30.0	−57.0, 20.5	−76.5, 30.0
Visit 11 (Week 36)	$n = 19$	$n = 13$	$n = 6$
Mean (SD)	13.2 (20.79)	17.2 (23.91)	4.5 (7.15)
Median	4.5	5.0	1.0
Min, Max	0.0, 66.0	0.0, 66.0	0.0, 18.0
Change from Pre–Surgery to Visit 11	$n = 18$	$n = 12$	$n = 6$
Mean (SD)	−21.2 (30.05)	−14.8 (28.05)	−31.8 (33.69)
Median	−17.5	−12.8	−24.5
Min, Max	−76.0, 32.5	−64.0, 32.5	−76.0, 1.0

For the change from pre-surgery, a positive number represents an increase in pain. A negative number represents a decrease in pain.

Mean overall VAS score improvements were comparable at 12 weeks (14.7 for Augment™ versus 14.1 for ABG). The mean ABG donor site VAS scores are listed in Table 6.

The mean and SD pre- and postoperative AOFAS, FFI, and SF-12 scores are reported for the mid and final time points (12 and 36 weeks) in the study in Table 7. Note that, unlike the other outcomes parameters, improvement in the FFI is demonstrated by a decrease rather than an increase in numeric values over time. Both study groups had similar preoperative outcomes scores, all of which trended toward a positive clinical outcome throughout the followup period.

Adverse events

Five of six ABG patients experienced at least one adverse event (AE), versus ten of 14 Augment™ patients. There were no serious adverse events (SAEs) reported for any

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Table 6: Graft Site VAS Pain Assessment

	ABG ($n = 6$)
Visit 2 (Post-Surgery)	($n = 5$)
Mean (SD)	45.3 (39.37)
Median	60.5
Min, Max	0.0, 91.5
Visit 3 (Day 7–14)	($n = 6$)
Mean (SD)	42.1 (26.60)
Median	41.3
Min, Max	5.5, 74.0
Visit 5 (Week 6)	($n = 6$)
Mean (SD)	24.6 (30.10)
Median	18.8
Min, Max	0.0, 80.0
Visit 8 (Week 12)	($n = 5$)
Mean (SD)	14.9 (26.52)
Median	6.0
Min, Max	0.0, 62.0

patient, nor any AEs felt to be specifically associated with the Augment™ device. A summary of adverse events is listed in Table 8. There were a total of 12 AEs in the ABG group and a total of 36 AEs in the Augment™ group. The most commons AEs for both groups were fusion site warmth, tenderness, and swelling. There were no wound infections in either group that required reoperation. Although the few patients who developed delayed or non-union were recorded specifically as treatment failures rather than 'adverse events,' they could also be comprised as such.

Anti-rhPDGF-BB antibody analysis

Serum samples were available for 18 of the 20 subjects treated in the study. Of the two rhPDGF-BB subjects out of the 13 who tested Ab-positive in the Augment™ treatment group, one returned to Ab baseline at the 24 week followup and the other's Ab titer decreased to near baseline levels. None of the subjects tested positive for neutralizing anti-rhPDGF-BB Abs.

DISCUSSION

The recent advent of orthobiologic technology promises to change not only how, but also how well bony healing is achieved. Currently, an estimated five to 10% of the 5.6 million fractures sustained annually in the USA heal in delayed or impaired fashion.[19] Further, the number of foot and ankle fusion surgeries continues to climb at an annual rate of approximately 7%, and is now estimated to exceed 100,000 cases by 2011.[7] Historically, nonunion rates for foot and ankle fusion have averaged 10%, although they have ranged between zero and 40%.[6,8] The added surgical and anesthetic time, cost, and overall morbidity in the 340,000 patients per year who undergo autologous bone graft harvest is a significant cost to the health care system. Given that the rate of complications with autologous bone graft can approach 25%, room for improvement exists.[10,26,27] These cost and patient complication issues have driven the medical community to search for bioactive alternatives like PDGF. The encouraging data reported within the last 15 years by surgeons using rhPDGF in human maxillofacial defects[13] and by others using PDGF in a canine periodontal model[16] have spurred interest in its potential utility for other challenging healing situations, such as those common to foot and ankle surgery. Data from a recent multi-center, randomized, controlled clinical trial in treatment of periodontal defects demonstrated the safety and effectiveness of rhPDGF-BB delivered in a β-TCP matrix and resulted in FDA clearance of GEM 21S for routine use in periodontal surgery.[18] Interest in the utility of rhPDGF was also spurred by a recent prospective, open label Canadian study by Daniels and colleagues that suggested the potential of rhPDGF/TCP to enhance the clinical and radiographic outcome of foot arthrodesis in a single cohort patient group.[4]

The primary purposes of this investigation were to establish the relative safety and potential efficacy of the Augment™ device and to determine its feasibility for use in a phase III study. Our investigation represents the first randomized, controlled evaluation in the United States of any biosynthetic bone graft substitute utilizing a recombinant growth factor in foot and ankle surgery. Based on the preliminary merits of these pilot data, the FDA has approved a large-scale prospective, randomized, multicenter pivotal trial of similar design, comprised of 37 sites and 434 patients. Our current feasibility study was designed to understand the data variance for a power analysis between those patients receiving ABG and those receiving rhPDGF in a β-TCP matrix, and to provide a safety profile for the investigational drug.

The data suggest that at 3 months, the radiographic union rate of Augment™ compares favorably with that of ABG. Using the stricter radiographic criteria of 3/4 aspects, early healing rates approached 42% versus 33% respectively, and this relationship persisted at 69% versus 60% when using a similarly stringent CT criterion of greater than 50% osseous bridging. Even by the conclusion of the study (9 months), these values remained comparable: 77% versus 50% by radiograph, and 85% versus 100% by CT. The two groups also experienced similar times to full weightbearing (57% versus 50% by Week 10, and 100% for all patients by 9 months), which could arguably serve as a surrogate for 'clinical success'. Our data also corroborate previously published data supporting the safety of Augment™ in human subjects, as there were no device-related AEs or SAEs reported in this study.

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Table 7: AOFAS Ankle-Hindfoot Scale, Foot Function Index Scores, and SF-12 Scores

		Overall ($n = 20$)	**Augment™ ($n = 14$)**	**ABG ($n = 6$)**
Screening	Total score	$n = 20$	$n = 14$	$n = 6$
	Mean (SD)	38.4 (19.44)	39.2 (17.93)	36.3 (24.35)
	Median	45.0	45.0	33.0
	Min, Max	13.0, 70.0	13.0, 68.0	14.0, 70.0
Week 12	Total score	$n = 19$	$n = 14$	$n = 5$
	Mean (SD)	55.8 (11.06)	56.2 (10.86)	54.8 (12.87)
	Median	55.0	56.0	48.0
	Min, Max	38.0, 78.0	38.0, 78.0	46.0, 77.0
Week 36	Total score	$n = 19$	$n = 13$	$n = 6$
	Mean (SD)	74.6 (17.19)	71.1 (19.38)	82.2 (7.86)
	Median	79.0	79.0	80.5
	Min, Max	31.0, 93.0	31.0, 92.0	71.0, 93.0
Foot Function Index Scores				
Screening	Total score	$n = 20$	$n = 14$	$n = 6$
	Mean (SD)	47.0 (15.19)	47.4 (15.59)	45.9 (15.59)
	Median	47.9	47.9	47.5
	Min, Max	23.9, 70.4	23.9, 70.4	26.7, 70.2
Week 12	Total score	$n = 20$	$n = 14$	$n = 6$
	Mean (SD)	39.7 (23.10)	37.2 (21.87)	45.7 (26.91)
	Median	41.6	39.9	49.0
	Min, Max	3.2, 83.7	3.2, 81.8	5.6, 83.7
Week 36	Total score	$n = 19$	$n = 13$	$n = 6$
	Mean (SD)	21.0 (23.51)	23.6 (26.35)	15.6 (16.45)
	Median	14.7	14.7	10.9
	Min, Max	0.7, 72.5	2.2, 72.5	0.7, 38.1
SF-12 Scores				
Screening	Physical summary (PCS)*	$n = 20$	$n = 14$	$n = 6$
	Mean (SD)	35.3 (8.74)	34.1 (7.45)	38.2 (11.47)
	Median	31.4	31.2	33.2
	Min, Max	26.6, 56.6	26.6, 50.5	29.2, 56.6
	Mental summary (MCS)*	$n = 20$	$n = 14$	$n = 6$
	Mean (SD)	49.1 (10.78)	49.8 (11.16)	47.5 (10.65)
	Median	51.1	51.5	50.7
	Min, Max	25.6, 63.3	25.6, 63.3	30.2, 57.7
Week 12	Physical summary (PCS)*	$n = 19$	$n = 14$	$n = 5$
	Mean (SD)	37.4 (6.85)	36.9 (7.20)	38.8 (6.25)
	Median	37.5	37.5	36.1
	Min, Max	26.7, 50.5	26.7, 50.5	32.1, 48.4
	Mental summary (MCS)*	$n = 19$	$n = 14$	$n = 5$
	Mean (SD)	48.2 (9.81)	48.6 (10.53)	47.1 (8.42)
	Median	51.5	52.3	50.2
	Min, Max	26.4, 62.7	26.4, 62.7	35.8, 56.8
Week 36	Physical summary (PCS)*	$n = 19$	$n = 13$	$n = 6$
	Mean (SD)	41.5 (9.77)	38.8 (9.86)	47.2 (7.27)
	Median	42.4	41.6	48.4
	Min, Max	25.0, 57.8	25.0, 57.8	35.6, 54.8
	Mental summary (MCS)*	$n = 19$	$n = 13$	$n = 6$
	Mean (SD)	51.7 (9.87)	52.5 (10.23)	49.9 (9.69)
	Median	54.6	56.6	53.5
	Min, Max	28.5, 62.2	28.5, 62.2	30.5, 56.5

* PCS and MCS are norm-based (50, 10) scores.
Note: Numbers and percents are based on observed data at each visit. Subject 27-06 (Augment™) withdrew prior to study completion; subject 27-05 (ABG) missed the Week 12 visit.

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Table 8: Summary of Adverse Events and Surgical Complications

	Augment™ (n = 14)	ABG (n = 6)	Fisher's Exact Test p value
Subjects with at least one adverse event not including normal sequelae*	10 (71.4%)	5 (83.3%)	1.000
Subjects with at least one adverse event considered normal sequelae*	12 (85.7%)	4 (66.7%)	0.5492
Subjects with at least one study device related adverse event	0 (0.0%)	0 (0.0%)	
Subjects with at least one hardware related adverse event	3 (21.4%)	0 (0.0%)	0.5211
Subjects with at least one serious adverse event	0 (0.0%)	0 (0.0%)	
Subjects with at least one serious hardware related adverse event	0 (0.0%)	0 (0.0%)	
Subjects with at least one surgical complication	12 (85.7%)	3 (50.0%)	0.1313
Subjects with at least one serious surgical complication	0 (0.0%)	0 (0.0%)	
Hardware-related adverse events:	3 (21.41%)	0 (0.0%)	0.5211
a. Primary device	0 (0.0%)	0 (0.0%)	
b. Accessory hardware	1 (7.1%)	0 (0.0%)	
c. Immobilization issue	2 (14.3%)	0 (0.0%)	
d. Indeterminant	0 (0.0%)	0 (0.0%)	

Note: Percents are based on the number of subjects in the intent to treat population.
Related adverse events are those events categorized as having a definite or likely relationship to study treatment.
* Normal sequaelae includes feeling hot, local swelling, edema peripheral, swelling, tenderness, post procedural pain, pain in extremity and hypoesthesia.

Despite these promising results using Augment™ bone graft substitute, there were, notably, two impending non-unions in the Augment™ group that required re-operation. Both patients were revised using ABG, and one of these revisions also failed to unite after this additional surgery. Historically, β-TCP has been used successfully as an osteoconductive matrix for delivery of rhPDGF-BB. In review of both delayed unions in this study, though, it was felt that there had perhaps been an excessive volume of β-TCP implanted between the joint spaces intended for fusion, which may have acted as a mechanical distractor of the joint. Based on this early observation, greater attention was subsequently paid to Augment™ implant insertion in successive patients to avoid what might be considered a technical error causing β-TCP impediment to primary host bone to bone apposition. Another factor noted in the Augment™ group which may have potentiated the risk of nonunion was the excessive number of patients who exhibited a smoking history as compared to those in the ABG group (50% versus 17%). Further study will be necessary to answer these questions definitively.

The two most unanticipated but certainly interesting findings in our study were that CT examination seemed far more accurate than radiographic assessment in quantifying and qualifying bony healing rates, and that there appeared to be a poor correlation between the rate of radiographic healing as determined by the radiologist and the rate of clinical "union" (success) as measured by the clinician.[3,5] Notable inaccuracies and difficulties encountered with the radiographic data were summarized as a combination of inherent limitations involving interpretation of three-dimensional problems via two-dimensional instruments, challenges associated with interpreting joints radiographically given osseous overlap, beam obliquity, poor imaging technique, or superimposed hardware, and the complexity of interpreting cross-trabeculation throughout a non-linear joint surface. It was noted that there was a tendency to overcall osseous union using the radiographic interpretation as compared to the CT data, even though our radiographic criteria would be considered relatively strict by today's standards. Our second interesting observation, that the clinicians' perceptions of their patients' "clinical unions" generally exceeded the patients' actual radiographic healing rates, was also noteworthy. Despite widespread use of the term "clinical union" in today's orthopaedic literature, based on this observation we later chose to rename this "clinical success," since we felt "union" is more aptly relegated to use only as a radiographic descriptor. The observed trend suggested to us that either we as physicians sometimes over-interpret the outcomes of our patients, our patients tend to understate their reservations, there is no clear correlation between the degree of radiographic fusion demonstrated by and the degree of clinical success experienced by the patient, or, most likely, given that recent data have suggested the need for perhaps only 25 to 50% cross-trabeculation to create a solid, asymptomatic fusion, perhaps "clinical success" actually requires very little cross-trabeculation within a fusion mass.

The study (Augment™) group demonstrated a reduction in surgical time of 22% (118 versus 144 minutes) compared to those patients with ABG, and were spared any potential

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donor site morbidity or pain associated with graft harvest. Although underpowered to assess the significance of these findings, these important observations may become more evident during a larger scale pivotal trial. The outcomes measures between these two groups were, overall, comparable at study conclusion (36 weeks). The AOFAS and SF-12 scores remained very similar between groups at both the 12- and 36-week time points. The FFI as well as the fusion site VAS pain scores, excepting those from the donor site harvest, also improved substantially for both populations. We believe the promising early trends and ultimate relative equivalency rates in outcome scores between these data support the use of Augment™ as a potential orthobiologic alternative.

Complications in the study were relatively few. The most common adverse events reported for both groups were fusion site warmth, tenderness, and swelling, which the investigators considered indicative of the normal healing process. Aside from those patients who went on to delayed or nonunion, surgical complications were minor in this study, and totaled four in the Augment™ group and two in the ABG group. There were no serious adverse events reported in the study, and all reported adverse events were considered mild to moderate in severity and of doubtful relation to the study device. The two patients who required return to the operating room for revision fusion surgery ("clinical failures") were both in the Augment™ group. One underwent ABG and later healed uneventfully, and the other required several subsequent procedures including ABG as a second procedure and then repeat ABG with INFUSE™ augmentation as a third intervention, although the patient still remains symptomatic. Of the two of 13 Augment™ subjects confirmed to be rhPDGF-BB Ab positive, one returned to Ab baseline at the 24-week followup and the other decreased the Ab titer to near baseline levels but did not return to the baseline titer levels. Importantly, none of these subjects tested positive for neutralizing anti-rhPDGF-BB antibodies.

Despite some remarkable findings and Level I evidence provided by this feasibility trial, there exist several recognized weaknesses of this investigation. We believe the greatest shortcoming was our intention to assess union by radiographic assessment, which was made more difficult by the occasionally uninterpretable or missing films in these patients. Curiously, although this continues to remain the standard for orthopaedic surgeons across the United States today, our experience with interpretation of serial radiographic evaluations as a means of assessing osseous union was marred by multiple inherently confounding factors. This became increasingly evident over the course of our study as we had the advantage of contemporaneous CT examination at many of these same radiographic time points. Based on corroboration of our own CT and radiographic data with that of recent work by Coughlin et al.[3] and Dorsey et al.,[5] we not only now consider radiographic assessment of healing to be both a comparatively poor and confusing indicator of fusion, but also a substandard primary endpoint for any orthopaedic fusion study. Our small enrollment numbers also precluded meaningful statistical comparisons between groups, hence the recommendation for a pivotal trial that is appropriately powered to draw statistically significant conclusions. The subject numbers did, however, provide useful information on device safety and aided design and technical considerations relative to the phase III trial. Finally, our pilot design did not include a patient arm without an added bone graft product, so we are only able to compare our fusion rates to historic controls of similarly unaugmented patients undergoing fusion procedures.

Further, as with any growth factor, rhPDGF-BB must be implanted in a milieu optimized for tissue regeneration. Thus, the principles implicit to fusion surgery, including rigid fixation, direct bone to bone apposition, and presence of viable host cells, are paramount for ensuring optimal osteobiologic activity. Despite the inclusion of multiple surgeons and very heterogenous patient comorbidities in this study, which could at some level also confound these variables and our results, we believe these important principles have been reasonably universalized and followed accordingly. In the future, we will consider additional stratification with respect to surgical technique/instrumentation criteria for future studies to minimize any such potential bias. It is also important to note that the orthobiologic materials being tested in this investigation were neither studied for nor implied to be a replacement to structural bone graft during foot and ankle surgery. Finally, one additional weakness of the study regarded overall VAS comparison. Three of six autograft patients had distal tibial autograft and, particularly in the early phases of recovery when immovable casts were in place, it might have been difficult for patients to differentiate pain localization given the proximity of the fusion site to the harvest site. However, this weakness was mitigated during the later phases of the study because both clinician and patient were better able to differentiate the harvest site from the surgical site due to improved access and visibility.

CONCLUSION

Even with the limited data available to us from our pilot study, it appears evident that CT examinations are likely to replace radiographs as a means of quantifying fusion in the future. We need to explore the degree of bone bridging that is needed to be "clinically successful," and it appears that the threshold of 75% we used (and perhaps even that of 50%) may be too rigorous and not clinically applicable. Our data suggest that a threshold of 25 to 50% might be more clinically relevant and of greatest benefit to any future study attempting to quantify the presence of a stable fusion.

We believe this pilot study presents very encouraging data. It suggests that Augment™ may be a safe and effective alternative to ABG for maximizing foot and ankle fusion rates. Equally important, there were no serious adverse events noted in the investigation. Union rates with Augment™

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were comparable to ABG. The use of this biosynthetic alternative avoided the morbidity and increased pain and surgical time routinely associated with bone graft harvest. Although these results are preliminary and qualitative in reporting, the planned subsequent randomized, prospective, controlled, multicenter pivotal clinical trial will provide more comprehensive answers.

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