Clinical Study Report: BMTI-2006-01

1 TITLE PAGE

Study Title:	A Prospective, Randomized, Controlled, Multi-Center, Pivotal Human Clinical Trial to Evaluate the Safety and Effectiveness of Augment™ Bone Graft Compared to Autologous Bone Graft as a Bone Regeneration Device in Foot and Ankle Fusions
Study Number:	BMTI-2006-01
Study Phase:	Pivotal study under an Investigational Device Exemption
Study Design:	Prospective, randomized, controlled, non-inferiority, multi-center trial
Product Name:	Augment™ Bone Graft (previously called GEM OS1™)
Formulation:	Two Components: Package of β-tricalcium phosphate with rhPDGF-BB (becaplermin) solution
Indication:	Bone regeneration device in foot and ankle fusions
Study Initiated (first patient enrolled):	09 April 2007
Study Completed (last patient completed):	18 January 2010
Principal Investigators:	Multicenter
Sponsor:	BioMimetic Therapeutics, Inc. 389-A Nichol Mill Lane Franklin, TN 37067 Telephone: 615-844-1280
Responsible Medical Officer:	Neil Green, MD
Report Date:	Version 2.00 – 17 Nov 2010

Confidentiality Statement

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2 SYNOPSIS

Sponsor:
BioMimetic Therapeutics, Inc.

Name of Finished Product:
Augment™ Bone Graft

Name of Active Ingredient:
Two components: Package of
β-TCP with rhPDGF-BB
(becaplermin) solution

Study Title:
A Prospective, Randomized, Controlled, Multi-Center, Pivotal Human Clinical Trial to Evaluate the Safety and Effectiveness of Augment™ Bone Graft Compared to Autologous Bone Graft as a Bone Regeneration Device in Foot and Ankle Fusions

Investigators and Study Centers:
Multicenter

Publication (reference):
Not applicable.

Studied Period:
09 April 2007 (first patient enrolled) to
18 January 2010(last patient completed)

Phase of Development:
Pivotal study under an Investigational Device Exemption

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

Methodology:
This prospective, randomized, controlled, non-inferiority, multi-center clinical trial was undertaken to evaluate the safety and effectiveness of Augment Bone Graft compared to autologous bone graft as a bone regeneration device. The study intent was to enroll up to 396 patients requiring fusion in either the hindfoot or ankle (tibiotalar) requiring the use of bone graft. Each patient was to have a physical exam of the anatomical region to be treated, incorporating medical history and injury/disease etiology. Upon confirmation of eligibility, patients were randomized into one of two treatment groups: standard rigid fixation plus autologous bone graft or standard rigid fixation plus Augment Bone Graft. Randomization was conducted at a 2:1 ratio of Augment Bone Graft to autologous bone graft. The patients then

underwent a hindfoot/ankle fusion procedure using open surgical technique with supplemental bone graft or Augment, according to the randomization assignment. The fusion construct required adequate reduction and stabilization with rigid fixation intra-operatively in order to meet final study eligibility. Both treatment groups were immobilized according to standardized operative and post-operative protocols.
The investigators, who were fellowship trained and board certified foot and ankle surgeons, performed clinical and radiographic assessments (as required by protocol) to monitor healing/union status. A masked independent radiographic assessment was performed by a designated fellowship trained and board certified musculoskeletal radiologist who assessed radiographic parameters for fusion. All enrolled patients were to be monitored over a 52 week period to evaluate for clinical and safety outcomes, including incidence of loss of reduction, infection, non-union, need for revision fusion surgery, and associated complications with hindfoot and ankle fusion procedures, in addition to the occurrence of other adverse device effects.

Number of Patients (Planned and Analyzed):
396 patients were planned; 435 patients were randomized (331 in US and 104 in Canada); 434 patients were analyzed. The patient population totals for this final analysis are identical to those defined in the Premarket Application (PMA):

Intent-to-treat (ITT): 434

Safety: 414

Modified intent-to-treat (mITT): 397

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

Test Therapy:
Standard rigid fixation + Augment Bone Graft, containing beta-tricalcium phosphate (β-TCP) and 0.3 mg/mL recombinant human platelet-derived growth factor (rhPDGF-BB) in sodium acetate buffer

Reference Therapy:
Standard rigid fixation + Autologous Bone Graft

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

Duration of Follow-up:
52 weeks (primary endpoint at 24 weeks)

Criteria for Evaluation:

Effectiveness:
Radiographic, clinical and functional endpoints were assessed. The primary effectiveness endpoint was fusion based on assessment of osseous bridging across the joint space as determined via computed tomography (CT) scan at 24 weeks, the most rigorous criterion to assess fusion currently available. Outcomes were assessed on a patient level, for which the full complement of treated joints had to have a successful outcome (termed "full complement"), as well as at the joint level for which the outcome for each individual treated joint was assessed (termed "all joints").

Secondary radiographic endpoints included CT and plain film radiograph -based assessments. Such assessments included degree of osseous bridging based on CT scan and radiographic fusion; supplemental radiographic parameters for healing, which include presence of heterotopic bone formation, assessment of β-TCP resorption, hardware (i.e., screw) complications; time to fusion based on CT scan.

Additional secondary endpoints reflected clinical evaluations, including: healing status based on physical exam at the patient level; healing status based on physical exam at the individual joint level; clinical and composite success; therapeutic failure (non-union, delayed union or requiring secondary therapeutic intervention); time to clinical healing; and operative time. Secondary endpoints based on patient evaluations were also assessed, including: pain with weight-bearing; pain at graft harvest site; and quality-of-life assessments, which include Short Form (SF)-12, American Orthopaedic Foot and Ankle Society (AOFAS) outcomes score, and Foot Function Index (FFI).

Safety:
The analysis of safety-related data include frequency, severity, and relationship to study device for all adverse events; surgical site complications associated with injury or standard surgical treatment, including non-union; system organizational class (SOC) classification of adverse events by treatment group; serious adverse events with narratives, patients who discontinued the study due to death or other significant adverse events; and serum sample analysis for presence of anti-rhPDGF-BB antibodies.

Statistical Methods:
For the primary effectiveness endpoint, the analysis goal was to establish non-inferiority. Non-inferiority was tested using a one-sided 95% lower confidence bound for the Augment™ Bone Graft week 24 fusion rate minus autologous bone graft week 24 fusion rate difference, using the population-specific denominators with all population-specific patients achieving union included in the numerator. If a 10% non-inferiority margin could be ruled out, then superiority was to be tested declaring superiority if the one-sided 97.5% lower bound for the difference between Augment Bone Graft and autologous bone graft was >0%; this was a penalty-free test given the format of the null hypothesis.

A closed testing procedure was used to investigate the secondary effectiveness endpoints. Significance for non-inferiority was achieved at a one-sided 0.05 level with pre-specified offsets in a pre-specified order, while superiority was achieved at a one-sided 0.025 level in the event that non-inferiority was first established. Non-inferiority was tested for all endpoints before superiority was tested.

Summary of Results

Effectiveness:
The results from the statistical analyses revealed both statistically significant and clinically relevant benefits for the Augment Bone Graft, compared to the gold standard of autograft. In addition, the results from both study groups are comparable to available historical literature for union rates associated with autograft, particularly considering the relatively compromised patient population. The results from the effectiveness analysis are presented based upon the mITT patient population which is defined as all randomized patients who were eligible, properly randomized, and received treatment according to the study protocol. The ITT population is used as support for analysis of safety and effectiveness and includes surgical screen failures and patients who were randomized but never treated.

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

Results at 24 weeks

No changes to the results for the primary effectiveness endpoint are reported as the primary endpoint was fusion (defined as at least 50% osseous bridging via CT) in the mITT population at 24-weeks.

Secondary Endpoints (mITT Population):

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

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

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

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

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

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

group (improvement from 40.5 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

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

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

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

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

Week 24 Results Summary

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

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

Data Source: Table 2.1.1, Table 2.3.1, Table 2.3.3, Table 2.4.1, Table 2.5.1, Table 2.6.1, Table 2.6.3, Table 2.7.1, Table 2.8.1.1, Table 2.9.1.1, Table 2.10.1.1, Table 2.11.1, Table 2.12.1.1, Table 2.13.1

Results after 24 Weeks

Week 36 Results

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

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

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

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

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

Quality-of-life and functional outcomes scores included SF-12, FFI, and AOFAS Ankle-Hindfoot questionnaires. At week 36, the Augment Bone Graft patients reported a mean SF-12 Physical Component Score (PCS) of 41.4 (improvement from 31.0 at screening), compared with 44.2 in the autologous bone graft group (improvement from 31.6 at screening); a mean FFI total score of 22.0 (improvement from 51.6 at screening), compared with 18.2 in the autologous bone graft group (improvement from 48.6 at screening); and a mean AOFAS Ankle-Hindfoot total of 75.0 (improvement from 40.4 at screening), compared to 77.3 in the autologous bone graft

group (improvement from 40.8 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

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

A summary of results at Week 36 is presented below:

Week 36 Results Summary

	Augment™ Bone Graft	Autologous Bone Graft	Noninferiority test p-value
Subjects (N=397)	**(N=260)**	**(N=137)**	
Individual joints [All Joints] (N=597)	**(N=394)**	**(N=203)**	
CT Fusion Rates			
Full Complement of Joints:	63.5%	69.3%	0.202
All Joints (assessed individually):	68.8%	73.9%	0.103
Plain Film Radiographic Union Rates (3 Aspects)			
Full Complement of Joints:	30.0%	35.8%	0.198
All Joints (assessed individually):	39.1%	42.9%	0.072
Plain Film Radiographic Union Rates (2 Aspects)			
Full Complement of Joints:	62.7%	69.3%	0.249
All Joints (assessed individually):	70.3%	72.4%	**0.021**
Clinical Healing Status at the Patient Level:	84.6%	88.3%	**0.038**
Clinical Healing Status by Joint			
Full Complement of Joints:	84.2%	86.9%	**0.022**
All Joints (assessed individually):	86.8%	85.7%	**<0.001**
Composite Success Rate:	71.5%	77.4%	0.179
Clinical Success Rate:	73.8%	75.9%	**0.041**
Therapeutic Failure Rate*:	7.7%	9.5%	**<0.001**
SF-12 Mean PCS:	41.4	44.2	**0.020**
FFI Mean Total Score:	22.0	18.2	**0.001**

AOFAS Mean Total Score:	75.0	77.3	**<0.001**
Fusion Site Pain:	16.2	13.9	**<0.001**
Weight-bearing Pain:	18.8	15.7	**0.005**
Graft Harvest Site Pain:	n/a	6.1	**<0.001**

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

Data Source: Table 2.1.1, Table 2.3.1, Table 2.3.3, Table 2.4.1, Table 2.5.1, Table 2.6.1, Table 2.6.3, Table 2.7.1, Table 2.8.1.1, Table 2.9.1.1, Table 2.10.1.1, Table 2.11.1, Table 2.12.1.1, Table 2.13.1

Week 52 Results

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

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

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

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

Quality-of-life and functional outcomes scores included SF-12, FFI, and AOFAS Ankle-Hindfoot questionnaires. At week 52, the Augment Bone Graft patients reported a mean SF-12 Physical Component Score (PCS) of 42.4 (improvement from 31.0 at screening), compared with 45.0 in the autologous bone graft group (improvement from 31.6 at screening); a mean FFI total score of 20.1 (improvement from 51.6 at screening), compared with 17.5 in the autologous bone graft group (improvement from 48.6 at screening); and a mean AOFAS Ankle-Hindfoot total of 77.8 (improvement from 40.4 at screening), compared to 78.2 in the autologous bone graft

group (improvement from 40.8 at screening). The quality-of-life data supported non-inferiority of Augment Bone Graft versus autologous bone graft for all three measures.

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

A summary of results at Week 52 is presented below:

Week 52 Results Summary

	Augment™ Bone Graft	Autologous Bone Graft	Non-inferiority test p-value
Subjects (N=397)	**(N=260)**	**(N=137)**	
Individual joints [All Joints] (N=597)	**(N=394)**	**(N=203)**	
Plain Film Radiographic Union Rates (3 Aspects)			
Full Complement ofJoints:	36.9%	36.5%	**0.020**
All Joints (assessed individually):	48.5%	44.3%	**<0.001**
Plain Film Radiographic Union Rates (2 Aspects)			
Full Complement of Joints:	70.8%	75.2%	0.115
All Joints (assessed individually):	77.2%	77.8%	**0.005**
Clinical Healing Status at the Patient Level:	87.7%	88.3%	**0.003**
Clinical Healing Status by Joint			
Full Complement of Joints:	86.2%	87.6%	**0.008**
All Joints (assessed individually):	88.3%	87.2%	**<0.001**
Clinical Success Rate:	76.9%	78.1%	**0.022**
Therapeutic Failure Rate*:	7.3%	8.0%	**<0.001**
SF-12 Mean PCS:	42.4	45.0	**0.015**
FFI Mean Total Score:	20.1	17.5	**<0.001**

AOFAS Mean Total Score:	77.8	78.2	**<0.001**
Fusion Site Pain:	13.2	12.9	**<0.001**
Weight-bearing Pain:	15.6	15.8	**<0.001**
Graft Harvest Site Pain:	n/a	6.1	**<0.001**

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

Data Source: Table 2.1.1, Table 2.3.1, Table 2.3.3, Table 2.4.1, Table 2.5.1, Table 2.6.1, Table 2.6.3, Table 2.7.1, Table 2.8.1.1, Table 2.9.1.1, Table 2.10.1.1, Table 2.11.1, Table 2.12.1.1, Table 2.13.1

Safety:
The following safety results were presented separately in a safety update report dated 06 May 2010.

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

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

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

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

A low percentage of patients tested positive for non-neutralizing binding antibodies to rhPDGF-

BB (13.9% of Augment Bone Graft patients and 3.6% of autologous bone graft patients). At the 24 week follow up, 14 patients had a titer of binding antibodies and were asked to submit at least 2 additional serum samples three months apart. One patient at visit 6 who had a titer of binding antibodies, but did not give a sample at visit 8, was also asked to submit additional serum samples. Following subsequent serum analyses, 13 of 14 patients have tested negative for anti-drug antibody (ADA), i.e. antibody level returned to baseline. The one remaining patient has been requested to return for serum sample acquisition and testing. Results for this patient will be reported upon completion of testing.

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

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

	Augment™ Bone Graft (N=272)	Autologous Bone Graft (N=142)	Fisher Exact Test p-value
Pre-Treatment Signs and Symptoms	2.6%	2.8%	>0.999
Treatment Emergent Adverse Events (TEAEs)	77.9%	73.9%	0.393
Serious TEAEs	10.3%	14.8%	0.201
Related TEAEs	2.2%	4.2%	NA
Overall complications	35.3%	38.7%	0.519
Complications associated with surgical procedure	23.9%	30.3%	NA
Serious complications	5.1%	6.3%	0.654
Infections	8.5%	11.3%	0.378
Data Source: Table 3.1.1, Table 3.2.4, Table 3.2.6 **Final Report Date: Final 1.0 – 06 May 2010**			

CONCLUSIONS

Effectiveness Conclusions:

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

randomized but never treated.

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

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

- Plain film radiographic union rate (at 3 aspects) for all individual joints
- Plain film radiographic union rate (at 2 aspects) for all individual joints
- Clinical healing status for the full complement of joints, all individual joints
- Therapeutic failure rate (non-union, delayed union or requiring secondary therapeutic intervention
- Composite Success Rate
- SF-12 mean PCS
- FFI mean total score
- AOFAS mean total score

Data after 24 Weeks

Success rates for Augment Bone Graft patients continued to improve for radiographic and clinical endpoints after week 24, consistent with success rates for autograft. This continued success was hypothesized after review of the primary effectiveness analysis at week 24.

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

Safety Conclusions:

The key safety conclusions from the trial are that patients treated with Augment Bone Graft had fewer serious TEAEs, fewer overall complications, fewer complications associated with the surgical procedure, fewer serious complications, fewer serious surgical complications and fewer

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

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

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Primary Endpoint:					
CT fusion (%)	Full Complement of Joints	Week 24	61.2	62.0	0.038
Secondary Endpoints:					
Radiographic :					
CT fusion (%)	All Joints	Week 24	66.5	62.6	<0.001
	All Joints	Week 36	68.8	73.9	0.103
	Full Complement of Joints	Week 36	63.5	69.3	0.202
Radiographic Union (3 Aspects) (%)	Full Complement of Joints	Week 24	30.8	32.8	0.054
	Full Complement of Joints	Week 36	30.0	35.8	0.198
	Full Complement of Joints	Week 52	36.9	36.5	0.020
Radiographic Union (3 Aspects) (%)	All Joints	Week 24	38.3	37.9	0.007
	All Joints	Week 36	39.1	42.9	0.072
	All Joints	Week 52	48.5	44.3	<0.001
Radiographic Union (2 Aspects) (%)	Full Complement of Joints	Week 24	60.8	66.4	0.194
	Full Complement of Joints	Week 36	62.7	69.3	0.249
	Full Complement of Joints	Week 52	70.8	75.2	0.115
Radiographic Union (2 Aspects) (%)	All Joints	Week 24	67.5	70.9	0.049
	All Joints	Week 36	70.3	72.4	0.021
	All Joints	Week 52	77.2	77.8	0.005
Clinical Union:					
Clinical Healing (%)	Patient	Week 24	83.1	83.9	0.010
	Patient	Week 36	84.6	88.3	0.038

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
	Patient	Week 52	87.7	88.3	0.003
Clinical Healing (%)	Full Complement of Joints	Week 24	82.3	83.2	0.011
	Full Complement of Joints	Week 36	84.2	86.9	0.022
	Full Complement of Joints	Week 52	86.2	87.6	0.008
Clinical Healing (%)	All Joints	Week 24	83.5	83.3	<0.001
	All Joints	Week 36	86.8	85.7	<0.001
	All Joints	Week 52	88.3	87.2	<0.001
Delayed/Non-Union (%)	Patient Level	Week 24	8.8	10.2	<0.001
		Week 36	6.5	8.0	<0.001
		Week 52	4.2	5.8	<0.001
Therapeutic Failure Rate (%)	Patient Level	Week 24	9.2	10.9	<0.001
		Week 36	7.7	9.5	<0.001
		Week 52	7.3	8.0	<0.001
Composite Success (%)	Patient Level	Week 24	70.8	69.3	0.009
		Week 36	71.5	77.4	0.179
Clinical Success (%)	Patient Level	Week 24	74.6	78.1	0.071
		Week 36	73.8	75.9	0.041
		Week 52	76.9	78.1	0.022

Summary of Results (mITT Population)

Endpoint	Joint Analysis Summary	Timepoint	Augment	Autograft	p-value
Functional:					
SF-12 (Mean PCS)	Patient Level	Week 24	39.9	41.4	<0.001
		Week 36	41.4	44.2	0.020
		Week 52	42.4	45.0	0.015
FFI (Mean Total Score)	Patient Level	Week 24	27.38	22.30	0.012
		Week 36	21.96	18.19	0.001
		Week 52	20.08	17.52	<0.001
AOFAS (Mean Total Score)	Patient Level	Week 24	71.7	73.9	<0.001
		Week 36	75.0	77.3	<0.001
		Week 52	77.8	78.2	<0.001
Pain:					
Fusion Site Pain (Mean)	Patient Level	Week 24	18.9	16.5	0.001
		Week 36	16.2	13.9	
		Week 52	13.2	12.9	<0.001
Weight-Bearing Pain (Mean)	Patient Level	Week 24	23.5	19.3	0.016
		Week 36	18.8	15.7	0.005
		Week 52	15.6	15.8	<0.001
Significant Graft Site Pain (%)	Patient Level	Week 24	0	12.4	<0.001
		Week 36	0	7.3	<0.001
		Week 52	0	8.8	<0.001
Graft Harvest Site Pain	Patient Level	Week 24	0	8.1	<0.001

Summary of Results (mITT Population)

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

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