Clinical Study Report: BMTI-2005-04

1 TITLE PAGE

Study Title:	A Prospective, Randomized, Controlled, Multi-Center Human Clinical Feasibility Trial to Evaluate the Preliminary Safety and Effectiveness of GEM OS1™ Bone Graft Compared to Autologous Bone Graft as a Bone Regeneration Device
Study Number:	BMTI-2005-04
Study Phase:	Pilot (Feasibility)
Study Design:	Prospective, randomized, controlled, multi-center trial
Product Name:	*GEM OS1™*
Formulation:	Two Components: Package of β-TCP with rhPDGF-BB (becaplermin) solution
Indication:	Bone Regeneration Device for Foot and Ankle Arthrodesis
IDE No.:	G050118
Study Initiated (first subject enrolled):	07 Mar 2006
Study Completed (all subjects followed for 36 weeks):	05 Apr 2007
iDMC Meeting Date	27 October 2006
Principal Investigators:	Multicenter (see Appendix 15.1.4); 3 Centers
Sponsor:	BioMimetic Therapeutics, Inc. 389-A Nichol Mill Lane Franklin, TN 37067 615-844-1280 615 844 1281 (fax)
Responsible Medical Officer:	Ken Carlson, MD
Final Date:	06 July 2009

GCP Compliance Statement

This study was conducted in compliance with Good Clinical Practices and with all applicable federal, state and local regulations.

2 SYNOPSIS

Sponsor: **BioMimetic Therapeutics, Inc.**

Name of Finished Product: ***GEM OS1™***

Study Title:
A Prospective, Randomized, Controlled, Multi-Center Human Clinical Feasibility Trial to Evaluate the Preliminary Safety and Effectiveness of GEM OS1™ Bone Graft Compared to Autologous Bone Graft as a Bone Regeneration Device

Investigators and Study Centers: Multicenter (see Appendix 15.1.4)

Publication (reference): Not Applicable

Studied Period:

March 2006 (first subject enrolled) to
April 2007 (all subjects have been followed to the Week 36 visit)

Phase of Development: Pilot (Feasibility)

Hypothesis: *GEM OS1*™ is safe and effective as a bone grafting substitute to autologous bone graft in a representative clinical model (hindfoot and ankle fusions)

Methodology:

This is a prospective, randomized, controlled, multi-center feasibility clinical trial designed to evaluate the preliminary safety and effectiveness of *GEM OS1*™ compared to autologous bone graft (ABG) in hindfoot/ankle fusion procedures. The study included 20 subjects requiring fusion in the hindfoot/ankle. Study subjects were randomized to either *GEM OS1*™ or ABG (in a 2:1 ratio) as a bone grafting material. They then underwent an ankle/hindfoot fusion procedure using, using standardized surgical technique and hardware fixation devices for a given procedure across both treatment groups.

The subjects completed follow-up visits at the Day 7-14, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 24, and Week 36 timepoints. At these visits, the site investigator assessed clinical and functional outcomes, and plain film radiographs were taken, with CT scans taken for supplemental and confirmatory information at Week 6, Week 12, and Week 16 (if there was evidence of delayed union at Week 12, or at investigator's discretion). The radiographs were used by a centralized independent radiologist, who was blinded to the treatment groups, to assess pre-determined criteria for union/fusion at the fusion site.

Number of Subjects (Planned and Analyzed):
A total 20 subjects were enrolled for this study. Subjects were analyzed for safety and efficacy at each of the timepoints noted above.

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

Test Therapy:
Standard Rigid Fixation + *GEM OS1*, with sodium acetate buffer containing 0.3 mg/ml rhPDGF-BB

Duration of Planned Follow-up: 9 months

Reference Therapy:

Standard Rigid Fixation + Autologous Bone Graft

Criteria for Evaluation:

Effectiveness:

The primary efficacy endpoint was the mean time to Radiographic Union, as assessed by an independent radiologist blinded to study treatment looking at plain film radiographs. Radiographic Union was rigorously defined as osseous bridging across subchondral surfaces on 3 of the 4 aspects: anterior, posterior, medial and lateral cortices (with supplemental aspects including superior and inferior).

Secondary endpoints included semi-quantitative radiographic and CT scan assessments, clinical union rate, time to full weight-bearing, Visual Analog Scale pain assessment, AOFAS Scale, Foot Function Index, clinical utility assessment and evidence of nonunion.

Safety:

Any complications associated with injury or standard surgical treatment were recorded. All adverse events, both anticipated and unanticipated, were recorded and evaluated whether or not they were considered related to study treatment. Events considered to be normal sequelae to surgery (such as swelling, edema, and pain) were also collected.

Statistical Methods:

Descriptive statistics only were performed for the efficacy parameters to conduct a preliminary evaluation of effectiveness. The current sample size is too small to perform formal statistical analyses, so no statistical testing was performed. In these analyses, categorical data are displayed as percents, and continuous data are displayed using descriptive statistics (N, mean, standard deviation, median, minimum and maximum). Time to event data are displayed using life tables.

The overall incidence of adverse events and of device-related complications are compared between the treatment groups using a Fisher exact test with an α-level for statistical significance set at 0.05.

Effectiveness:

The number and percent of subjects achieving radiographic union (as defined by the protocol and using existing literature standards) are displayed overall and by treatment group. The time to radiographic union (in days) are summarized by treatment group with lifetables displaying Kaplan-Meier estimates, and corresponding survival curves. For each of the radiographic assessments (osseous bridging, abnormal bone formation at fusion site), the number and percent of subjects in each category are displayed overall and by treatment at each time the data is collected.

The number and percent of subjects achieving clinical union and the number and percent of subjects achieving full weight bearing at each visit are displayed overall and by treatment group. The time to full weight bearing (in days) is summarized by treatment group with lifetables displaying Kaplan-Meier estimates, and corresponding survival curves.

The number and percent of subjects who report evidence of infection or ulceration are summarized overall and by treatment group at each timepoint. The number and percent of subjects in each response category of each question in the Clinical Utility Assessment are displayed overall and by treatment group. The VAS pain assessment at each visit and the change from surgery to each visit are displayed overall and by treatment group at each timepoint. The total AOFAS Ankle Hindfoot scale as well as subscale scores are summarized overall and by

treatment group at each timepoint.

Safety:

The number and percent of subjects overall and in each treatment group who experience at least one adverse event, device related adverse event, serious adverse event, or related, serious adverse event are displayed. The treatment groups were compared using a Fisher exact test. The number and percent of subjects experiencing these events were also summarized by body system, preferred term, and by the highest severity. These events are further broken down by local and systemic event categorization.

The number and percent of subjects experiencing at least one adverse event identified as a surgical complication are displayed overall and by treatment group. The treatment groups were compared using a Fisher exact test. The number and percent of subjects experiencing each of the individual complications are similarly displayed, as well as by highest severity.

Summary of Results

Effectiveness:

As determined by available and interpretable plain film assessment by the independent radiologist, 5 of 12 *GEM OS1* subjects (41.7%) were considered radiographic unions at 12 weeks, compared to 1 of 3 in the ABG group (33.3%), At the final Week 36 visit, using imputed Week 24 data when available, 10 of the 14 *GEM OS1* assessments (71.4%) were radiographic unions, compared to 3 of the 4 ABG subjects (75.0%). Overall, radiographic union (as defined in the study protocol) was positively assessed in 10 of the *GEM OS1* subjects (71.4%) and 3 of the ABG subjects (50.0%). The median time to radiographic union for the *GEM OS1* subjects was 145.0 days. It should be noted that some radiographic views were considered to be uninterpretable or were not available for assessment, therefore the N's may vary based upon available data.

At Week 12, 7 of the 14 *GEM OS1* subjects (50.0%) had demonstrated clinical union, while all 5 of the ABG subjects had been assessed to have achieved clinical union. At the Week 24 and Week 36 visits, 11 of 13 *GEM OS1* subjects (84.6%) had been assessed as complete clinical unions, while all 6 ABG subjects were considered clinical unions. Overall, 12 of the 14 *GEM OS1* subjects (85.7%) showed clinical evidence of union.

At Week 12, 9 of the 13 *GEM OS1* subjects (69%) showed moderate (4 subjects) or complete (5 subjects) osseous bridging per independent assessment of CT scans. This compared to 3 of the 5 ABG subjects (60%). These data suggest that subjects treated with *GEM OS1* have an equivalent and potentially favorable trend of early osseous bridging assessed by rigorous CT evaluation as compared to ABG. There was no abnormal bone formation observed in the *GEM OS1* treatment group. Additionally, no radiographic evidence of infection was seen in any subjects, which is a clinically significant observation.

At Week 24, 12 of the 13 *GEM OS1* subjects (87.1%) had achieved full weight bearing, while all 6 ABG subjects had done so. The median time to full weight bearing was 72.0 days for the *GEM OS1* group and 75.5 days for the ABG group.

Overall, 2 of the 14 subjects (14.3%) in the *GEM* OS1 treatment group showed clinical evidence of infection. It is notable that the independent radiologist did not detect any radiographic evidence of infection for these subjects.

In both treatment groups, pain at the fusion site started to improve at 4 weeks after surgery. The mean VAS scores at Week 4 were 21.0 (median of 12.0) for *GEM OS1* subjects, and 24.7 (median of 10.3) for ABG subjects. For *GEM OS1* subjects, this was a mean -11.9 change

(median of -18.5) from pre-surgery. The mean change seen from pre-surgery for ABG subjects was -11.7 (median of -3.3). The VAS pain assessments at the fusion were comparable between both treatment groups across all timepoints.

At the Day 7-14 visit, ABG subjects reported a mean VAS pain score of 42.1 (median of 41.3) at the site of the bone graft harvest. At Week 6, subjects reported pain at the graft harvest site at a mean VAS score of 24.6 (median of 18.8). At Week 12, there was still one subject who reported a VAS pain score of 62.0 at the bone graft harvest site, this subject was still reporting a graft harvest site VAS pain score of 32.5 at Week 24 and 9.5 at Week 36. All *GEM OS1* subjects were spared the pain and morbidity associated with a separate autograft harvest site.

At Week 36, the median overall AOFAS score was comparable in both groups (80.5 for ABG, 79.0 for *GEM OS1*), though the mean trended higher in the ABG group (82.2 compared to 71.1 for *GEM* OS1). The overall AOFAS scores were comparable between treatment groups up to Week 12, and demonstrate that subjects in both groups demonstrated an upward trend for implicit outcomes.

At Week 36, the average foot function index trended slightly better for the ABG group (mean total score of 15.6, median of 10.9) compared to the *GEM OS1* subjects (mean total score of 23.6, median of 14.7). This was largely due to the poor scores from subjects who did not achieve clinical union in the *GEM OS1* study group. Both treatment groups showed a downward trend throughout the study, indicating improved foot function as subjects recovered from their fusion procedure.

At Week 36, the mean SF-12 Physical Component Summary score was 38.8 for *GEM OS1* (median of 41.6) compared to 47.2 (median of 48.4) in the ABG group. The scores for the Mental Component Summary were more comparable, with a mean of 52.5 for *GEM OS1* (median of 56.6) compared to 49.9 (median of 53.5) for the ABG subjects.

No investigator assessed *GEM OS1* or ABG as Unacceptable in any category of the Clinical Utility Assessment six months after treatment. In the category "Overall Satisfaction with the Treatment Outcome, the investigators assessed *GEM OS1* as Excellent for 7 out of the 13 assessments (54%), as Good for 4 assessments (31%) and as Average for 2 assessments (15%).

There were two subjects in the *GEM OS1* group who required revision surgeries after the failure of their study procedure.

Safety:

In the *GEM OS1* group, there were 49 adverse events reported in 13 subjects (92.9% of subjects), and in the ABG group there were 15 events reported in 5 subjects (83.3% of subjects). 34 adverse events in the *GEM OS1* group were considered surgical complications, in 12 subjects (85.7% of subjects). In the ABG treatment group, there were 7 surgical complications reported in 3 subjects (50.0% of subjects). There were 3 adverse events in the *GEM* OS1 group related to procedure hardware; none of these events were related to the study device, with 1 event related to accessory hardware (screws) and 2 related to cast discomfort. It is notable that none of the differences in study groups approached statistical significance.

There were no severe or life-threatening adverse events reported in the study. There were no serious adverse events reported in the study. No subjects discontinued the study due to an adverse event. None of the adverse events reported were considered probably related or definitely related to study treatment.

Of the 49 adverse events reported in the *GEM OS1* treatment group, 29 adverse events were

among those considered normal sequelae for a hindfoot/ankle fusion procedure, such as pain, swelling, edema, and warmth at the fusion site. There were 10 of the 15 adverse events in the ABG subjects considered normal sequelae.

The most commonly reported adverse events were feeling hot, local swelling, and tenderness. Swelling and tenderness were seen in both treatment groups, but feeling hot (warmth at the fusion site) was only seen in the *GEM OS1* group during this study. 7 *GEM OS1* subjects (21.4%) reported warmth at the fusion site, which is a generally accepted event associated with surgical procedures.

The most common complications reported were local swelling, seen in 8 *GEM OS1* subjects (57.1% vs. 33.3% in the ABG group); feeling hot (warmth at fusion site) seen in 7 *GEM OS1* subjects (50.0% vs. 16.7% for ABG); and tenderness, observed in 5 *GEM OS1* subjects (35.7% vs. 0.0% for ABG subjects).

CONCLUSIONS

Effectiveness Conclusions:

The rate of radiographic union as determined by the radiologist based on available and interpretable studies of subjects followed through 12 weeks (41.7%), 16 weeks (58.3%) and 36 weeks (71.4%) was favorable for *GEM OS1* when compared to the rates seen for the subjects who received autologous bone graft. The observed rates of complete clinical union and full weight bearing at the same time points were also positive.

The amount of observed early osseous bridging based on available and interpretable studies in *GEM OS1* subjects at 12 weeks was also positive compared to ABG subjects. The study by Coughlin et al (2006) indicated that osseous bridging (observed in CT scans) of >50% was clinically significant. In this study, CT scans at Week 6 indicate >50% osseous bridging for 39% of *GEM OS1* subjects. At Week 12, 69% of *GEM OS1* subjects demonstrated osseous bridging of >50% in CT scans.

There were two subjects in the *GEM OS1* group who required revision surgeries after the failure of their study procedure. The fact that there were not comparable failures in the small ABG group resulted in lower mean quality of life scores for the *GEM OS1* subjects, although median scores were comparable in the AOFAS Ankle-Hindfoot and Foot Function Index scales.

The use of *GEM OS1* as a synthetic grafting material in lieu of having to obtain autograft was considered to be a practical and potentially clinically useful alternative for the surgeons who were performing the ankle and hindfoot fusion procedures. Post-operative product utility assessments for *GEM OS1* were favorable in all categories. The total time spent on anesthesia and actual surgery for *GEM OS1* was noticeably shorter when compared to ABG procedures, with a mean procedure times of 143.7 minutes for the ABG group compared to 117.6 minutes for the *GEM OS1* group. In the Clinical Utility Assessment made six months after the study procedure for the category "Overall Satisfaction with the Treatment Outcome, the investigators assessed *GEM OS1* as Excellent for 7 out of the 13 assessments (54%), as Good for 4 assessments (31%) and as Average for 2 assessments (15%).

The amount of pain felt at the fusion site, as reported by subjects on a visual analog scale, was similar in both treatment groups, and the average change in pain assessment from pre-surgery to Week 4 was favorable for *GEM OS1*. Further, all *GEM OS1* subjects were spared the additional harvest of autograft which can be associated with significant pain and morbidity.

There was no abnormal bone formation observed in the *GEM OS1* treatment group.

Additionally, no radiographic evidence of deep infection or nonunion was seen in any subject, which is a clinically significant observation.

Human serum samples were collected and analyzed for the presence of anti-rhPDGF-BB antibodies. Of the 13 evaluable subjects in the GEM OS1 group, 2 (15.4%) tested positive for anti-rhPDGF-BB antibodies. No neutralizing antibodies were detected, and no subjects in the autograft group tested positive for anti-rhPDGF-BB antibodies.

Safety Conclusions:

There were no safety concerns noted during this study. There were no serious adverse events or serious surgical complications reported, and all reported adverse events were of mild or moderate severity. None of the adverse events were considered probably or definitely related to the study device.

There were higher rates of mild and moderate warmth at the fusion site seen in the *GEM OS1* treatment group. There was also a higher rate of surgical complications in the *GEM OS1* procedures (12 of 14 subjects, 85.7%, compared to 3 of 6 ABG subjects, 50.0%), though this was not statistically significant and may be due to the small sample size in the ABG group. No other unusual trends were observed in the safety data. The rates and types of adverse event occurrence were as expected for subjects who underwent an ankle or hindfoot fusion procedure.

Summary:

The results of this study provide preliminary support that the use of *GEM OS1* in hindfoot/ankle fusions may be an alternative safe and effective means of obtaining radiographic and clinical union without having to harvest autologous bone graft. Although there were two clinical nonunions observed in the *GEM OS1* clinical study group, it is noted that in both cases, the investigators felt that perhaps too much TCP matrix was placed within the fusion site, which may have prevented primary direct host bone to host bone apposition, an environment considered paramount to successful fusion surgery. It can reasonably be concluded that that neither autograft nor *GEM OS1* should be applied in such a way that prevents primary bony apposition or rigid internal fixation. It should also be noted that one of the clinical nonunions, which was revised using autograft, still did not achieve bony union on the first revision attempt.

There were no serious surgical complications observed with *GEM OS1*, and no adverse events that were considered related to study treatment. The rates and types of adverse event occurrence were as expected for subjects who underwent an ankle or hindfoot fusion procedure.

The above noted observations, although limited by the number of subjects studied, indicate that *GEM OS1* appears to be a safe and clinically useful bone graft substitute for use in foot and ankle fusions. As this study is designed to provide preliminary data establishing *GEM OS1* as a non-inferior treatment alternative to ABG, the safety and efficacy data for clinical and radiographic endpoints (plain films and CT scans) suggest that equivalent or superior outcomes to ABG may be achieved, while eliminating the established morbidity and increased surgical time associated with harvesting bone graft:

The study also highlights some potentially important benefits of *GEM OS1* compared to the use of autologous bone graft:

- Improved de facto safety profile due to elimination of ABG harvest site
  - Reduced pain burden to subject by elimination of harvest site
  - Eliminating a potential locus of infection and/or other morbid complications due to reduction of surgical sites and surgical time

- Decreased procedure / anesthesia time
- Ease of use for the surgical team versus harvest and preparation of autograft

These potential benefits, in light of the lack of safety concerns, warrant further investigation in a study designed to achieve statistical significance. A follow-up pivotal study is currently underway.

Final Report Date: 06 July 2009

Prepared in: Microsoft Word 2003