1 TITLE PAGE

Study Title: A Human Clinical Trial to Evaluate the Clinical Utility of GEM OS™ Bone Graft as a Bone Regeneration Device in Foot and Ankle Arthrodesis Procedures

Study Number: BMTI-2005-03

Study Phase: Registration

Study Design: Prospective, open-label, multi-center trial

Product Name: GEM OS™

Formulation: Two Components: Package of β-TCP with 0.3 mg/ml rhPDGF-BB (becaplermin solution) in a sodium acetate buffer

Indication: Bone Regeneration Device for Foot and Ankle Arthrodesis

Canadian ITA: 99061

Study Initiated (first subject enrolled): 24 Jan 2006

Study Completed (all subjects followed for 36 weeks): 14 Sep 2007

Initial Independent Data Monitoring Committee (iDMC) Meeting: 27 Oct 2006

Principal Investigators: Multicenter (see Appendix 15.1.4.1); 3 centers

Sponsor: BioMimetic Therapeutics, Inc.

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Responsible Medical Officer: Michael Czorniak, MD, MS

Final Date: 29 May 2008

GCP Compliance Statement
This study was conducted in compliance with Good Clinical Practices and with all applicable federal and local regulations.
2 SYNOPSIS

Sponsor: BioMimetic Therapeutics, Inc.
Name of Finished Product: GEM OSI

Study Title:
A Human Clinical Trial to Evaluate the Clinical Utility of GEM OS™ 1 Bone Graft as a Bone Regeneration Device in Foot and Ankle Arthrodesis Procedures

Investigators and Study Centers: Multicenter (see Appendix 15.1.4.1)

Publication (reference): Not Applicable

Studied Period:
January 2006 (first subject enrolled) to September 2007 (all subjects have been followed for a minimum of 36 weeks)

Phase of Development: Registration

Objectives:
Evaluate the clinical utility of GEM OSI as a bone regeneration device in foot and ankle fusions by demonstration of safety and effectiveness.

Methodology:
Many musculoskeletal procedures, such as the surgical treatment of fractures, fusions, and non-unions require bone graft to ensure adequate bone healing. One of the most widely used options for bone graft is autologous bone due to the fact that there is no risk of cross contamination with autologous bone in contrast to allografts or xenografts, as well as its bioactivity; however, clinical difficulties have been associated with autograft, including persistent pain and morbidity related to the harvest site. While bone grafting is frequently employed in the treatment of foot and ankle fusions, there are currently no generally accepted alternatives to autograft for these fusion procedures. A nearly identical therapeutic device (GEM 21S) has demonstrated the safety and effectiveness of β-TCP and rhPDGF-BB for promoting bone regeneration in the jaws. The present study was designed to assess the safety and effectiveness of this formulation in patients undergoing foot and ankle fusions.

This is a prospective, open-label, multi-center trial designed to evaluate the safety and effectiveness of GEM OSI as bone graft material in foot/ankle fusion procedures. During the study, 60 subjects requiring fusion in the foot/ankle underwent at least one foot/ankle fusion procedure using GEM OSI applied to the fusion site at the time of open surgical treatment and in conjunction with internal rigid fixation. To the extent possible at each site, standardized surgical technique and hardware fixation devices were used for a given procedure. Plate fixation was excluded.

The subjects completed follow-up visits at the Day 7-14, Week 6, Week 9, Week 12, Week 16, Week 24, and Week 36 timepoints. Subjects were followed by the investigators beyond the study period, when necessary, according to standard follow-up intervals. At these visits, the site investigator assessed clinical and functional outcomes, and plain film radiographs were taken, with CT scans made for supplemental and confirmatory information at Week 6, Week 12, and Week 16 (if necessary). The radiographs (CT scans and plain films) were assessed by a central independent radiologist for evidence of union and other radiographic parameters at the fusion site.

Number of Subjects (Planned and Analyzed):
A total of 60 subjects were enrolled for this study. Of these subjects, 39 (65%) had at least one identified risk factor for failure of fusion, with 21 (35%) listing multiple risk factors, and 20 (33%) reporting a previous history of revision.

**Diagnosis and Main Criteria for Inclusion:**
Male and female subjects over the age of 16 years requiring a foot or ankle fusion procedure requiring a bone graft.

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

**Duration of Treatment:** 9 months

**Reference Therapy:**
No control group was used for this study. A nearly identical therapeutic device (GEM 21S) was studied in a 180-patient blinded randomized controlled trial compared with β-TCP alone for promoting bone regeneration in the jaws. The current study was designed to determine if this combination of β-TCP and rhPDGF-BB was also safe and effective in promoting bone regeneration in foot and ankle fusions. The outcomes of the GEM OS1 treatment were planned for comparison to literature-based historical controls for foot and ankle fusions.

**Criteria for Evaluation:**

**Effectiveness:**
The primary efficacy endpoint was the rate of radiographic healing (union), as assessed by an independent radiologist assessing plain film radiographs and CT scans. Secondary endpoints included radiographic and CT scan assessments, time to full weight-bearing, range of motion, pain, and Quality of Life (QOL) and outcomes assessments. Subjects were also assessed for clinical healing and/or lack of need for revision surgery. The clinical and radiographic endpoint data are combined in composite success and aggregate success endpoints, which are defined in the protocol and statistical analysis plan, and provide overall assessments of treatment success.

**Safety:**
Any complications associated with the underlying condition or standard surgical treatment, including nonunion, were evaluated. All adverse events, both anticipated and unanticipated, were recorded and evaluated whether or not they were considered related to study treatment.

**Statistical Methods:**
Subject success is evaluated in the following manners: clinical success (lack of need for revision surgery within 12 months), radiological/CT success (bridging on at least 2 out of 4 radiologic aspects from plain film radiographs, or osseous bridging >50% from CT scans), mean time to radiographic union, functional success (weight bearing, lack of significant pain and edema, etc), and composite/aggregate success (a conservative combination of the above).

Categorical data will be displayed as percents, and continuous data will be displayed using descriptive statistics (N, mean, standard deviation, median, minimum and maximum). Time to event data will be displayed using life tables. For time to event analyses, the start date will be Visit 2, the date of surgery. For all other measures, the earliest visit date prior to surgery will serve as the baseline.

**Effectiveness:**
The effectiveness endpoints are assessed using data from all treated subjects, and are also
presented for those subjects who had risk factors for nonunion, and for those subjects who had hindfoot/ankle surgery.

The number and percent of subjects achieving radiographic union are displayed. The time to radiographic union (in days) is summarized with a lifetable displaying Kaplan-Meier estimates, and a corresponding survival curve. For each of the secondary radiographic assessments (osseous bridging, abnormal bone formation, callus formation), the number and percent of subjects in each category are displayed at each time the data is collected.

The number and percent of subjects who were not recommended for revision surgery within 12 months of the study treatment are displayed. A listing of subjects recommended for revision surgery with risk factors for nonunion are also displayed. The nonunion rate is assessed for treated subjects who had ankle surgery only (ankle subgroup) and for treated subjects who had subtalar surgery only (subtalar subgroup). These subset analyses allow for direct comparison to historical controls, as defined in the literature.

The composite success endpoint is summarized overall with and then without the edema parameter of the endpoint, which independently may not be a negative indicator of success. The aggregate 6 Month/9 Month success endpoints are summarized at Week 24 follow-up and Week 36 follow-up, respectively. Each of these success endpoints were determined independently by two statisticians using the data listings.

The number and percent of subjects achieving complete union (radiographic and clinical) are summarized at each timepoint. The number and percent of subjects achieving full weight-bearing (FWB) are displayed. The time to full weight bearing is summarized with a lifetable displaying Kaplan-Meier estimates.

The number and percent of subjects who report evidence of infection/ulceration are summarized at each timepoint. The number and percent of subjects in each response category of each question of the Clinical Utility Assessment are displayed separately for the post-surgery and six-month assessments. Descriptive statistics for pain are displayed at each timepoint. The total AOFAS scale, as well as the pain, function, and alignment subscale scores are summarized at each timepoint.

The predictive ability of the Week 12 and Week 16 CT scans is presented in 2 x 2 tables of Week 12-16 CT scan result (< 50% osseous bridging, ≥ 50% osseous bridging) by radiographic outcome (union, nonunion). The predictive ability of the CT scans for Months 6 and 9 radiographic outcomes is presented using a two-sided Fisher Exact test.

Safety:
The number and percent of subjects who experience at least one adverse event, device related adverse event, serious adverse event, or device related serious adverse event are displayed. The number and percent of subjects experiencing these events are also summarized by body system, preferred term, and by the highest severity. These events are further broken down by local and systemic event categorization. A listing of adverse events resulting in discontinuation from the study is also displayed. Adverse events are coded using the MedDRA 8.0 dictionary or higher.

The number and percent of subjects experiencing at least one adverse event identified as a complication are displayed. Adverse events (AEs) were reviewed to identify those that are considered to be related to the hardware used during surgery and/or related to post-surgical immobilization. These hardware-related AEs will be classified by the designated Medical Monitor into one of four categories: primary device (GEM OS1) complication, accessory hardware complication, immobilization complication or indeterminate. Upon review of the
adverse event data, only three categories were utilized, as there were no primary device complications observed. Time to first complication is displayed in a Kaplan-Meier survival curve. The number and percent of subjects experiencing each of the individual complications are similarly displayed, as well as by highest severity. A listing of complications resulting in discontinuation from the study is also displayed.
**Summary of Results:**

**Effectiveness:**
The independent radiologic assessment consisted of review of CT scans during the early healing timeframe, as well as plain film radiographs taken throughout the duration of the study. The assessment of healing was made if bridging of subchondral bone (on at least 2 radiologic aspects) was detected upon independent review of plain film radiographs.

A total of 44/55 subjects (80% of assessments) with sufficient evaluable radiographs had achieved radiographic union after 16 weeks, 46/54 (85%) at week 24, and 52 of 59 subjects (88%) had achieved radiographic union after being followed for 36 weeks. Literature-reported rates of radiographic union include 90% for ankle fusions, and 84% in subtalar fusions. In subjects achieving radiographic union, the median time to radiographic healing was 87 days.

CT scans provide a robust and complete assessment of early healing, and are predictive of the prognosis of the fusion. These data are available at 6 and 12-16 weeks post-operatively. At the Week 6 assessments, 22 of the 51 subjects (43%) were judged to show moderate (13 subjects) or complete (9 subjects) osseous bridging as determined by the independent radiologist upon review of CT scans. At Week 12-16, 44 of the 59 assessments (75%) showed moderate (10 subjects) or complete (34 subjects) osseous bridging.

Of the 60 subjects treated in the study, 54 (90.0%) achieved clinical success, with the investigator indicating that they did not require or were not recommended for revision surgery within 12 months of the index surgery. This revision rate of 10% compares to a published rate of 9% observed in a large (1262 patients) meta-analysis of ankle arthrodeses. A total of 130 joints were treated with GEM OSI for all 60 subjects. Taking into account the total number of joints treated with GEM OSI, a clinical success rate of 124/130 (95.4%) was observed in this study.

The aggregate and composite success endpoints were used to quantify the success of the study procedure using a combination of subject-specific radiologic and clinical/functional data. The aggregate success rate, the parameters of which were defined during the study through discussion with the investigators and iDMC, was 83.1% at both 6 and 9 months.

The composite success rate was 52.7% at 6 months and 54.2% at 9 months; if it is calculated using all criteria except for edema (an expected occurrence in this population post-operatively, which is considered normal sequelae to the surgical procedure), the rate increases to 81.4% at both 6 and 9 months.

At Week 16, 33 subjects (56%) were considered complete clinical unions by the investigator. At Week 36, complete clinical union was assessed for 42 subjects (71%). At Week 36, 7 subjects (12%) were considered "not united" by the investigator's subjective assessment which takes into account both clinical and radiologic observations.

All 60 subjects attained full weight bearing during the study. The median time to full weight bearing was 84 days. Overall, evidence of infection was detected clinically in 6 (10%) of the 60 subjects. Notably, there were no deep wound infections observed during the study.

An assessment of intense pain was unusual at any time during the study. The percentage of subjects reporting intense pain went from 12% of assessments at Screening, to 3% at Week 12, 2% at Week 24, and 7% at Week 36. By the Week 36 assessment, 17 of 57 subjects (30%) reported no pain and 15 subjects (26%) reported minimal pain, while 21 (37%) reported episodic or ongoing pain, a finding consistent with foot and ankle surgery. It should be noted that all patients were spared the pain and morbidity associated with harvesting autograft.
At Week 12, the mean overall AOFAS Ankle-Hindfoot score was 60.7 (±17.99), with a median of 65, which represented a mean improvement of 19.0 points from baseline. At the Week 36 assessment, the overall score showed a mean of 64.1 (±23.36) with a median of 73.5.

*GEM OSI* was not considered Unacceptable in any category of the post-operative clinical utility assessment. The overall ease of surgical procedure was considered Excellent in 38% of the procedures, and Good in 53%. In the six-month clinical utility assessments, the overall satisfaction of the investigators with the treatment outcomes was rated as Excellent for 69% of the procedures, Good for 17%, Average for 8%, and Poor for 5%.

The data from various effectiveness endpoints at 9 months are summarized in the table below. The table includes the rates used for the non-inferiority hypothesis testing, and equivalent rates from the literature on foot and ankle fusions.

**Summary of Key Effectiveness Endpoints at 9 Months**

<table>
<thead>
<tr>
<th>Effectiveness Endpoint</th>
<th>Study Population</th>
<th>Hypothesis Testing Assumption</th>
<th>Literature Reported Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiographic Union Rate</strong></td>
<td>ITT 88%</td>
<td>Hindfoot/Ankle 88%</td>
<td>At Risk 84%</td>
</tr>
<tr>
<td><strong>Radiographic Non-union Rate</strong></td>
<td>12%</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Revision Rate</strong></td>
<td>10%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Aggregate Success Rate</strong></td>
<td>83%</td>
<td>91%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Composite Success Rate</strong></td>
<td>81%</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Mean Time to Full Weight Bearing (days)</strong></td>
<td>84</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td><strong>AOFAS Hindfoot/Ankle Overall Score</strong></td>
<td>Mean 64.1</td>
<td>Median 73.5</td>
<td></td>
</tr>
<tr>
<td><strong>AOFAS Midfoot Overall Score</strong></td>
<td>Mean 72.5**</td>
<td>Median 77**</td>
<td></td>
</tr>
</tbody>
</table>

* When edema criterion is not included.
** This parameter for midfoot population only.
*** High risk patients include subjects who possess at least one of the following risk factors: diabetic.
Safety:
There were 230 adverse events reported in 55 subjects (91.7%), with 117 of these events among those considered normal sequelae for a foot fusion procedure (e.g. increased pain, edema, warmth observed during the study period), however, investigators were asked to report any and all adverse events. There were 20 reported adverse events associated with hardware used during the procedure, which were classified by the Medical Monitor as to the specific procedure hardware. None of these events were associated with the *GEM OSI* device.

The investigators also made an assessment of each adverse event’s possible relationship of causality to *GEM OSI*. There were 22 adverse events in 4 subjects that the investigator assessed as likely or definitely related to the study device. A total of 20 of these 22 events (warmth at fusion site, impaired healing, swelling, tenderness, motion at the fusion site, broken screw) were associated with a decline in the course of the subject’s post-operative healing, and occurred at least 9 weeks after study treatment. The other two events (muscle spasms and foot pain) occurred in a single subject 11 days after the study procedure. Notably, 3 of these 4 subjects were recommended for revision surgery. It is of also of note that all adverse events assessed as possibly or definitely related to the investigational device occurred in subjects receiving midfoot fusion procedures.

There were 4 serious adverse events reported during this study, in 4 different subjects, all clearly unrelated to *GEM OSI*. The majority of the reported events (216 of 230) were considered moderate or mild. The 10 non-serious adverse events assessed as severe (warmth at the fusion site, impaired healing, swelling, tenderness, muscle spasms, foot pain, motion at the fusion site) occurred in 4 subjects who were recommended for revision surgery. Therefore, the severity of some of these events are likely attributed to the poor overall healing and union status of the subject.

The incidence rates of the most commonly reported events were unremarkable for subjects recovering from a foot and ankle fusion procedure. These included feeling hot (e.g. warmth noted at the fusion site), local swelling, tenderness, medical device complications (including problems with accessory hardware such as screws, or immobilization such as casts or braces), impaired healing (any digression in healing status noted on the CRF, seen in 16.7% of subjects), pain in extremity, sensory disturbance, and post procedural pain.

There were no serious or life-threatening complications associated with the surgical procedure, and no adverse events that required device removal.

The safety data are summarized in the table below.

<table>
<thead>
<tr>
<th>Summary of Safety Data</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Any AE, excluding normal sequelae</td>
</tr>
<tr>
<td>Device-related Adverse Event (per Investigator)</td>
</tr>
<tr>
<td>Serious Surgical Complication</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Concussion</td>
</tr>
<tr>
<td>Colon Cancer</td>
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<tr>
<td>Pulmonary Embolism</td>
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</tbody>
</table>

Conclusions

Effectiveness Conclusions:
When assessing the success of fusion, it is meaningful to consider multiple parameters, including clinical, functional, and radiographic (CT and plain films). One must also consider baseline co-morbidities, such as diabetes, previous fusion surgery, smoking history, and underlying pathology/injury when evaluating the effectiveness of foot and ankle fusion procedures.

Currently, there are no generally accepted alternatives to autograft for fusion procedures of the foot or ankle. Evaluation of bone graft substitutes traditionally involves comparisons to autologous bone graft, with the objective being demonstration of equivalent bone formation, equivalent time to bony union, or equivalent union rates than those established in the historical literature for fusion procedures where autograft was used. The use of GEM OSI as grafting material in foot/ankle fusion procedures during this study demonstrated safety and effectiveness in obtaining radiographic union, clinical union, overall osseous bridging, and full weight bearing status. The availability of GEM OSI as a bone graft alternative would be especially welcome considering the many clinical difficulties associated with harvesting of autologous bone graft.

The relevant data from this study demonstrates safety and effectiveness for GEM OSI as a bone regeneration device in foot and ankle fusion procedures. The rate of radiographic union for subjects was favorable for GEM OSI as early as 12 weeks after the study procedure (74%). At Week 24 and Week 36, the observed radiographic union rate was 85% and 88%, respectively. The clinical success rate, based on the lack of need for a revision at the fusion site within 12 months, was 90% in the study. This finding is particularly noteworthy considering that 33% of the patients had failed a previous surgery at the site.

This effectiveness data compare favorably with the historical data reported in the literature. The published literature suggests high nonunion and failure rates for current treatment options, which include allografts, autografts, and composite materials. Nonunion rates have been reported from 10-40%, depending on risk factors and predispositions for nonunion. The effectiveness results were used to test three preplanned non-inferiority hypotheses from the statistical analysis plan, which were formulated using the current literature on foot and ankle fusion procedures. The data from this study was consistent with the non-inferiority hypotheses for revision and radiographic non-union for all subjects, as well as the hindfoot/ankle and at-risk subgroups. The data also supported non-inferiority for aggregate success in all patient populations, as well as composite success when the parameter for edema (not an independent measure of treatment failure) was not included. The positive results observed in the At Risk population, which were comparable to results seen in the entire study population, were especially notable given the noted historical difficulty of patients with identified risk factors, and the prevalence of high-risk subjects enrolled in the study (65% reported one risk factor at baseline, with 35% reporting more than one risk factor).

The above noted observations indicate that GEM OSI appears to be a safe and clinically useful bone graft substitute for use in foot and ankle fusions. It is especially notable that the use of GEM OSI allows the surgeon and patient to avoid the morbidity and cost of autograft, with a similar benefit of enhanced bone regeneration. The rates of radiographic non-union and clinical success observed in this study were similar to those observed in the literature-based historical controls associated with autograft, even with a high-risk patient population (39 of the 60 subjects had at least one known risk factor for non-union).

**Safety Conclusions:**

There were no unusual adverse events or trends noted in the safety data. The rates and types of adverse event occurrence were as expected for subjects who underwent a fusion procedure. The
serious adverse events reported in this study were clearly unrelated to study treatment. All patients were spared the additional pain and morbidity associated with autograft harvest, which is associated with complication rates as high as 39\%.2

**Final Report Date:** 29 May 2008

**Prepared in:** Microsoft Word 2003