Protocol Amendment 1

BMTI-2006-01 PROTOCOL NAME:	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: Evaluation Extension
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TABLE 1. STUDY FLOW CHART AND FOLLOW-UP ASSESSMENTS

Procedure	**Post-treatment Follow-up Evaluations**		
	Visit 11	**Telephone Visit 12**	**Telephone Visit 13**
	36 months ± 3 months[1]	**48 months ± 3 months**	**60 months ± 4 months**
Revised informed consent[2]	X		
Review demographic information[3]	X		
Review previous visit's physical exam[3]	X		
Clinical healing	X	X[4]	X[4]
Serum for rhPDGF-BB Ab Testing	X[5]		
Revision rate/other medically important surgery (i.e. same extremity as index procedure)	X	X[4]	X[4]
Clinically significant serious and/or device-related adverse events	X	X[4]	X[4]

1. This visit should occur 36 months' post-surgery and following appropriate regulatory and IRB/REB approvals. Deviations to this window are allowed based on IRB/REB approval timelines.
2. Must occur prior to any study-specific procedures.
3. This data will be obtained from the BMTI-2006-01 pivotal study and verified by the site.
4. Information will be obtained via telephone.
5. Sample to be drawn into 5ml serum tube. For patients who test positive for antibodies to rhPDGF-BB, additional serum samples will be requested in order to monitor patients until antibody titers return to baseline. Patients testing positive for anti-rhPDGF-BB antibodies will be tested for neutralizing activity.

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STUDY SYNOPSIS

BMTI-2006-01 STUDY TITLE:	A randomized, controlled, multi-center pivotal clinical trial to evaluate the safety and effectiveness of *Augment™ Bone Graft* compared to autologous bone graft (ABG) as a bone regeneration device in hindfoot and ankle fusions: Evaluation Extension
STUDY OBJECTIVES:	Evaluate the long term safety of *Augment Bone Graft* vs. autologous bone graft (autograft; ABG)
STUDY HYPOTHESIS:	The long-term safety profile for *Augment Bone Graft* is comparable to that of autologous bone graft.
STUDY RATIONALE:	Evaluate the long-term safety of *Augment Bone Graft* vs. autologous bone graft
REGULATORY PHASE:	Investigational Device Exemption (IDE) for Premarket Application (PMA) as a bone regeneration system
STUDY DESIGN:	Prospective, controlled, multi-center trial
NUMBER OF STUDY CENTERS:	Up to 37
NUMBER OF PATIENTS:	Up to 414 patients (see "Study Population")
STUDY POPULATION:	Male and female patients over the age of 18 years of age, who were randomized, treated and analyzed as part of the safety population of the BMTI-2006-01 protocol.
TREATMENT GROUPS:	Group I: Standard rigid fixation + ABG Group II: Standard rigid fixation + *Augment Bone Graft*, with sodium acetate buffer containing 0.3 mg/ml rhPDGF-BB
STUDY DURATION:	Sixty months follow-up post-randomization
VISIT SCHEDULE:	Months 36, 48 and 60
SAFETY CRITERIA:	Primary: Absence of study device-related serious adverse events Secondary: Durability of original fusion from the BMTI-2006-01 study with lack of need for revision

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1 BACKGROUND INFORMATION

1.1 Background

Introduction

Musculoskeletal problems are pervasive throughout the population in all age groups and in both sexes. Half of Americans will need services for fractures at some point in their lifetime according to a widely published article presented at the 2003 annual meeting of the American Academy of Orthopedic Surgeons (AAOS). More than $10 billion per year is spent in the U.S. on hospital care associated with fracture treatment according to this report.

Many musculoskeletal problems, such as fractures 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 in contrast to allografts or xenografts; however, clinical difficulties have been associated with autograft. Most of these difficulties result from the harvest of the bone graft, including increased operative time, hospital stay and cost, increased blood loss, post-operative pain, risk of infection and/or fracture. Other reported complications associated with autograft include a potential nidus for infection associated with avascular bone, limited tissue supply, and variability in cellular activity of the bone graft (Younger et al, 1989). In addition to these complications, limitation exists in the amount of bone graft that may be harvested. The morbidity associated with autograft and its limited amount available to be harvested has directed surgeons to look for a better alternative for a chemotactic, mitogenic, and angiogenic bone graft substitute as an alternative for fracture augmentation to accelerate healing (St. John et al, 2003).

Currently, there are no generally accepted alternatives to autograft for fusion procedures of the foot or ankle. In order to demonstrate a product's effectiveness, it is necessary to show equivalence to autologous bone graft in terms of safety and effectiveness. This may be manifested via equivalent or greater rates of bone formation or equivalent/faster time to bony union. A positive impact in either setting would have significant implications for treatment associated with foot and ankle fusions, as well as many other orthopaedic disorders, including fractures, osteotomies, and general bone defects.

Hindfoot and ankle fusion procedures, such as triple (three hindfoot articulations), subtalar fusions, and ankle fusions involve the same treatment principles of creating a peri-articular osteotomy, stabilizing the joint with rigid fixation, placing autograft bone harvested locally, and following standard post-operative regimen of physical therapy and gradually increasing load on the fusion site.

The time to healing after fusion procedures is longer than that after more conservative and potentially less predictable treatment methods due to the time required to fusion/union. Historically, it takes an average of three months to achieve bony union and full weight-bearing status after these operations. For example, the current non-union rate of the Lapidus procedure ranges between 5-10%, and salvage of such failures imposes significant strains on the patient, physician, and health care system (Coetzee et al, 2004, Coetzee et al, 2004, Patel et al, 2004, Sangeorzan et al, 1989, Hansen et al, 1996). Non-union rates of other hindfoot and ankle fusion procedures (0-40%) may be higher than those cited from the Lapidus procedure. The literature consensus on non-union rates associated with foot and ankle procedures is

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approximately 10% (Thordarson et al, 2003). The non-union rate has been reported to be significantly higher for at-risk patient populations, including smokers (previous or current), diabetics, patients with post-traumatic deformities, and/or obese patients. Subtalar fusions have been reported to have a non-union rate of 27% in smokers and 29% in patients undergoing revision surgery (Easley et al, 2000). Another recent study demonstrated that diabetics undergoing subtalar arthrodesis were 18.7 times ($p < 0.05$) more likely to develop a malunion than non-diabetics (Chahal et al, 2006). This study confirmed that smokers are at greater risk for complications including non-union and malunion, and these patients may have improved outcomes with the use bone graft. Ankle non-unions in high-risk patients have been reported to be as high as 41% (Frey et al, 1994).

Arthrodesis of the foot and ankle is a commonly utilized procedure for the treatment of multiple etiologies of foot and ankle pathology, including post-traumatic arthritis, inflammatory arthropathy, seronegative arthropathy, significant joint instability, suboptimal malalignment and/or pain. Hindfoot and ankle fusion procedures, such as the triple (three hindfoot articulations), subtalar , talonavicular, and ankle fusions, involve the same treatment principles of taking down any residual cartilage to the subchondral surface at the level of the involved joint without disturbing its anatomy, stabilizing the joint thereafter with rigid fixation, placing autograft bone (harvested locally or from iliac crest) or other appropriate fusion preparation with osteoinductive or osteoconductive agents into surrounding interstices and defects across the joint surface, followed by a relatively standard post-operative regimen of short-term immobilization, physical therapy, and gradually increasing load on the fusion site(s). These articulations (hindfoot and ankle) work in concert with one another, are in intimate anatomic proximity, are of relatively the same size (and hence require similar amounts of bone graft during fusion), represent a similar vascular inflow and healing rate based on location, have similar non-union rates, require equivalent operative times for fusion, are fixed with equivalent (if not identical) and reasonably standard fixation methods, are frequently involved with similar disease processes and thus often fused simultaneously for treatment, require comparable surgical exposures that are extensions of one another, and have equivalent post-operative therapy, immobilization, and weight-bearing regimens.

Several studies have analyzed various types of foot and ankle arthrodesis in order to further the clinical care of patients requiring such procedures. For example, in Bibbo et al (2005), a total of 123 procedures were performed (21 involved the ankle, 26 involved the hindfoot, 66 involved the midfoot, and 10 within the forefoot) in 62 patients. This study examined the clinical results and complications after the adjuvant use of autogenous platelet concentrate (APC) in high-risk patients undergoing elective foot and ankle surgery. Patients at risk for bone-healing complications were prospectively enrolled over a six-month period for the intraoperative application of APC. Patients were followed every two weeks for radiographic union and complications. Overall, a 94% union rate was achieved at a mean clinical healing time of 41 days. For APC alone, the mean time to union was 40 days; when APC was used with autograft, the mean time to union was 45 days ($p = 0.173$, two-tailed t test). These data suggest that adjuvant APC results in an acceptable time to union and may be a useful adjunct to promote osseous union in high-risk patients undergoing elective foot and ankle surgery. In addition, the results of this study demonstrated that midfoot, hindfoot, and ankle fusions generally have similar mean times to union and nonunion rates.

There is a paucity of literature reporting radiographic results using CT scan to demonstrate outcomes of foot and ankle fusions. However, CT scanning is accepted as the most reliable and rigorous assessment of fusion. One recent study reported that CT scanning appears to be the most reliable and sensitive method to determine fusions (Coughlin et al, 2006). The study demonstrated that the mean observed

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fusion rate for subtalar fusions ranged from 41% at 6 weeks to 61% at 12 weeks, and to 86% at 6 months; however the fusion rates as determined by independent assessment of CT scans for the same time intervals were 23%, 48%, and 64%. This study demonstrated that CT scans provide a more robust and rigorous assessment of fusion (i.e., osseous bridging) than clinical and plain film radiographic assessment due to the fact that CT scans were reported to be more sensitive in estimating the magnitude of joint fusion.

The similarity of these joints is reinforced by the common descriptor of three of these four joints (subtalar, talonavicular, and calcaneocuboid) as the 'hindfoot', and, in some cases, designation of the ankle and subtalar joints as the 'upper' and 'lower' ankle joints, reinforcing the widespread recognition of this series of joints as part of a unit. Discussion of midfoot, hindfoot, and ankle data is also frequently combined in salient foot and ankle literature and distinguished, for example, from diseases or surgeries affecting other areas of the foot such as the forefoot articulations (which comprise multiple articulations that are also grouped together based on similar rationale as noted above). It is therefore expected that data extrapolated from surgery in this region would be reasonably applicable amongst all these joints, and for the above-noted reasons, it is reasonable and appropriate to consider midfoot, hindfoot, and ankle fusions as a unit and thus be included as a grouped region of study. This study, however, will only include hindfoot and ankle fusion procedures.

As previously stated, the time to healing after fusion procedures is longer than that after more conservative and potentially less predictable treatment methods due to the time required to fusion/union. Historically, it takes an average of two to three months to achieve complete bony union and full weight-bearing status after these operations. Non-union rates of other hindfoot and ankle fusion procedures (0-40%) may be higher than those cited from the forefoot. The literature consensus on non-union rates associated with foot and ankle procedures is approximately 10% in an otherwise healthy patient population (Myerson et al, 2000, Thordarson et al, 2003). The non-union rate has been reported to be significantly higher for at-risk patient populations, including smokers (previous or current), diabetics, patients with post-traumatic deformities, and/or obese patients. Subtalar fusions have been reported to have a nonunion rate of 27% in smokers and 29% in patients undergoing revision surgery (Easley et al, 2000). Another recent study demonstrated that diabetics undergoing subtalar arthrodesis were 18.7 times ($p < 0.05$) more likely to develop a malunion than non-diabetics (Chahal et al, 2006). Ankle non-unions in high-risk patients have been reported to be as high as 41% (Frey et al, 1994).

Non-unions will be detected by eight months radiographically and are generally clinically well established by 6-9 months (hence the clinically accepted standard of six months without evidence of bony progression to declare delayed union and nine months for declaring non-union). The presence of multiple clinical factors such as persistent pain, warmth, motion, and residual significant swelling are excellent clinical indicators of nonunion and typically are present well before nine months time in such patients. Thus, a nine-month study period represents a reasonable, conservative and resource-efficient time frame to evaluate such patients for union and/or nonunion. Further, canine studies have demonstrated that TCP matrices without incorporated growth factors are resorbed within 6-12 weeks; therefore, graft incorporation will be accomplished far in advance of the 12-month study timepoint (Erbe et al, 2001). For all these reasons stated above, the length of follow-up selected for the original study period was 12 months.

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The potential elimination of risk associated with use of autologous bone graft and minimization of complications associated with fusion procedures of the foot and ankle by using a synthetic and osteogenic bone regeneration system would be of clinical significance to the orthopedic community and patient population desiring to treat common but debilitating bone disorders.

The purpose of this study is to examine the long-term safety and durability of fusion of *Augment Bone Graft* (rhPDGF-BB in a tricalcium phosphate (TCP)-based matrix) as compared to autologous bone graft in this foot and ankle fusion model.

Investigational Device

The fully synthetic study device, *Augment Bone Graft*, physically fills bone defects providing a biocompatible, osteoconductive scaffold for new bone formation and promoting cellular ingrowth into the osseous defect. *Augment Bone Graft* is composed of two components—beta tricalcium phosphate (β-TCP) and becaplermin, which is a highly purified recombinant human platelet-derived growth factor (rhPDGF-BB). Both components have been previously approved/cleared by the Food and Drug Administration (FDA) for specific indications, as noted below. In addition, *Augment Bone Graft* is composed of materials that are otherwise identical to the GEM 21S™ device which was approved for use in both the U.S. and Canada as a bone regenerative system in the jaw.

The *Augment Bone Graft* device is supplied in "kit" form – a package of β-TCP and a separate syringe containing a solution of rhPDGF-BB (becaplermin). At the time of surgery, the clinician fully saturates the β-TCP particles with the rhPDGF-BB solution. After mixing, the hydrated graft is then manually packed into and around the osseous defect and standard surgical techniques are employed to complete the procedure.

Augment Bone Graft has undergone pilot / feasibility studies in both Canada and the U.S. using equivalent surgical procedures to those described in this protocol.

β-TCP

β-TCP is a purified, multicrystalline, porous form of calcium phosphate with a Ca:PO4 ratio similar to natural bone mineral. Extensive animal and human clinical studies over the past 25 years have demonstrated biocompatibility of the β-TCP with no reports of any adverse reactions (Bhaskar et al., 1971; Levin et al., 1974; A and B; Nery et al., 1975; Cameron et al., 1977; McDavid et al., 1979). The β-TCP physically fills bone defects, preventing the collapse of soft tissue into the bone defect, and provides a matrix or scaffolding for new bone formation, subsequently undergoing remodeling and finally being replaced by host bone. This has been demonstrated in numerous animal and human clinical studies (Bhaskar et al., 1971; Nery et al., 1975; Cameron et al., 1977; Nery, 1978; Ferraro, 1979; Strub and Gaberthal, 1979; Snyder et al., 1984; Baldock et al., 1985; Stahl and Froum, 1987; Saffar et al., 1990; Gatti et al., 1990; Buser et al., 1998; Muschik, M. et al., 2001). The β-TCP component used in *Augment Bone Graft* is approved for use as a bone void filler in orthopedic and periodontal applications, and received marketing approvals in Australia (March 2001) and the European Union (October 2000). This β-TCP received marketing approval in United States (December 2000 and August 2003) for orthopedic applications, only.

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Platelet-derived Growth Factor

Platelet-derived growth factor (PDGF) has been one of the most thoroughly studied bone growth factors. Since PDGF was first discovered to promote regeneration of bone and other tissues in the late 1980s (Lynch et al., 1989) nearly 100 studies have been published on its effects on periodontal tissue regeneration in dental applications.

Regranex gel (becaplermin), rhPDGF-BB was approved for use in the treatment of diabetic ulcers, received marketing approvals in the European Union (March 1999), Australia (August 1999), Canada (December 1998), and the United States (December 1997). rhPDGF-BB has been FDA-approved and clinically available for about five years under the trade name Regranex® for the treatment (improved healing) of chronic neuropathic, diabetic cutaneous ulcers.

In preclinical study in diabetic rats, it was reported that diabetes affects the early stage of fracture healing by inhibiting cell proliferation through decreased expression of platelet derived growth factor (Tyndall et al., 2003). This correlation was also noted in a study of normal rats in which a paracrine and autocrine mechanism for PDGF in fracture repair was observed (Fujii H et al., 1999).

An initial human clinical trial in periodontal osseous defects for the application of 0.15 mg/ml of rhPDGF-BB and 0.15 mg/ml recombinant human insulin-like growth factor I (rhIGF-I) resulted in a significant improvement in bone fill compared to conventional surgery plus a buffer (Howell et al., 1997). In addition, a pivotal human clinical trial using rhPDGF-BB in combination with an FDA-approved β-TCP resulted in no serious and/or unanticipated adverse events attributable to the study device. Further, this study demonstrated the effectiveness of this combination in regeneration of bone in periodontal osseous defects (Nevins et al, 2005). Thus, it is reasonable to hypothesize that rhPDGF-BB, in combination with an osteoconductive β-TCP matrix, will result in equivalent time to radiographic union as ABG in a fracture or fusion model.

Regulatory Status

Based on the recommendation of approval by the FDA Dental Devices Panel on July 13, 2004, the safety and effectiveness of a similar product (β-TCP + 0.3 mg/ml rhPDGF-BB) was established for the treatment of bony defects around teeth (periodontal). Subsequently, the FDA granted market approval for that product (GEM 21S™) per PMA P040013. The GEM 21S device has also been approved for use in Canada.

Human feasibility trials were initiated in both Canada and the U.S. Both the Canadian and U.S. trials were performed in accordance with regulatory authorization and Ethical Committee (EC) or Institution Review Board (IRB) approval(s).

The Canadian open-label surgical protocol was similar to this study with some differences in the study design, including the use of a historical control rather than a direct autologous bone graft comparison group. The Canadian feasibility trial was designed to include 20 patients. Based upon the initial successful results of that feasibility trial, Health Canada and the associated REBs approved the expansion

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of that study to 60 patients. Data from the trial supported a license application to Health Canada and resulted in the Canadian market approval under Device Licence number 80956 in November 2009 for use as an alternate to autograft in foot and ankle procedures, including ankle, hindfoot and midfoot fusion; where the use of supplemental bone graft is indicated. These data are also meant to provide supplementary data for the US approval of the device.

The results of the 60-patient Canadian trial referenced above demonstrated significant improvements of Augment Bone Graft compared to historical controls, and was the basis for progression to a pivotal randomized controlled trial (Daniels et al, 2010).

A pre-market application (PMA# P100006) has been filed for *Augment Bone Graft*. The PMA is currently under review. FDA has requested that the sponsor continue follow-up in a post approval study.

2 PURPOSE

The Food and Drug Administration (FDA) has requested additional long-term data to compare the safety profile of *Augment Bone Graft* to that of autologous bone graft. This protocol amendment is intended to supplement study protocol BMTI-2006-01, Version 4.1, dated April 5, 2007.

3 STUDY DESIGN AND OVERVIEW

The objective of this long-term extension study is to evaluate the long-term safety of *Augment Bone Graft* versus autologous bone graft. The study involves evaluation of patients from Protocol BMTI-2006-01.

An attempt to contact will be made and documented for all patients who were randomized, treated and analyzed as part of the safety population (defined as randomized and treated) from Protocol BMTI-2006-01 for participation in the extended evaluation period described in this protocol (Exhibit 13.1). All investigators who randomized patients into the aforementioned protocol will be asked to participate in the long-term extension study and must obtain IRB approval of this protocol amendment and administer the revised informed consent form prior to performing any additional evaluations.

Comparisons will be made between the two different treatment groups from Protocol BMTI-2006-01. The hypothesis to be tested is that the long-term safety profile for *Augment Bone Graft* is comparable to that of autologous bone graft.

TABLE 2. STUDY TIMELINE SUMMARY

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Visit 11 Post Tx Follow-up	Telephone Visit 12 Post Tx Follow-up	Telephone Visit 13 Post Tx Follow-up
↓	↓	↓
36 months ± 3 months*	48 months ± 3 months	60 months ± 4 months

*Deviations to this window are allowed based on IRB/REB approval timelines.

3.1 Primary Objectives of the Long-term Extension Study

The long-term safety of this device will be evaluated by the following:

- Primary endpoint:
  - Presence of study device-related serious adverse events
- Secondary endpoint:
  - Durability of original fusion, including lack of need for revision
  - rhPDGF antibody status

4 SELECTION OF PATIENTS

The study population will consist of up to 414 patients from Protocol BMTI-2006-01, who meet the inclusion and exclusion criteria described below. A list of patients for inclusion in the study will be provided to each site prior to study start (see Exhibit 13.1).

4.1 Inclusion Criteria

Patients who meet the following criteria may be included in the study:

1) Must be willing and able to provide informed consent and be available for at least one follow-up visit/telephone contact for the duration of the study; and
2) Must have been randomized, treated and considered inclusive of the safety population of Protocol BMTI-2006-01 (see Exhibit 13.1).

4.2 Exclusion Criteria

1) Patients that were excluded from the safety analysis in the BMTI-2006-01 study (subjects not listed in Exhibit 13.1). These patients were consented, but never treated as part of the BMTI-2006-01 protocol.

4.3 Enrollment Log

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Participating centers are required to document all enrolled patients initially considered for inclusion in this study, and to specifically document the reason(s) for non-participation.

4.4 Patient Withdrawal Criteria

Patients will be discontinued from the study before the sixty-month visit if:

- The patient is non-compliant with at least one of the follow-up visits;
- The patient requests to be withdrawn from the study; or
- The Principal Investigator decides that it is in the patient's best interest due to concerns unrelated to fusion surgery.

If a patient withdraws from the study at any time either at his request or at the Principal Investigator's discretion, the reason(s) for withdrawal will be recorded by the Principal Investigator on the relevant page of the case report form (CRF). All final visit tasks will be completed for all patients who withdraw from the study. Patients withdrawn due to device-related SAEs will be monitored for safety until resolution of the device-related serious adverse event throughout the course of the study.

4.5 Study Procedures

Clinical Assessments

All patients will be clinically evaluated by the investigator or licensed/trained designee. The physical exam data from the last completed visit of the BMTI-2006-01 study will be provided for each patient for review at the 36-month visit. The site will record any changes to the provided data.

Serum Collection

Serum collection will be performed for antibody analysis. Blood should be drawn to obtain up to 3ml of serum in a sterile tube. Blood draws occur at Visit 11 (36+ Months). These samples are to be labeled with subject ID number and date of collection. The samples will be shipped to BMTI for analysis for presence of neutralizing and non-neutralizing antibody formation to rhPDGF-BB. For patients who test positive for antibodies to rhPDGF-BB, additional serum samples will be requested in order to monitor patients until antibody titers return to baseline. Patients testing positive for anti-rhPDGF-BB antibodies will be tested for neutralizing activity.

5 INVESTIGATIONAL PRODUCT

All investigational product from Protocol BMTI-2006-01 has been returned to the Sponsor and/or designee or destroyed on site by the Sponsor and/or designee prior to initiation of this long-term safety extension study. This study protocol is for long-term safety evaluation of study patients. No new treatments are administered based on this study protocol.

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6 ASSESSMENT OF SAFETY

Safety will be assessed by the frequency and severity of clinically significant serious and/or device-related adverse events. The events to be collected are as follows:

- Non-unions
- Therapeutic failures
- DVT/PE associated with the fusion site procedure
- Neoplasms, deaths and SAEs related to the following system organ classes:
  - Infections and infestations (LLT of cellulitis, wound infection, post-operative wound infection);
  - Musculoskeletal and connective tissue disorders (pain in ankle/joint, swelling in ankle/joint, arthralgia associated with the surgical foot/ankle);
  - Neoplasms, benign(including cysts and polyps) (all lower level terms associated with neoplasms)
  - Neoplasms, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)
  - Complications related to bone graft harvest site and/or fusion site
- Death, regardless of relationship to the study device
- Clinically significant device related adverse events

6.1 Serious Adverse Events Related to the Study Device

Device-related events are classified as serious if they meet any of the following criteria (in accordance with 21 CFR 812.3(s)) and the recommendations of International Conference on Harmonization [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):

- Any death.
- Any life-threatening event, i.e., an event that places the patient, in the view of the investigator at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death).
- Any event that requires or prolongs in-patient hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a patient who participated in this study following the study procedure.
- Other medically important events that in the opinion of the investigator may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- Any serious problem associated with the device that relates to the rights, safety or welfare of study patients.

6.2 Unanticipated Adverse Device Effect (UADE – United States)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or

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application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients (21 CFR 812.3(s)).

The Principal Investigator shall make an accurate and adequate special report of any unanticipated device related serious adverse event to BioMimetic Therapeutics, Inc. or its designee, and to any institutional review board (IRB) or ethics committee (EC) that has reviewed and is continuing to review the investigation.

Reporting of device-related SAEs (anticipated or unanticipated serious adverse events)—for any event, the Principal Investigator must notify the Sponsor or its representative within 24 hours.

Any unanticipated device-related serious adverse event will be reported to the Food and Drug Administration (FDA) by BioMimetic Therapeutics, Inc. within 10 working days after the Sponsor receives notice of the event.

7 STATISTICAL ANALYSIS PLAN

7.1 Study Design

BMTI 2006-01 PAS is a follow-up extended evaluation of patients enrolled in the BMTI-2006-01 protocol in order to document and assess long-term safety of *Augment Bone Graft*. BMTI-2006-01 aimed to demonstrate equivalent clinical, radiologic and safety outcomes for *Augment* and the "gold standard" (autologous bone graft) in foot and ankle fusions. A 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 from April 2007 to January 2010. The study enrolled male and female patients, over the age of 18 years, requiring fusion in either the hindfoot or ankle (tibiotalar) requiring the use of bone graft. Patients were randomized into one of two treatment groups: standard rigid fixation plus autologous bone graft or standard rigid fixation plus *Augment Bone Graft*. Patient randomization was implemented at a 2:1 ratio of *Augment* to autograft. The patients then underwent a hindfoot/ankle fusion procedure using open surgical technique with supplemental bone graft or *Augment* according to the randomization assignment. Patients in both treatment groups were immobilized according to standardized operative and post-operative protocols. Independent radiographic assessments of parameters for fusion were done by a certified radiologist. All patients were monitored over a 52-week period to evaluate for clinical and safety outcomes, including incidence of 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. A safety population, including all randomized and treated patients, of 414 patients was realized, where 272 received *Augment Bone Graft* and 142 patients received autograft. These patients are listed in Exhibit 13.1. As a requirement for PMA, this post-approval study aims to conduct a follow-up evaluation of these patients in order to assess the long-term safety and document device-related serious adverse events of *Augment Bone Graft* that may occur over a longer period of time. Patient follow-up will be conducted at 36, 48 and 60 months post-surgery.

7.2 Sample Size

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There will be at most 414 patients for this long-term extended evaluation study. This sample size comprised the safety population of the BMTI-2006-01 protocol where study patients were properly randomized and actually received the treatment assigned to them.

7.3 Statistical Analysis Considerations

Evaluation of the long-term safety of *Augment Bone Graft* will utilize the patient physical examination aspects and adverse events collected at 36, 48 and 60 months post-surgery. Reports and analysis of safety will be done at each pre-determined follow-up period. The hypothesis that the long-term safety profile for *Augment* is comparable to that of autograft will be tested at 0.05 Type I error.

Descriptive statistics will be provided for all relevant data obtained. Statistics for all patients and by treatment group and at each follow-up time will be presented. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median) while frequency counts and percentages will be provided for categorical data. Ninety-five (95) percent confidence interval may also be presented, as appropriate. The number of patients reporting for that follow-up period will be the basis for computing rates.

7.4 Analysis of Long-term Safety and Durability of Device

For the primary endpoint, device safety of *Augment* is comparable to that of autograft if the rate of device-related serious adverse event (DR-SAE) of *Augment* patients is not more than 10% compared to the DR-SAE rate of autograft patients. The null (Ho) and alternative (Ha) hypotheses:

$$\text{Ho: } P_{Augment} - P_{ABG} \geq 10\% \quad \text{vs. Ha: } P_{Augment} - P_{ABG} < 10\%$$

will be tested, where $P_{Augment}$ and P_{ABG} are the rate of DR-SAE of *Augment* and ABG patients, respectively. One-tailed Fisher's exact test will be used to test the hypothesis. A 95% upper bound for the rate difference will be constructed, with Agresti-Caffo corrections for better coverage probability (Agresti and Caffo 2000). An upper bound less than 10% will lead to rejection of Ho, indicating that the rate of DR-SAE of *Augment* patients is comparable to those patients treated with ABG. Treatment comparison will also be made for DR-SAE at 48 months and then at 60 months post-surgery.

The durability of original fusion will be assessed by the rate of patients who maintained a clinical union status at 36 months' post-surgery. The rate of maintained 36-month union refers to the subset of patients that achieved clinical union of the original fusion, without re-surgery, within one year (52 weeks) and up to 36 months' post-surgery. The fusion durability using *Augment* is comparable to autograft when the rate of 36 months' post-surgery durable fusion for *Augment* patients is more than the rate of autograft patients by 10%. The Ho: $P_{Augment} - P_{ABG} \leq 10\%$ will be tested against Ha: $P_{Augment} - P_{ABG} > 10\%$, where $P_{Augment}$ and P_{ABG} are the rates of 36 months' post-surgery durable fusion for *Augment* and autograft patients, respectively. One-tailed Fisher's exact test will be used and 95% lower bound for the rate difference will be constructed. A lower bound that is greater than 10% indicates that rate of original fusion durability for *Augment* patients is comparable to that of autograft patients. Rates of fusion durability will also be compared for *Augment* vs. autograft patients at 48 and then at 60 months post-surgery.

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Clinical and functional assessments of the original fusion are also indicators of fusion durability. Fusion site motion, warmth, swelling, tenderness, neurovascular status and weight-bearing status are all clinical indicators of fusion durability. *Augment* patients will also be compared to autograft patients with respect to these clinical assessments. Specifically, the rates of patients experiencing fusion site infection, stable fusion and intact neurovascular status at 36 months post-surgery will each be compared for *Augment* vs. ABG patients using one-tailed Fisher exact test.

The frequency and rates of patients exhibiting positive for anti-rhPDGF-BB antibodies will be computed separately for Augment Bone Graft and Autologous Bone Graft, and then for all patients. Rates will be calculated based on the corresponding number of subjects with serum samples collected. Additional samples will be requested for patients who will exhibit positive anti- rhPDGF-BB antibodies and will be further tested for the presence of neutralizing antibodies. Rates and frequency by treatment groups who confirm positive for anti-rhPDGF-BB binding antibodies will be computed.

7.5 Other Analyses

Treatment comparison of long-term safety will be done for different subgroups of the population such as subgroups of surgery sites (hindfoot, ankle), patients with no risk factor, or at least one risk factor, patient groups by pre-specified risk factor (diabetic, non-diabetic, smokers, non-smokers, obese, non-obese, having previous surgery at fusion site and having no previous surgery at fusion site). Other subgroups of patients such as males, females, young and old may also be considered for subgroup analysis.

7.6 Safety Analysis

Post-operative serious adverse events that are device-related will be summarized and include details of the nature, onset, duration, severity, and outcome of this complication. Adverse events will be organized as device related (DR) or not device-related and using the most current Medical Dictionary for Regulatory Affairs (MedDRA) groupings. At each specific post-surgery follow-up (36, 48 and 60 months), these safety endpoints will be reported as frequency and rates by treatment group, as appropriate, with two-sided p-values from the comparison of *Augment* vs. autograft patients.

Of major interest for device safety are the occurrence and severity of the following complications:

1. Deep vein thrombosis;
2. Pulmonary embolism associated with the fusion site procedure;
3. Infections and infestations (lower level term of cellulitis, wound infection, post-operative wound infection) ;
4. Musculoskeletal and connective tissue disorders (pain in ankle/joint, swelling in ankle/joint, arthralgia associated with the surgical foot/ankle);
5. Neoplasms benign, malignant and unspecified (including cysts and polyps, all lower level terms associated with neoplasms);
6. Complications related to bone graft harvest site and/or fusion site; and
7. All deaths.

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The rate of occurrence of each of these adverse events will be compared for *Augment* and ABG patients. Frequency and rates will be presented for all and by treatment group with p-value of treatment comparison.

Each occurrence of a serious adverse event (SAE) that is considered related to the use of *Augment* will be reported. A patient report of each SAE will be made to include a narrative and its relation to patient demographic and clinical characteristics.

7.7 Procedure for Accounting of Patients

A table to account for the status of each patient will be constructed to include frequency of patient withdrawals, patient retention rates and deaths at each follow-up period. The reasons for patient withdrawal and causes of death will also be summarized.

7.8 Procedure for Accounting for Missing Data

No missing data will be imputed. All data will be analyzed as collected. Rate of an outcome category will be computed using the number of patients reporting for that outcome. Numbers of present and missing data points will be made evident in all analysis display.

7.9 Procedure for Reporting Deviations from Statistical Plan

Modifications or changes to the statistical plan will be documented in the final formal statistical plan that will be finalized prior to data base unblinding. Adjustments made to the plan will be documented in the final study report.

8 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All aspects of the study will be carefully monitored by BioMimetic Therapeutics, Inc. or its designee for compliance with applicable government regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator. HIPAA waivers will be signed by all study patients as part of the IRB-approved informed consent process.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Source Data and Records

Source data/records contain all information that is necessary for the reconstruction and evaluation of the study. Source data/records are—1) original records, 2) certified copies of original records, 3) observations, 4) laboratory reports, 5) paper case report forms and/or data sheets provided by the sponsor that are used to enter original data for the first time.

Source data are to be kept within the control of the investigator until the end of the regulatory retention period. All electronic data will be stored in a central server that is not located at an investigator's site; user

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access to the electronic source data will be controlled by the investigator or designee. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source data/records.

9.2 Electronic Data Capture

The electronic case report form (eCRF) is an integral part of the study and is used to capture all study data. Office visit data will be entered by the Investigator, or a designated representative into e*CRF® (Target Health Inc., New York, NY), a validated, 21CFR Part 11-compliant, Internet-based, electronic data collection (EDC) system. All details of the eCRF completion and modification will be explained to the investigator. Prior to data entry, a list of users and their roles and responsibilities is created by the sponsor. This list is updated as necessary (e.g., as new staff members are assigned to or retired from the study).

If the investigator authorizes persons to make entries in the eCRF, the names and positions of these persons must be available to the Sponsor.

The completed online eCRF must be reviewed and signed electronically by the investigator named in the study protocol or by a designated sub investigator authorized to sign. A certification must be obtained from all authorized to sign electronically indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with their user name and password and reenter their password on the page(s) requiring a signature(s).

9.3 Study Monitoring

A clinical monitoring plan will be generated to specifically identify monitoring requirements.
The monitor is responsible for performing initial review of entered data as well as at least one on-site monitoring visit during the course of the study to verify adherence to the protocol and local regulations on the conduct of clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF. Like all users to the systems, the monitor will log in with their user name and password. The monitor has read-only permission to view the clinical data, but is able to generate queries.

At a minimum, a data entry form with a patient's screening number, the date the informed consent form was signed and the reason for a screening failure will be generated for each patient who signed an informed consent form.

9.4 Data Management

The clinical database is held and managed by Target Health Inc. during the lifetime of the study.

e*CRF® will be used for online edit checks, batch edit checks and query management. In order to build the EDC application, an application setup instructions (ASI) document is created. The ASI document contains the specific instructions to both the EDC and data management (DM) programmers. A clinical

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data monitoring plan (cDMoP) is created to specifically identify how data management will be performed for the study.

Data validation is performed according to the specifications in the data validation plan (DVP), within which there are three types of validation checks:

- Online checks. Performed by the EDC system during data entry. Target Health personnel are responsible for programming any hits based on these checks. BMTI data management personnel are responsible for resolving any hits based on these checks.
- Batch edit checks. Target Health personnel are responsible for programming any hits based on these checks. BMTI data management personnel are responsible for resolving any hits based on these checks.
- Manual checks performed by the monitor and BMTI clinical data management personnel. In some cases the data manager (DM) is responsible for providing listings to monitors to be used for manual checks.

Queries are handled within the e*CRF® application. The monitors and DMs are the only persons who can generate a query. Under direction of the investigator, the site coordinator addresses the query. If the query is due to a data entry error, the coordinator can immediately make the corrections in the applicable eCRF pages. If the query needs clarification, the coordinator contacts the investigator for resolution. The coordinator then enters the correct value or submits an answer to the query without modifying the data. The monitor then reviews the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, the monitor closes the query. If the answer is not acceptable, the monitor submits an additional query for clarification. All changes to the database require a “reason for change” and are subject to an audit trail. The audit trail identifies the changed data, reason(s) for change, who changed the data and the time and date of the change (based on the e*CRF server’s time).

9.5 Trial Master File

The electronic trial master file will be maintained within Target Document® (Target Health Inc.), which is 21 CFR Part 11-compliant software.

10 ETHICS

This study will be conducted in accordance with 21 CFR Parts 50, 54, 56, and 812 and the ethical principles originating from the Declaration of Helsinki and GCPs and in compliance with local regulatory requirements.

10.1 Informed Consent

Prior to any testing under this protocol, including screening tests and evaluations, written informed consent must be obtained from the patient in compliance with 21 CFR Part 50.

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The Principal Investigator should be involved in this procedure. The background of the proposed study and the benefits and risks of the procedures and study will be explained to the patient. A copy of the informed consent form will be submitted by the Principal Investigator to the IRB/EC for review and approval prior to the start of the study. A copy of the signed and dated informed consent form must be given to the patient and the consent process must be documented in the source documentation. Confirmation of a patient's informed consent and the fact that a copy of the signed informed consent was given to the patient must also be documented in the patient's medical records prior to any testing under this protocol, including screening tests and evaluations.

10.2 Institutional Review Board (IRB)/Ethics Committee (EC)

The Principal Investigator will provide the IRB/EC with all appropriate material, including a copy of the informed consent. The study will not be initiated until the IRB/EC provides written approval of the protocol, the informed consent form and any advertising, and until approval documents have been obtained by the Principal Investigator and copies received by BioMimetic Therapeutics, Inc. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/EC and BioMimetic Therapeutics, Inc. in accordance with the applicable government regulations and in agreement with policy established by the sponsor.

10.3 Protocol Adherence

The investigator must read the protocol thoroughly and must follow the protocol. Any change must be agreed to by prior discussion between the Sponsor and the Investigator, with appropriate written protocol amendments made prior to effecting the changes agreed upon. Any amendment containing major modifications (particularly if it may involve an increased risk to the patients) must be approved by the local ethics committee(s) before it may be implemented.

Any changes in the study conduct will be documented with a protocol amendment prior to implementation.

10.4 Confidentiality

All information provided to the Principal Investigator by BioMimetic Therapeutics, Inc. or its designates including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be provided in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to BioMimetic Therapeutics, Inc. or its designates or in confidence to the IRB, except if required by law.

11 FURTHER TOPICS AND GENERAL INFORMATION

11.1 Changes to Final Study Protocol

Protocol violations should be submitted to the IRB/EC for approval prior to implementation.

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All protocol amendments must be submitted to the IRB/EC and regulatory authorities, as required. Protocol modifications that impact on patient safety, the scope of the investigation, or affect the scientific quality of the study must be approved by the IRB/EC and submitted to the appropriate regulatory authorities before implementation of such modifications to the conduct of the study. However, BioMimetic Therapeutics, Inc. may, at any time, amend this protocol to eliminate an apparent immediate hazard to a patient. In this case, the appropriate regulatory authorities will be subsequently notified. In the event of a protocol modification, the informed consent form may require modifications, which must also be approved by the IRB/EC.

11.2 Data Handling and Recordkeeping

All records relating to the conduct of this study are to be maintained by the Principal Investigator until notified by the Sponsor that the records may be destroyed. If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to the Sponsor or to a person who will accept responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.3 Publication Policy

Following completion of the study, the study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In such a case, BioMimetic Therapeutics, Inc. will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Under no circumstances may any results of this investigation be publicly reported without first submitting the information to the U.S. Food and Drug Administration by the Sponsor and clearance for such dissemination made by either the U.S. FDA or the Sponsor.

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12 SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read and understand the aforementioned protocol, "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: Evaluation Extension" and agree to conduct the study as detailed herein and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator's Signature: _____ Date: _____

Principal Investigator's Name (print): _____

Investigational Site (print): _____

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13 EXHIBITS

13.1 List of Patients to be Included in the Study

Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
40	40S01	[redacted]
	40S03	[redacted]
	40S04	[redacted]
	40S99	[redacted]
41	41S01	[redacted]
	41S02	[redacted]
	41S03	[redacted]
	41S04	[redacted]
	41S05	[redacted]
	41S06	[redacted]
	41S08	[redacted]
	41S09	[redacted]
	41S10	[redacted]
	41S11	[redacted]
	41S12	[redacted]
	41S13	[redacted]
	41S14	[redacted]
	41S15	[redacted]
	41S16	[redacted]
	41S17	[redacted]
	41S18	[redacted]
	41S19	[redacted]
	41S20	[redacted]
	41S21	[redacted]
	41S22	[redacted]
	41S23	[redacted]
	41S24	[redacted]
	41S25	[redacted]
	41S26	[redacted]
	41S27	[redacted]
	41S28	[redacted]
	41S29	[redacted]
	41S30	[redacted]
	41S31	[redacted]
42	42S01	[redacted]
	42S02	[redacted]
	42S03	[redacted]
	42S04	[redacted]

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
	42S05	[redacted]
	42S06	
42 (continued)	42S07	
	42S08	
	42S10	
	42S11	
	42S12	
	42S13	
	42S14	
	42S15	
	42S17	
	42S18	
	42S19	
	42S20	
	42S21	
	42S22	
	42S24	
	42S25	
	42S26	
43	43S01	
44	44S01	
	44S02	
	44S03	
	44S04	
	44S05	
	44S06	
	44S07	
	44S09	
	44S10	
	44S11	
	44S12	
	44S13	
	44S16	
	44S17	
	44S18	
	44S19	
	44S20	
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	45S03	
	45S04	
	45S05	
	45S06	
	45S07	
	45S08	

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
	45S09	[redacted]
	45S10	[redacted]
45 (continued)	45S11	[redacted]
	45S13	[redacted]
	45S14	[redacted]
	45S15	[redacted]
	45S16	[redacted]
46	46S01	[redacted]
	46S03	[redacted]
	46S05	[redacted]
	46S09	[redacted]
	46S10	[redacted]
	46S11	[redacted]
	46S12	[redacted]
	46S13	[redacted]
	46S15	[redacted]
	46S17	[redacted]
	46S19	[redacted]
	46S21	[redacted]
	46S23	[redacted]
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	46S35	[redacted]
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	46S37	[redacted]
	46S39	[redacted]
	46S40	[redacted]
	46S41	[redacted]
	46S42	[redacted]
47	47S01	[redacted]
	47S02	[redacted]
	47S03	[redacted]
	47S04	[redacted]
	47S06	[redacted]
	47S11	[redacted]
	47S15	[redacted]

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
	47S16	[redacted]
	47S17	[redacted]
47 (continued)	47S18	[redacted]
	47S22	[redacted]
	47S23	[redacted]
	47S24	[redacted]
	47S25	[redacted]
	47S30	[redacted]
	47S31	[redacted]
	47S32	[redacted]
	47S33	[redacted]
	47S35	[redacted]
	47S36	[redacted]
	47S37	[redacted]
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	48S03	[redacted]
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	48S10	[redacted]
	48S11	[redacted]
	48S12	[redacted]
49	49S01	[redacted]
	49S02	[redacted]
	49S03	[redacted]
	49S04	[redacted]
	49S05	[redacted]
	49S06	[redacted]
	49S07	[redacted]
	49S12	[redacted]
	49S13	[redacted]
	49S14	[redacted]
	49S15	[redacted]
	49S16	[redacted]
50	50S01	[redacted]
	50S02	[redacted]
	50S03	[redacted]
	50S04	[redacted]
	50S05	[redacted]
51	51S01	[redacted]
52	52S03	[redacted]
53	53S01	[redacted]
	53S02	[redacted]

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
54	54S03	[redacted]
	54S07	[redacted]
54 (continued)	54S11	[redacted]
	54S15	[redacted]
	54S17	[redacted]
	54S21	[redacted]
	54S22	[redacted]
55	55S01	[redacted]
	55S04	[redacted]
	55S05	[redacted]
	55S12	[redacted]
	55S18	[redacted]
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	55S21	[redacted]
	55S22	[redacted]
56	56S01	[redacted]
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	56S31	[redacted]
	56S32	[redacted]
	56S33	[redacted]
	56S34	[redacted]

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
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	56S36	[redacted]
56 (continued)	56S37	[redacted]
	56S38	[redacted]
	56S39	[redacted]
	56S40	[redacted]
	56S41	[redacted]
	56S42	[redacted]
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	64S11	[redacted]
	64S12	[redacted]
	64S13	[redacted]
	64S14	[redacted]

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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
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	64S16	[redacted]
64 (continued)	64S17	[redacted]
65	65S01	[redacted]
	65S02	[redacted]
	65S03	[redacted]
	65S04	[redacted]
	65S05	[redacted]
	65S08	[redacted]
	65S09	[redacted]
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Patients for Inclusion in PAS Study		
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Patients for Inclusion in PAS Study		
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Patients for Inclusion in PAS Study		
Site No.	**Screening No.**	**Patient No.**
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	79S14	[redacted]

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