

CLINICAL STUDY PROTOCOL

Study Title: **A Multi-Center, Sham-Controlled, Double-Blind Randomized Withdrawal Study of Pulsed Electromagnetic Field (PEMF) Therapy to Evaluate Vibration Perception Threshold and Thermal Sensory in Subjects with Diabetic Peripheral Neuropathy in the Lower Extremity**

Protocol Number: RBI.2017.001

Version: F

Phase: Proof of Concept

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PROTOCOL SIGNATURE PAGE – SPONSOR

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DOCUMENT REVISION HISTORY		
	Date	Summary of changes
Version A	10 JAN 2017	Original document
Version B	10 FEB 2017	Changed Painful Peripheral Diabetic Neuropathy to Diabetic Peripheral Neuropathy to allow for a broad symptomatology to be included. Added information to how many times VPT test will be conducted to obtain the average value at each time point. Added additional primary endpoint to capture changes in both large and small nerve fiber responses. Updated response assessment from VPT change to change in 1-point decrease in NPRS over the last 24 hours. Added additional instruction and a visual for collecting the foot measurement, updated introduction and background section, and added additional medications to “allowed medications” section. Removed EQ-5D questionnaire and replaced with Neuro-QoL questionnaires.
Version C	22 FEB 2017	Change testing of plantar aspect to dorsal aspect for QST heat and cold testing. Updated Exclusion #3 added a timeframe of within 6 months of the Screening Visit and an upper limit of 1.4 for the ABI.
Version D	27 MAR 2017	Removed Summary of Diabetes Self Care Activities Questionnaire (SDSCA) to reduce patient fatigue with answering questionnaires. Switched NeuroQoL questionnaire with a single neuropathy-and foot ulcer-specific quality of life instrument.
Version E	19MAY2017	Updated locations for biopsies to be taken as well as the central lab used in analyzing the samples.
Version F	12JUN2017	Increase the number of sites from 2 to 4. Update Inclusion/Exclusion criteria to allow for a broader population to be enrolled. Allow all patients to voluntarily consent to biopsies.

Study Synopsis

Study Title	A Multi-Center, Sham-Controlled, Double-Blind Randomized Withdrawal Study of Pulsed Electromagnetic Field (PEMF) Therapy to Evaluate Vibration Perception Threshold and Thermal Sensory in Subjects with Diabetic Peripheral Neuropathy in the Lower Extremity
Protocol Number	RBI.2017.001
Name of Study Device	PROVANT® Therapy System
Phase of Development	Proof of Concept
Objective	To demonstrate the effectiveness of PEMF treatment compared to sham treatment in changing Vibration Perception Threshold (VPT) and Thermal Sensory (QST) in patients with diabetic peripheral neuropathy (DPN) when treatment is administered twice daily through 120-day period.
Number of Subjects	Up to 40 subjects randomized 1:1.
Study Design	This is a multi-center, sham-controlled, double-blind, enriched enrollment, randomized withdrawal clinical trial conducted on subjects with bilateral symmetrical diabetic peripheral neuropathy. Eligible subjects will include those between 22 and 80 years of age with Type 1 or Type 2 diabetes having persistent pain, numbness, tingling, or burning in both feet despite treatment. Eligible subjects will receive two active treatment devices (one for each foot, to allow simultaneous treatment) and treat at home, twice daily for 60 days after which they will return to the clinic at Day 61 for a response assessment. Subjects that are determined to be responders at Day 61 (subjects that achieve a 1-point decrease in the average pain score over the last 24 hours using the Numeric Pain Rating Scale (NPRS)) will be randomized 1:1 to either active treatment or inactive sham devices and will continue treating through Day 120. Subjects that are determined to be non-responders at Day 61 will continue treating with the active devices given at enrollment and will return to the clinic at Day 75 and Day 91 for a response assessment. If a subject is determined to be a responder at Day 75, they will be randomized 1:1 to receive either active treatment or inactive sham and will continue treating through Day 120. If a subject is determined to be a responder at Day 91, they will be randomized 1:1 to receive either active treatment or sham and will continue to treat through Day 120. If a subject continues to be a non-responder at Day 91 they will be terminated from the study.

Endpoints	<p>For this proof of concept study, the primary endpoints will be changes in Vibration Perception Threshold and Quantitative Sensory Testing between baseline and end of treatment. Secondary endpoints will be changes in nerve conduction velocity (NCV) of the sural nerve and amplitude from baseline to end of treatment, changes in Skin Perfusion Pressure (SPP) from baseline to end of treatment, change in Pain Intensity using the 11-point Numeric Pain Rating Scale (NPRS) from baseline to end of treatment, change from baseline in Brief Pain Inventory (BPI) and Brief Fatigue Inventory (BFI), change from baseline in Patient Global Impression of Change (PGIC), change from baseline in Hospital Anxiety and Depression Scale (HADS), and changes from baseline in neuropathy and foot ulcer specific quality of life instrument (NeuroQoL).</p> <p>Safety will be assessed through review of Adverse Event (AE) reports and concomitant treatments and medications. All concomitant drug or non-drug treatments used during the study will be recorded. Safety outcomes will be assessed at the interim visits and the end of study visit.</p>
Study Procedures	<p>Following informed consent and assessment of eligibility, subjects will complete Section A-History of the Michigan Neuropathy Screening Instrument (MNSI) with Section B-Physical Assessment completed by the site. A measurement of the depth of the right foot will be measured from the most inferior aspect of the medial malleolus to the plantar aspect of the foot when residing on the treatment pad. The depth should not be more than 8cm for eligibility. A finger stick will be performed on the subject to obtain a baseline HbA1c value (A1C Now[®] test kit) and subjects will complete a Urine Drug Screen in office. Subjects will undergo the Ankle-Brachial Index (ABI), Venous Insufficiency Assessment, and Pain Phase evaluation (at least 10 subjects in each of the 2, 3, and 4 pain phases will be enrolled). For subjects of child bearing potential a urine pregnancy test will be obtained.</p> <p>At the Enrollment Visit (can be combined with Screening), subjects will have a finger stick performed to collect a baseline glucose value. If the Screening Visit and Enrollment Visit are not combined, eligibility will be re-assessed to confirm no changes, concomitant medications and assessments of Adverse Events will be obtained. Subjects will provide their baseline pain score over the last 24 hours using the Numeric Pain Rating Scale (NPRS) and will also complete baseline health economic questions, questionnaires including the Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), Hospital Anxiety and Depression Scale (HADS), and the NeuroQoL Questionnaire.</p>

	<p>Vibration Perception Threshold (VPT), Quantitative Sensory Test (QST) and Nerve Conduction Velocity (NCV) will be performed. Skin Perfusion Pressure (SPP) will be performed to obtain a baseline value of the plantar and dorsal aspect of the right foot. Eligible subjects will receive 2 active treatment devices (1 device for each foot). Subjects will be instructed in the use of the devices and will self-treat both feet twice daily (morning and evening; 8am \pm 2 hours and 8pm \pm 2 hours) for 60 days in the home environment. Each treatment will be 30 minutes in duration, treating both feet simultaneously. Subjects will be provided with a study diary for capturing their daily pain scores based on a 11-point numerical pain rating scale (NPRS) and weekly Patient Global Impression of Change Score (PGIC). Subjects will document pain scores each day after the morning treatment as instructed by the site at the Enrollment Visit. Every week the PGIC will be collected in the diary and the subject will document their overall status since the beginning of treatment. Subjects will either provide consent or not for biopsies to be obtained. Subjects that consent to the biopsies will have two 3mm punch skin biopsies obtained, one biopsy at the distal leg (10cm above the lateral malleolus) and one biopsy at the distal thigh (10cm above the superior margin of patella). Biopsies will be taken from the right leg to represent small nerve fiber innervation emanating from the deep peroneal nerve. At least two subjects in each pain phase category (2, 3, and 4 Pain Phase) will be obtained.</p> <p>The site will contact the subject via telephone on Day 3 to assess subject adherence to treatment, completion of the diary, and any safety concerns and/or changes in concomitant treatments/medications.</p> <p>At Days 15 and 45, subjects will return to the clinic to have VPT and QST conducted and to have treatment satisfaction assessed. Subjects will also bring in the study devices and diary to assess treatment and diary compliance. A new study diary will be dispensed for the next two weeks.</p> <p>At Days 30 and 61, subjects will return to the clinic to complete the BPI, BFI and HADS questionnaires and to have treatment satisfaction assessed. VPT and QST will be conducted along with a finger stick to collect the subject's blood glucose level. Subjects will also bring in their study devices and diary to assess treatment and diary compliance. A new study diary will be dispensed for the next two weeks. At Day 61, SPP will be conducted and subjects will be assessed for a response. If a subject is determined to be a responder (decrease in average pain score over the last 24 hours using the NPRS of at least 1 point)</p>
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	<p>they will return the active devices and be randomized 1:1 to receive active treatment or inactive sham devices and be instructed to treat for an additional 60 days (through Day 120). If the subject is determined to be a non-responder, they will continue treating with the active devices for an additional 15 or 30 days and will be assessed at Day 75 and Day 91 for response.</p> <p>At Day 75, subjects will return to the clinic to have treatment satisfaction assessed, and have the VPT and QST conducted. All subjects will bring in their devices and diary to assess treatment and diary compliance. A new study diary will be dispensed for the next two weeks. For those subjects determined to be non-responders at Day 61, they will be assessed for response. If they become a responder by Day 75 they will return their active devices and be randomized 1:1 to receive active treatment or inactive sham devices, and instructed to treat through Day 120. If the subject is still considered a non-responder, they will continue treating through Day 90 with the active devices given at Enrollment.</p> <p>At Day 91, subjects will return to the clinic to complete the BPI, BFI and HADS questionnaires and to have treatment satisfaction assessed. The VPT and QST will be conducted along with a finger stick to collect the subject's blood glucose level. Subjects will also bring in the study devices and diary to assess treatment and diary compliance. A new study diary will be dispensed for the next two weeks. At Day 91, non-responders will be assessed for a response. If a subject is determined to be a responder at Day 91 (decrease in average pain score using the NPRS of at least 1 point) they will return the active devices and be randomized 1:1 to receive active treatment or inactive-sham devices and instructed to treat for an additional 30 days (through day 120). If the subject is determined to be a non-responder, they will be terminated from the study at the end of the Day 91 visit.</p> <p>At Day 105, all subjects will have VPT and QST completed and have treatment satisfaction assessed. Diaries will be collected and a new diary dispensed. Subjects will also bring in the study devices and diary to assess treatment and diary compliance.</p> <p>At Day 121, end of study visit, subjects will have their weight, ABI, NCV, SPP, and Venous Insufficiency assessed. Subjects will also receive a finger stick to obtain blood for the HbA1c and blood glucose values. The subject will complete the BPI, BFI, HADS, and NeuroQoL questionnaires and have treatment satisfaction assessed. The subject will return their study devices and diary, and the VPT and QST will be completed. Subject's that consented to having the biopsy, will have a 3mm punch skin biopsy obtained from the distal leg and distal thigh on the right</p>
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	<p>leg. The biopsy will be obtained to represent small nerve fiber innervation emanating from the deep peroneal nerve.</p> <p>Assessment of adverse events and concomitant medications will occur at each visit.</p>
Study Device	<p>The study device is the PROVANT[®] Therapy System (PEMF). The active devices will deliver Pulsed Electromagnetic Field (PEMF) energy therapy. The active treatment and inactive sham devices will be identical in appearance and all other physical characteristics in order to maintain the blinding of the treatment. Each device will be identified with a unique kit number.</p>
Study Sample	<p>The anticipated enrollment in this study is up to 40 subjects. The study will be conducted at up to 4 sites.</p>
Primary and Secondary Outcome Measures	<p>Several efficacy outcome measures will be assessed in order to allow for characterization of the response to PEMF therapy.</p> <p><u>Efficacy Assessments</u></p> <p>All efficacy assessments will be conducted at the Enrollment Visit (Baseline; Day 0) and at the end of study visit (Day 121).</p> <p>Vibration Perception Threshold (VPT): For large nerve fiber assessment. VPT is a non-invasive test used in quantifying sensation/sensitivity to vibration in evaluating sensory dysfunction associated with diabetic neuropathy. The hand-held vibratory stimulator will be placed against the midpoint of the plantar aspect and big toe of the right foot, the tester will initiate the automated test that will last between 5-10 minutes. Three tests will run at each location and the average of the 3 will be populated by the system. The VPT will be collected using the VSA-3000 Vibratory Sensory Analyzer at the midpoint on the plantar aspect and on the big toe of the right foot. VPT will be collected at the Enrollment Visit to obtain a baseline value and on Days 15, 30, 45, 61, 75, 91, 105 and 121.</p> <p>Quantitative Sensory Testing (QST): For small nerve fiber assessment. QST is a noninvasive test used in peripheral nervous system disorders for thermal sensory testing. Contact thermal stimulation will be delivered using the NerveCheck Master through a contact thermode. A cold test of 15°C - 25°C, heat test of 40°C - 46°C will be administered. When activated the patient will notify the staff performing the test when they begin to feel the cold and warm test. The heat and cold thermal stimulation will be applied over the dorsal aspect of the right foot. QST will be performed at the Enrollment Visit to obtain a baseline value and on Days 15, 30, 45, 61, 75, 91, 105 and 121.</p>

	<p>Nerve Conduction Velocity (NCV): For large myelinated nerve fiber assessments. Using the NC-stat® DPNCheck®, the subject will assume a comfortable position so that their right leg is visible (that the subject's outer ankle bone and Achilles tendon are visible). The patient preparation pad is then used to thoroughly clean the subject's outer lower leg and ankle bone area to remove any residue. The subject's outer ankle bone is then identified to align the anode and cathode just behind with the cathode just adjacent to the middle of the ankle bone. The device is aligned on the calf pressing firmly down on the foam to ensure contact. The sural nerve conduction velocity and amplitude will be recorded at the Enrollment Visit and end of study visit (Day 121).</p> <p>Skin Perfusion Pressures (SPP): Vasamed Sensilase PAD-IQ measures pressure (in mm Hg) of microcirculation using a laser Doppler sensor. Patient lies down in supine position and remains silent and still. The Laser Sensor Assembly (LSA) is inserted into the LSA Placement Guide and the optical sensor window is oriented toward the skin. For those subjects who will have biopsies performed, SPP will be obtained prior to the skin biopsies. A cuff is positioned so that the LSA is centered on the bladder both horizontally and vertically. The pressure of the cuff is then automatically increased to a pressure necessary to occlude blood flow and then released at a controlled rate and a measurement of the pressure in the angiosome is made. SPP (mmHg) at reactive hyperemia is recorded. A second measure of SPP will be obtained on the plantar aspect of the right foot directly below the location where the SPP was performed on the dorsal aspect of the right foot. SPP will be conducted at the Enrollment Visit, Day 61, and end of study visit (Day 121).</p> <p>Pain Intensity (PI): a validated 11-point Numeric Pain Rating Scale (NPRS) with scores (0-10) collected as patient-reported outcomes on a paper diary and at the Enrollment visit to obtain a baseline value and on Days 61, 75, and 91 to determine response. On the patient diary, PI will be assessed after each morning (8am \pm 2 hours) treatment. Subjects will report their average pain score over the last 24 hours. Diaries will be distributed and collected from the subjects every 2 weeks to ensure compliance.</p> <p>Brief Pain Inventory (BPI): is a 32-question long form questionnaire that assesses the severity of pain and its impact on specific daily functions. Cronbach's alpha reliability ranges from 0.77-0.91. The BPI long form will be administered at the Enrollment Visit, Day 30, 61, 91, and end of study visit (Day 121).</p> <p>Brief Fatigue Inventory (BFI): is a 4-question assessment that assesses the level of fatigue and the impact of the fatigue on daily</p>
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	<p>function over the last 24 hours. A global fatigue score is collected by averaging all items on the BFI. Cronbach's alpha reliability ranges from 0.82-0.97. BFI is patient reported and collected at the Enrollment Visit, Days 30, 61, 91, and end of study visit (Day 121).</p> <p>Patient Global Impression of Change (PGIC): a 7-point validated categorical scale of overall change in status since initiation of treatment with the study device. PGIC allows subjects to integrate, into one overall evaluation, the different aspects of their response to treatment, including pain reduction, improvement in functioning and side effects. PGIC will be collected every 7 days in the paper diary, immediately following the morning treatment. PGIC serves to anchor within-subject changes in pain over the course of treatment.</p> <p>Hospital Anxiety and Depression Scale (HADS): is a patient reported assessment that detects status of depression and anxiety. The subscales within the assessment assess the severity of the emotional disorder connected to having diabetic peripheral neuropathy. Subjects will complete the assessment at the Enrollment Visit, Days 30, 61, 91, and end of study visit (Day 121).</p> <p>NeuroQoL: is a validated assessment that measures the effects of diabetic peripheral neuropathy and its complications on an individual's quality of life. The questionnaire will be completed by the subject at the Enrollment Visit and end of study visit (Day 121).</p> <p><u>Experimental Outcome Assessment</u></p> <p>Skin Biopsy: To assess c-fiber nerve density. Subjects that provide consent to having biopsies taken will have two 3mm punch skin biopsies obtained, one biopsy at the distal leg (10cm above the lateral malleolus) and one biopsy at the distal thigh (10cm above the superior margin of patella) on the right leg at the Enrollment Visit. At least 2 subjects in each pain phase category (2, 3, and 4 Pain Phase) will have a biopsy obtained. The biopsy will be shipped overnight to the central lab for processing. At the Day 121 Visit, a second set of biopsies will be obtained to the right of each prior biopsy on the distal leg and distal thigh of the right leg. The samples will be shipped overnight to the central lab for processing. The lab will assess the samples for nerve fiber density and compare to baseline.</p>
Statistical Considerations	<p>This bi-phasic design includes 2 sequential periods: the <i>Induction Phase</i> and <i>Randomized Withdraw Phase</i>. All safety analyses will</p>

	<p>be performed on the safety analysis set, defined as all subjects who were enrolled into the study and issued study devices during the <i>Induction Phase</i> and followed through the <i>Randomized Withdraw Phase</i>. Once the subject is determined to be eligible, the subject will be issued active treatment devices and the subject will be formally enrolled into the study and become part of the <i>Safety Analysis Set</i>.</p> <p>All recorded data will be listed by subject and time point. Descriptive statistics will be tabulated for all randomized subjects for the change from baseline to study day 120 (Completers Analysis Set), and separately for the change from baseline to the last recorded set of evaluations (End of Study Evaluation Set). This latter set should include all subjects who were randomized and complete at least one set of evaluations after randomization.</p> <p>Treatment-emergent adverse events will be summarized by type, frequency, severity, and relationship to the study device. Adverse events will be provided in a listing.</p>
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LIST OF ABBREVIATIONS

ABI	Ankle Brachial Index
AE	Adverse Event
AGE	Advanced Glycation End Products
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CRA	Clinical Research Assistant / Associate
DAC	Disposable Applicator Cover
DFU	Diabetic Foot Ulcerations
DPN	Diabetic Peripheral Neuropathy
DTR	Deep Tendon Reflexes
DSPN	Distal Symmetric Sensorimotor Polyneuropathy
E-STIM	Electrical Nerve Stimulation
FCC	Federal Communication Commission
FDA	Food & Drug Administration
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
LOPS	Loss of the Protective Sensation
LSA	Laser Sensor Assembly
MedDRA	Medical Dictionary for Regulatory Activities
NCV	Nerve Conduction Velocity
NeuroQoL	Neuropathy and foot ulcer specific quality of life instrument
NOS	Nitric Oxide Synthase
NPRS	Numeric Pain Rating Scale
PEMF	Pulsed Electromagnetic Field
PGIC	Patient Global Impression of Change
POC	Proof of Concept
PRFE	Pulsed Radio Frequency Energy
PRN	As Needed

PT	Physical Therapy
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPP	Skin Perfusion Pressure
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants
QST	Quantitative Sensory Test
VPT	Vibration Perception Threshold

I. INTRODUCTION AND BACKGROUND

The Centers for Disease Control and Prevention (CDC) has estimated the number of diagnosed and undiagnosed level of diabetes mellitus to be 29.1 million people or 9.3% of the United States population.¹ The most common form of diabetes mellitus, type 2 diabetes mellitus, is projected to affect an estimated 366 million people worldwide by 2030.² About 60 to 70 percent of individuals diagnosed with type 1 or type 2 diabetes mellitus have some form of diabetic neuropathy ensuing from hyperglycemic-induced metabolic abnormalities. As such, diabetic neuropathy is major cause of morbidity in patients with diabetes mellitus. While symptomatic or asymptomatic neuropathy can be diagnosed at any time during disease course there tends to be an increased association with increased age and longer duration of diabetes.³ The highest rates of neuropathy are found in individuals diagnosed with diabetes for at least 25 years or greater and there has been an association with hypertension and obesity. Acute, aggressive glycemic control has been associated with improvement in the severity of neuropathy. Nonetheless, the sine qua non for the development and severity of diabetic neuropathy is chronic poor glycemic control.^{3, 4, 5}

Clinical neuropathy syndromes associated with diabetes mellitus are categorized according to their neurologic distribution. While overlap in presentation exists the categories are as follows: ⁽⁵⁾

Table 1—Classification for Diabetic Neuropathies

<p>A. Diffuse neuropathy Distal Sensorimotor Peripheral Neuropathy (DSPN)</p> <ul style="list-style-type: none"> • Primarily small-fiber neuropathy • Primarily large-fiber neuropathy • Mixed small- and large-fiber neuropathy (most common) <p>Autonomic Neuropathy Cardiovascular Neuropathy (CAN)</p> <ul style="list-style-type: none"> • Reduced HRV • Resting tachycardia • Orthostatic hypotension • Sudden death (malignant arrhythmia) <p>Gastrointestinal</p> <ul style="list-style-type: none"> • Diabetic gastroparesis (gastropathy) • Diabetic enteropathy (diarrhea) • Colonic hypomotility (constipation) <p>Urogenital</p> <ul style="list-style-type: none"> • Diabetic cystopathy (neurogenic bladder) • Erectile dysfunction • Female sexual dysfunction <p>Sudomotor Dysfunction</p> <ul style="list-style-type: none"> • Distal hypohydrosis/anhydrosis, • Gustatory sweating <p>Hypoglycemia Unawareness Abnormal Pupillary Function</p>	<p>B. Mononeuropathy (mononeuritis multiplex) (atypical forms)</p> <ul style="list-style-type: none"> • Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal) • Mononeuritis multiplex (if confluent may resemble polyneuropathy) <p>C. Radiculopathy or polyradiculopathy (atypical forms)</p> <ul style="list-style-type: none"> • Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy) • Thoracic radiculopathy <p>Nondiabetic neuropathies common in diabetes</p> <ul style="list-style-type: none"> • Pressure palsies • Chronic inflammatory demyelinating polyneuropathy • Radiculoplexus neuropathy • Acute painful small-fiber neuropathies (treatment-induced)
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Distal symmetric sensorimotor polyneuropathy (DSPN) is the most common form of diabetic neuropathy and accounts for approximately half of the diabetic-related neuropathy diagnosed in the US. Clinical presentation and clinical course of diabetic neuropathy varies in prevalence associated with both the duration of disease and maintenance of adequate glycemic control. Corresponding to length dependent nerve damage, patients present with distal symptoms that progress proximally affecting the lower extremities more prominently than upper extremities. Patients typically describe DSPN symptoms in terms of increased or decreased sensations resulting from damage of the myelinated and unmyelinated cutaneous nerve fibers.

Clinical Presentation of Distal Symmetric Sensorimotor Polyneuropathy (DSPN) initially involves the feet and hands. DSPN initially affects smaller unmyelinated C-fibers which convey light touch, pain and temperature with subsequent progression to involve larger myelinated A delta-fibers which convey vibratory sensation, proprioception and joint position. As the disease progresses motor function becomes impaired. Early in the process this may require nerve conduction velocity testing and assessment of reduced deep tendon reflexes (DTR) for detection prior to the development of noticeable weakness on flexion or extension of digits. Progressively severe disease may demonstrate weakness with foot and ankle dorsiflexion and extension and grip strength.^{4,5,6}

Management of Peripheral Diabetic Neuropathy⁵
(Adapted Bolton 2005)

Increased (Painful)	Decreased (Painless)
Burning pain	Asleep
Knife-like	“Dead”
Electrical sensations	Numbness
Squeezing	
Tingling	
Constricting	
Prickling	
Hurting	
Freezing	

Microvascular compromise of smaller arterioles demonstrating endothelial dysfunction progressing to calcification and dysfunction in larger vasculature add to the complexity of the medical presentation with overlapping syndromes of peripheral ischemia that may or may not contribute to the lower extremity pain experienced by patients. Diabetic-related metabolic abnormalities lead to an impaired immune response to infection and the effect of diabetes on bones, cartilage, tendons and fascial tissue causes mechanical and conformational changes in the architecture of the foot. Gait abnormalities, impaired balance and falls frequently ensue. In advanced peripheral diabetic neuropathy, the patient no longer senses pain developing a loss of the protective sensation (LOPS), the most common component in the pathway to the development of diabetic foot ulcerations (DFU) and for the development of Charcot’s neuroarthropathy.^{5,6,9} Combined with ischemia and infection,

LOPS frequently culminates in amputation. DFUs are responsible for more hospitalizations than any other complication of diabetes with 5% of diabetic patients developing foot ulcers in the U.S. each year and 1% of those patients requiring an amputation.⁷

Pathophysiology for DSPN, as noted above, is complex and involves multiple mechanistic pathways. Currently, a combination of direct and indirect axonal injury. Hyperglycemia in concert with insulin resistance and abnormal adiposity leads to the accumulation of advanced glycation end products (AGE), toxic effects of free fatty acids and pro-inflammatory adipokines. These factors damage nerve fibers, effecting initially smaller unmyelinated C-fibers and progressively advancing to damage larger myelinated fibers. Direct axonal injury occurs secondary to endothelial injury causing endothelial dysfunction, nitric oxide synthase (NOS) levels are reduced leading to small vascular vasoconstriction, larger vascular calcifications and constriction, which ultimately result in nerve ischemia.^{5,6,7}

Therapeutic Intervention for the prevention and treatment of distal symmetric sensorimotor polyneuropathy (DSPN) are generally related to counselling, antioxidant-rich nutrition, optimized glycemic control, weight management, moderate exercise, routine foot screening and proper foot wear, and avoidance of alcohol and tobacco. Care must be taken to ensure nondiabetic causes of neuropathy have been assessed and excluded- hereditary, malignant disease (e.g., bronchogenic carcinoma), metabolic disorders (e.g., thyroid, renal disease), toxic (e.g., alcohol), infective agents (e.g., Human Immunodeficiency Virus (HIV), Lyme's, Hepatitis B infection), vitamin B deficiencies (e.g., B1, B6, B12, tocopherol), iatrogenic interventions (e.g., isoniazid, vinca alkaloids, amiodarone, colchicine, Dapsone, Taxol), heavy metals (e.g., mercury, arsenic), and medication-related (chemotherapy, HIV treatment).^(4,5) Nonetheless, aside from adequate glycemic control and antioxidants, medical therapies for improving impaired nerve function have been lacking and the focus of diabetic neuropathy management has focused predominantly on pharmaceutical-based pain control. The wide variety of medical classifications represented reflect the diffuse nature of the disorder and the lack of specificity for improvement across the population of patients being treated. For patients who require pharmacologic treatment, first-line therapies include tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and anticonvulsants, specifically those which increase the availability of gamma-aminobutyric acid.

Modified Drug Class Drug Daily Dose (mg) Side Effects^{4,5,9}

Category	Agent	Daily Dosage	Side Effects
Tricyclics	Amitriptyline	25–150 mg	++++
	Imipramine	25–150 mg	++++
	Doxepine	10 mg	+++
SSRIs	Paroxetine	40 mg	+++
	Citalopram	40 mg	+++
Anticonvulsant Agents	Gabapentin	900–1,800 mg	++
	Pregabalin	160–600 mg	++
	Lamotrigine	200–400 mg	++

	Carbamazepine	up to 800 mg	+++
SNRI	Duloxetine	60 mg	+++
Anti-arrhythmic Agents	Mexilitene	up to 450 mg	+++
Opioids	Tramadol	50–400 mg	+++
	Oxycodone CR	10–60 mg	++++

While tricyclic antidepressants are the most studied agents used for neuropathic pain, physicians have been using TCAs, such as amitriptyline and nortriptyline (Pamelor), to treat neuropathic pain for years without approved labeling from the U.S. Food and Drug Administration (FDA). Duloxetine (Cymbalta®) and pregabalin (Lyrica®) are the only agents approved by the FDA specifically for the treatment of painful peripheral diabetic neuropathy. Patients frequently supplement oral agents with topical therapy- including capsaicin 0.075% cream, doxepin 5% solution or lidocaine 5% patches. Additionally, topical nitrates, alpha-lipoic acid antioxidant, and homeopathic agents such as evening primrose oil have been reported with variable success in reducing neuropathic pain. Opioids are generally prescribed for severe, unresponsive pain.

In an effort to avoid overuse of opioids for severe unrelenting pain, the American Pain Society and the Academy of Pain Medicine have generated guidelines that include the use of non-pharmaceutical interventions currently used to treat chronic pain, *Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain*. Non-pharmaceutical agents such as electrical nerve stimulation (E-Stim), acupuncture, electro-acupuncture, cognitive behavioral therapy (CBT), biofeedback, and physical therapy (PT) have some usefulness in treating painful peripheral DSPN.¹⁰

Trial: This proof-of-concept (POC) trial is being conducted to evaluate the therapeutic value of using pulsed electromagnetic energy fields (PEMF) in the treatment of diabetic neuropathy.

Study Product: PROVANT® Therapy System is a medical device manufactured by Regenesi Biomedical, Inc. (Scottsdale, AZ), that has been cleared by the FDA (**K972093, K091791, AND K131979**) “for adjunctive use in the palliative treatment of post-operative pain and edema in superficial soft tissue.” The device delivers self-administered, non-thermal, non-ionizing pulsed electromagnetic energy to the target tissue, using 27.12 MHz pulses lasting 42 microseconds and delivered 1000 times per second. The system generates an electromagnetic field that is continuously monitored and regulated to ensure consistent dosing. The therapeutic electromagnetic field is delivered by means of an applicator pad that is placed against the treatment site. The device is non-invasive and does not require placement of surface or deep electrodes, nor removal of bandages or clothing. Treatment is usually imperceptible and very well tolerated. Evidence suggests that PROVANT® Therapy System can reduce pain, promote healing, and promote restored range of motion following reparative surgery in wounded extremities. [Guo 2011, Moffett 2011] As an analgesic, it is non-addictive and does not alter the mental state of the user. Regenesi Biomedical, Inc., has marketed the device since 2004 and has treated over 10,000 patients within the U.S. Over two million individual treatments have been administered with rare adverse events reported. [FDA

MAUDE Database 2014] In addition, the safety of PEMF has been well documented. The 2012 meta-analysis by Guo et al [Guo 2012] of 25 clinical trials of PEMF in treatment of pain, edema and wound healing identified no serious adverse events among 1,332 patients treated with PEMF. In addition, the same meta-analysis found statistically significant evidence supporting the efficacy of adjunctive PEMF therapy for pain relief, edema reduction, and wound healing promotion. Finally, adjunctive PEMF therapy has been reported effective in alleviating pain resulting from trauma, [Comorosan 1991, Foley-Nolan 1992, Wilson 1972, Barclay 1983, Pennington 1993, Shandles 2002] and chronic pain. [Foley-Nolan 1990, Wagstaff 1986, Brook 2012].

In vitro and in vivo evidence suggest PEMF functions by modulating factors involved in pain signaling and soft tissue repair. In vitro studies demonstrated that PEMF treatment of cells in culture can mediate wide-spread changes in transcript levels encoding factors involved in pain and the inflammatory response (including endogenous opioids, growth factors, cytokines, and cell cycle regulating factors), [Moffett 2011, Moffett 2012, Rohde 2010] and can promote cell proliferation. [George 2002] Regenesys Biomedical, Inc. scientists recently found that PEMF increases endogenous opioid expression, which coincides with an increase in endothelin receptor B in keratinocytes, suggesting that PEMF treatment induces a localized analgesic effect by activation of these receptors by endothelin-1. [Moffett 2012a, Moffett 2012b] These findings have led to the proposition that PEMF activates peripheral endogenous opioids which, in turn, activate an analgesic cascade via the endothelin pain axis. In a recent clinical study, PEMF usage for post-operative pain not only reduced pain levels and opioid consumption relative to sham-treated patients, but was also associated with lower IL-1 β levels in post-operative wound exudates. [Rohde 2010] Together, these findings suggest that PEMF therapy reduces pain both by modulating inflammation and by activating peripheral endogenous opioids.

An exploratory prospective randomized, sham-controlled IRB-approved study was recently conducted at two sites using the PROVANT[®] Therapy System to evaluate small fiber nerve growth and function in subjects with painful peripheral diabetic neuropathy. Twenty-three subjects with painful peripheral diabetic neuropathy were treated for 60 days with twice-daily PEMF therapy.

Subjects were eligible for enrollment if they had type 2 diabetes having persistent numbness, tingling, or burning in at least one foot despite standard of care treatment.

Eighteen subjects in this study were evaluated for the effectiveness of the PROVANT[®] Therapy System in enhancing small fiber nerve growth and function. PEMF treatment twice daily for 60 days was associated with improved skin perfusion pressure, and improved nerve conduction.

The purpose of the current study is to further elucidate the underlying mechanisms of increased sensation and pain relief observed in patients receiving treatment with the PROVANT[®] Therapy System. In vitro studies have provided evidence that PEMF therapy improves nerve growth and may improve nerve function through up-regulation of genes involved in neurogenesis. [Data on File] In addition, genes related to angiogenesis have also been shown to be up-regulated. Through evaluation of vibration perception threshold, nerve conduction velocity, quantitative sensory testing, vascular changes (skin perfusion pressure), blood glucose (hemoglobin A1c), and quality

of life questionnaires, this study will evaluate if PEMF treatment in vibration perception and skin perfusion is enhanced in subjects that receive treatment with Provant compared to a group of subjects that receive treatment with a sham device.

II. STUDY OBJECTIVES

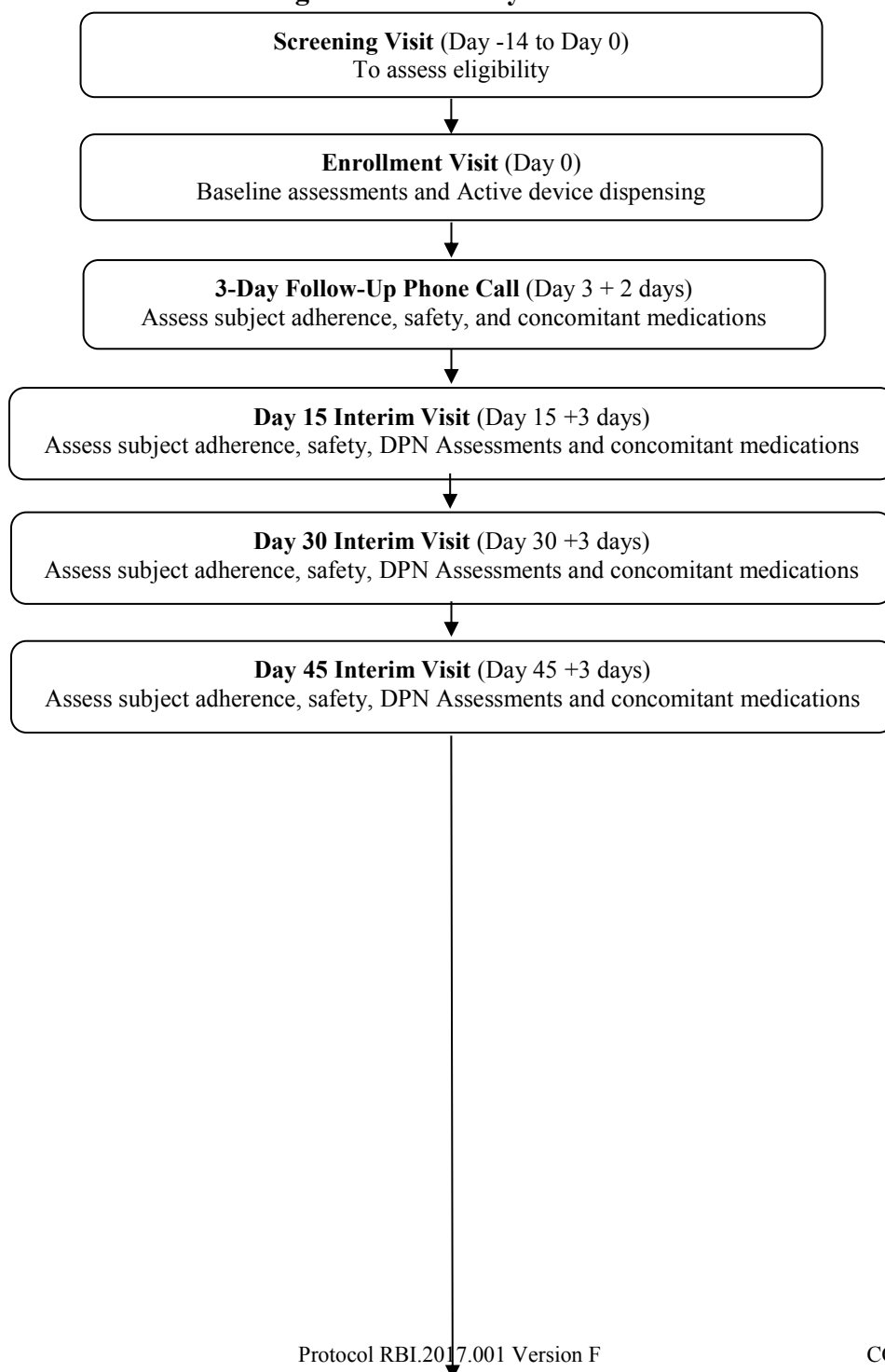
This study is designed to evaluate the effectiveness of the PROVANT® Therapy System (PEMF) in changing Vibration Perception Threshold (VPT) and Thermal Sensory Perception using Quantitative Sensory Testing (QST) in patients with bilateral symmetrical diabetic peripheral neuropathy (DPN) when treatment is administered twice daily through a 120-day period.

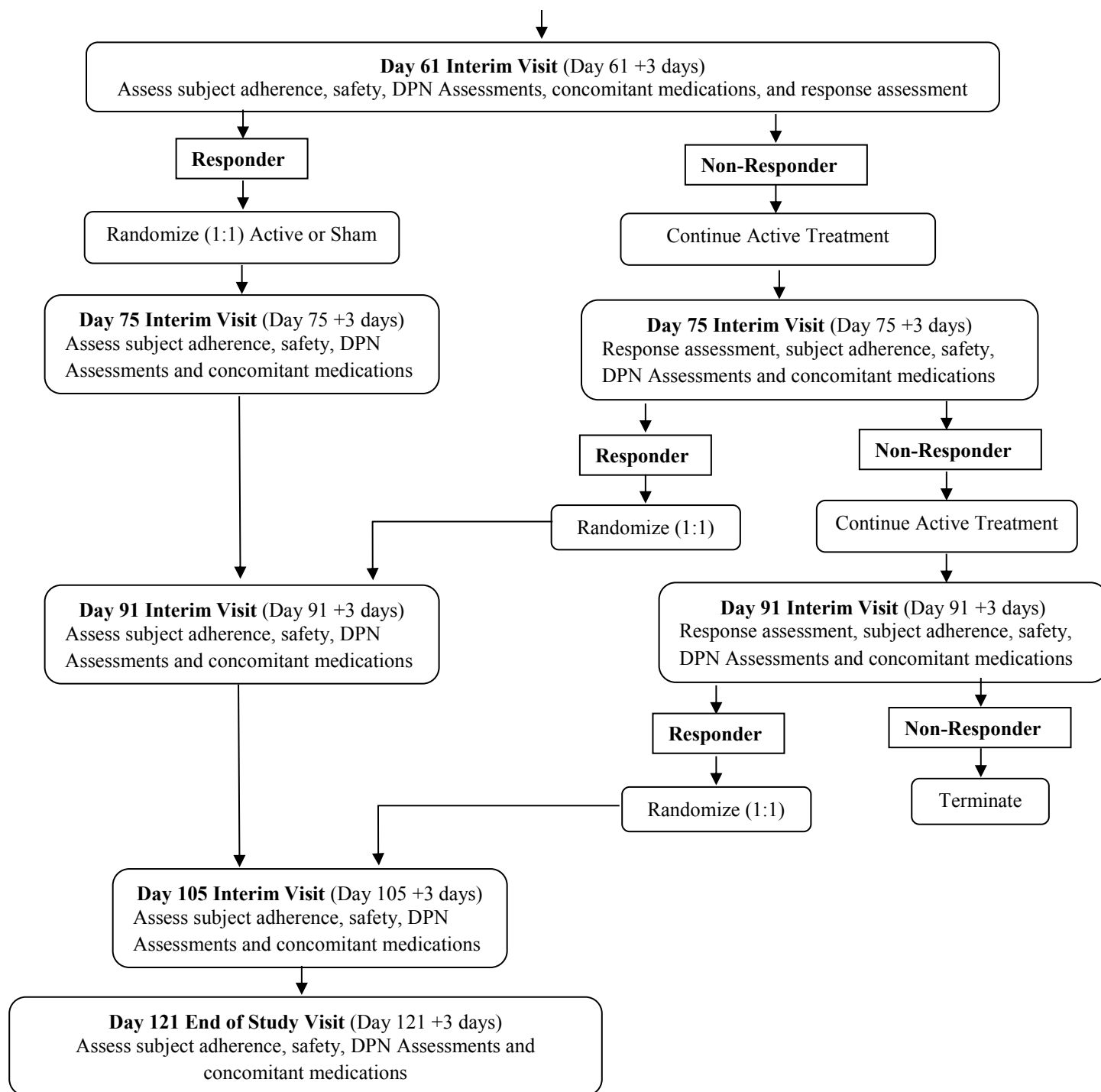
III. STUDY DESIGN

A. Study Design

The study is a multi-center, sham-controlled, double-blind, enriched enrollment randomized withdrawal study of the safety and efficacy of multi-dose PEMF therapy on subjects with bilateral symmetrical DPN. A graphic presentation of the study design is shown in Figure 1.

Figure 1. Study Flow Schematic





B. Efficacy Endpoints

This study will evaluate the changes in vibration perception threshold, thermal sensory perception, nerve conduction velocity, skin perfusion pressure, pain intensity, brief pain inventory, brief fatigue inventory, PGIC, hospital anxiety and depression scale, and neuropathy specific quality of life.

C. Safety Evaluation

All observed and reported adverse effects will be recorded by the research staff. Start dates, end dates, frequency, severity of the event, any treatment required to treat the event, and the investigator's judgment on causality and relationship to the study device will be assessed for each AE. Any AE occurring after the signing of the informed consent form will be recorded. Only those AEs occurring after initiation of the first treatment with the study device will be considered treatment-emergent AEs.

Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. While the primary presentation of adverse events will be subject-based, the number of adverse events will also be reported. The number and percentage of subjects reporting each event will be summarized during the treatment period by treatment assignment. Incidence of adverse events by maximum reported severity will also be tabulated. Serious adverse events and adverse events leading to discontinuation will be displayed.

D. Eligibility Criteria

Eligibility for participation in this study will be based on the inclusion/exclusion criteria. An individual subject may only be included in the study once.

1. Inclusion Criteria

1. Subject age is greater than or equal to 22 years and less than 80 years of age.
2. Subject has documented Type 1 or Type 2 diabetes mellitus (receiving insulin, diet controlled, or taking parenteral hypoglycemic agents)
3. Subject is on a stable antidiabetic regimen (medication and/or diet) to control their diabetes for at least 30 days prior to Screening.
4. Subject has an HbA1c <10% at Screening or within 2 months of Screening.
5. Subject has daily pain attributed to bilateral symmetrical Diabetic Peripheral Neuropathy with numbness, tingling, and/or burning based on clinical judgement for at least 6 months prior to screening.
6. Subject's pain or discomfort from DPN is identifiable.

7. Subject is in pain Phase 2, 3, or 4 as per the Phasing of Neuropathy Scale.
8. Subjects average pain over the last 24 hours is ≥ 3 based on the 11-point Numeric Pain Rating Scale (NPRS) at the Screening Visit.
9. Subject has adequate lower extremity pulse in both feet and no intermittent claudication.
10. Subject is able to ambulate independently with assistive devices, but not wheel chair bound.
11. Subject is willing and able to give written informed consent and to comply with all parts of the study protocol.
12. Female subjects must be post-menopausal, surgically sterile, abstinent, or practicing (or agrees to practice) an effective method of birth control if they are sexually active for the duration of the study (Effective methods of birth control include prescription hormonal contraceptives, intrauterine devices, double-barrier methods, and/or male partner sterilization).

2. Exclusion Criteria

1. Subject is in pain Phase 1 or 5 as per the Phasing of Neuropathy Scale.
2. Subject has an active, open ulcer on the lower extremities.
3. Subject has peripheral vascular disease defined as absence of more than one foot pulse per foot and/or ABI < 0.8 and > 1.4 and/or history of angioplasty or peripheral bypass surgery within 6 months of the Screening Visit.
4. Subject has venous insufficiency as classified by the Venous Insufficiency Classification System of grade C6.
5. Subject has undergone nerve decompression surgery on the lower extremities.
6. Subject has a history of previous kidney, pancreas, cardiac transplantation, or severe renal disease.
7. Subject has been diagnosed with non-diabetic chronic inflammatory neuropathic disease (e.g. end stage renal disease, hepatitis C, chemotherapy induced neuropathy, known connective tissue disease, systemic lupus).
8. Subject has peripheral vascular disease requiring revascularization of lower limb or amputation or evidence of ulcer amputation.

9. Subject has clinically significant cardiovascular disease within 6 months prior to screening (unstable or poorly controlled hypertension, transient ischemic attack, MI, unstable angina, arrhythmia, any heart surgery, stent placement, heart disease).
10. Subject has a history of any uncontrolled medical illness that in the Investigators judgment places the subject at unacceptable risk for receipt of PEMF therapy.
11. Subject requires or anticipates the need for surgery of any type or travel during the treatment period.
12. Subject has a total foot depth (most inferior aspect of the medial malleolus to the plantar aspect of the foot when residing on a treatment pad) of >8 cm.
13. Subject has received any investigational drug or device within 30 days prior to the Screening Visit or within 6 weeks prior to the Screening Visit for long acting lidocaine injection products.
14. Subject has used systemic corticosteroids within 3 months of the Screening Visit.
15. Subject has a history of malignancy within the past 5 years other than successfully treated non-metastatic basal cell or squamous cell carcinomas of the skin in the treatment area and/or localized in situ carcinoma of the cervix.
16. Subject has a serious psychosocial co-morbidity.
17. Subject has a history of drug or alcohol abuse, as confirmed by urine drug screen, within one year prior to the Screening Visit.
18. Subject has an implanted pacemaker, defibrillator, neurostimulator, spinal cord stimulator, bone stimulator, cochlear implant, or other implanted device with an implanted metal lead(s).
19. Subject is currently pregnant or planning on becoming pregnant prior to Day 121.
20. Subject has previously treated with PROVANT® Therapy System within 60 days on the lower extremity.
21. Subject is unwilling or unable to follow study instructions or comply with the treatment regimen, diary documentation, and study visits.
22. Subject has pain from any other source that can confuse the assessment of the pain associated with DPN.
23. Subject has a clinically significant foot deformity (Charcot's syndrome or club foot).

24. Subject has received nerve blocks for neuropathic pain within 4 weeks of the Screening Visit.
25. Subject has been diagnosed with mononeuropathy.
26. Subject has a skin condition that could alter their sensation.
27. Subject has had a previous surgery to the spine or lower extremity with residual symptoms of pain or difficulty with movement.
28. Subject has moderate or severe arthropathy (RA, OA, Gout) that causes discomfort during casual walking or stair climbing.

E. Recruitment

Recruitment for study subjects will be drawn from the patient population at the investigative study site. Recruitment efforts will be supplemented with IRB approved internet, radio and/or print advertising as necessary.

F. Randomization

The schedule for randomization of subjects and allocation to treatment will be prepared using SAS[®] (Statistical Analysis System; Cary, NC) to create a computer-generated scheme based on a permuted block algorithm. The randomization schedule will randomize in a 1:1 ratio (active : sham) to a device based on the randomization kit numbers. The kit numbers will be assigned sequentially to subjects that qualify for inclusion into the study.

G. Device Description

The PROVANT[®] Therapy System is a solid-state, fixed-power output radio frequency generator and transmitter designed to operate at the Federal Communication Commission (FCC) authorized medical device frequency of 27.12 MHz. The primary components are the control unit, the treatment applicator that generates and delivers the shortwave RF energy, and single-use Disposable Applicator Covers (DACs) intended to minimize contagion transmission and help protect the treatment applicator from biological contamination. Key functions and features of these components are as follows:

1. Control Unit

The control unit contains the main electronics, software, and user interface of the system. The control panel has a therapy Start/Stop switch and two therapy status indicators, described below, which are located on the top of the control panel, as well as a usage meter on the side of control panel.

Pressing the therapy Start/Stop switch initiates a preset, thirty (30)-minute therapy session by starting the Radio Frequency Identification Device (RFID) tag interrogation and treatment sequence described in greater detail below. Pressing the therapy start/stop

switch again after a therapy session has started will stop the RF energy generation. When pressed, the therapy Start/Stop switch generates an audible tone to inform the user that therapy is being initiated or terminated.

The two-therapy status indicators on the control panel indicate when therapy is underway and the amount of time (in minutes) remaining in the therapy session. When treatment is initiated, the message “CPI RUNNING” is displayed and green bars scroll from left to right across the indicator window. When the thirty-minute therapy session is concluded, the generation of RF energy is automatically terminated, the therapy status indicator windows go blank, and a brief audible beep is generated to alert the user that the treatment is finished. The user will then be instructed to turn off the power switch, remove the used Disposable Applicator Cover, and store the treatment applicator and cable until the next use.

In this study, the subject will treat both feet for 30 minutes, twice a day for the first 60 days (and up to 90 days) with active devices, and then continue to treat after randomization until Day 120. Response to treatment for randomization will be assessed at Days 61, 75, or 91.

2. Disposable Applicator Covers.

The PROVANT[®] Therapy System features Disposable Applicator Covers, which are placed over the treatment applicator (described below) before each therapy session. The Disposable Applicator Covers of the PEMF system are single-use-only and are intended to minimize contagion transmission and help protect the treatment applicator from biological contamination. Embedded in the Disposable Applicator Covers is RFID reader functionality that is controlled by software in the Provant control unit. This software prevents the reuse of a Disposable Applicator Cover by confirming that a new Disposable Applicator Cover is in place before allowing the generation and delivery of the therapeutic RF energy. If the user attempts to reuse a cover, the device recognizes the RFID tag on the cover at start up as “used” and will generate an audible alert to inform the user to replace the used cover with a new cover. If the user attempts to use the device without a Disposable Applicator Cover in place over the treatment applicator, the device will generate an audible alert to remind the user to place a new cover. In either scenario, the PEMF system will not initiate a therapy session until a new Disposable Applicator Cover is in place. The used Disposable Applicator Covers will be discarded as standard (not bio-hazard) waste.

3. Treatment Applicator

The PEMF system delivers pulsed RF energy to the desired treatment area via a spiral antenna in the treatment applicator. The treatment applicator contains a therapy emitter, an antenna matching circuit, and an RF therapy measuring circuit. The RF therapy measuring circuit automatically detects the level of RF signal that is radiated from the

treatment applicator and sends this information to the controller for the RF generator. This feedback circuit is used to regulate the RF therapy level, as the RF circuit reactance changes due to changes in body capacitance. In this way, the correct energy output is constantly monitored, regulated, and maintained at the preset therapy dose levels.

The PROVANT[®] Therapy System generates pulsed RF energy using a highly efficient Class-C RF amplifier. Subjects randomized to active treatment will receive treatment consisting of a pulse duration of 42 ± 4 microseconds, repeated every 1000 ± 25 microseconds, resulting in an output duty cycle of 4.2%, and requiring an average RF forward power level of <3 watts. The energy is transferred via cable and emitted by the radiator located on the treatment applicator circuit board for the preset 30-minute duration of therapy.

The amount of forward RF energy emitted from the treatment applicator is preset at 591 ± 44 V/m at a distance of 5.0 cm from the radiating surface of the treatment applicator. The amount of radiated RF energy diminishes with increasing distance from the radiating surface of the treatment applicator. Pulse rate, pulse width, and therapy session duration are regulated by the digital control component of the RF circuit board sub-assembly. If the RF therapy measuring circuit in the treatment applicator detects an absent or out of range therapy dosage level, treatment will not occur and the message “Service Required” will be displayed on the LED indicator window. In such an event, the research center will trouble shoot the issue as instructed in the Instruction Manual which accompanies the study device, and if unsuccessful in resolving the matter, will contact the sponsor to access a replacement device.

H. Logistics and Device Accountability

The study devices will be shipped via courier (FedEx) delivery or hand delivered when possible to the investigator or designee at regular intervals or as needed during the study. The investigator or delegated designee will ensure that all study devices are stored in a secured area, in accordance with applicable regulatory requirements.

Study device accountability will be overseen by the site study coordinator or other delegated staff member. These records should contain the dates, quantities of device received by the investigator, dispensed to specified subjects, or returned to sponsor. These inventories, along with shipment receipts must be made available for inspection by the sponsor or designees and all regulatory agency inspectors. At the conclusion of the study, photocopies of all study device accountability records must be provided by the site to the sponsor.

I. Labeling

The label on each study device kit will contain the protocol number and kit number. There will be sufficient space for study personnel to write the subject number, date dispensed, and the initials of the dispenser on the distribution label.

J. Preparation and Administration

Each subject will receive two devices to use during the study. Each treatment session with the study devices will be 30 minutes in duration. All treatment sessions will be self-administered by the subject or his/her family or caregiver in the home or similar setting.

The first treatment with the study devices will be administered on the morning of the day following the Enrollment Visit (Day 1) at 8am (\pm 2 hours). Subjects will assume a comfortable position and place their feet (both feet will be treated) on the treatment applicators of the PEMF devices, centering the applicators under the plantar surface (bottom of foot) of each foot as identified by the investigator. Treatment will be administered continuously for 30 minutes on both feet simultaneously. Thereafter, subjects will self-administer treatments twice daily, at 8am (\pm 2 hours) and 8pm (\pm 2 hours) up to Day 120 (Day 91 for non-responders).

Prior to initiation of each treatment session, the subject will take the treatment applicator of each study device and insert it into a new Disposable Applicator Cover. When inserted properly, the yellow starburst logo on the treatment applicator is aligned with the same logo on the Disposable Applicator Cover, and the words “This side towards patient” will be visible through the clear window of the Disposable Applicator Cover. When applied to the subject’s feet, the side of the treatment applicator with the yellow starburst logo is directed toward the bottom of the foot (plantar surface). Further directions for use for the PEMF system are found in the Instruction Manual. Upon completion of the treatment session, the subject will remove and discard the Disposable Applicator Covers, and store the PEMF devices until the time of the next scheduled treatment session. Disposable Applicator Covers may be discarded as standard waste.

K. Blinding

At the start of this study, all subjects will receive active devices. At Day 61, Day 75, or Day 91, if the subject becomes a responder based on a 1-point decrease in the average pain score using the Numeric Pain Rating Scale, the subject will be randomized 1:1 (active: sham). The sham devices will be PEMF devices that are de-activated such that no radiofrequency energy is generated or delivered when the device is started. All other functions, including the start sequence, display lights, audible start-beep and fan operation of the sham devices are identical to that of the active PEMF devices. Sham devices are indistinguishable from the active PEMF devices being used in the study. The subjects, research personnel at the investigative site, and sponsor will be fully blinded to the randomization assignment and unable to differentiate active and sham devices.

L. Study Assessments

All efficacy outcome measures will be assessed in order to allow for characterization of the response to PEMF therapy. All efficacy assessments will be conducted at the Enrollment Visit (Baseline; Day 0) and at the end of study visit (Day 121).

1. Primary Efficacy Assessments

Vibratory Perception Threshold (VPT): For large nerve fiber assessment. VPT is a non-invasive test used in quantifying sensation/sensitivity to vibration in evaluating sensory dysfunction associated with diabetic neuropathy. The hand-held vibratory stimulator will be placed against the midpoint of the plantar aspect and big toe of the right foot; the tester will initiate the automated test that will last between 5-10 minutes. Three tests will run at each location and the average of the 3 will be populated by the system. The VPT will be collected using the VSA-3000 Vibratory Sensory Analyzer at the midpoint on the plantar aspect and on the big toe of the right foot. VPT will be collected at the Enrollment Visit to obtain a baseline value and on Days 15, 30, 45, 61, 75, 91, 105 and 121.

Quantitative Sensory Testing (QST): For small nerve fiber assessment. QST is a noninvasive test used in peripheral nervous system disorders for thermal sensory testing. Contact thermal stimulator will be delivered using the NerveCheck Master through a contact thermode. A cold test of 15°C - 25°C and heat test of 40°C - 46°C will be administered. When activated the patient will notify the staff performing the test when they begin to feel the cold and warm test. The heat and cold thermal stimulation will be applied over the dorsal aspect of the right foot. QST will be performed at the Enrollment Visit to obtain a baseline value and on Days 15, 30, 45, 61, 75, 91, 105 and 121.

2. Secondary Efficacy Assessment

Nerve Conduction Velocity (NCV): For large myelinated nerve fiber assessments. Using the NC-stat[®] DPNCheck[®], the subject will assume a comfortable position so that their right leg is visible (that the subject's outer ankle bone and Achilles tendon are visible). The patient preparation pad is then used to thoroughly clean the subject's outer lower right leg and ankle bone area to remove any residue. The subject's right outer ankle bone is then identified to align the anode and cathode just behind with the cathode just adjacent to the middle of the ankle bone. The device is aligned on the calf pressing firmly down on the foam to ensure contact. The sural nerve conduction velocity and amplitude will be recorded at the Enrollment Visit and end of study visit (Day 121). An increase in velocity and a decrease in amplitude would be considered clinically meaningful.

Skin Perfusion Pressures: Vasamed Sensilase PAD-IQ measures pressure (in mm Hg) of microcirculation using a laser Doppler sensor. The patient lies down in a supine position and remains silent and still. The Laser Sensor Assembly (LSA) is inserted into the LSA Placement Guide and the optical sensor window is oriented toward the skin. For those subjects who will have biopsies performed, SPP will be obtained prior to the skin biopsies. A cuff is positioned so that the LSA is centered on the bladder both horizontally and vertically. The pressure of the cuff is then automatically increased to a pressure necessary to occlude blood flow and then released at a controlled rate and a measurement of the

pressure in the angiosome is made. SPP (mmHg) at reactive hyperemia is recorded. A second measure of SPP will be obtained on the plantar aspect of the right foot directly below the location where the SPP was performed on the dorsal aspect of the right foot. SPP will be conducted at the Enrollment Visit, Day 61, and end of study visit (Day 121). An increase in SPP would be considered clinically meaningful.

Pain Intensity (PI): a validated 11-point Numeric Pain Rating Scale (NPRS) with scores (0-10) collected as patient-reported outcomes on a paper diary, at Screening for eligibility, at the Enrollment Visit for a baseline value, and Days 61, 75 and 91 to assess response (1-point decrease from baseline in average pain score over the last 24 hours). On the diary, PI will be assessed after each morning (8am \pm 2 hours) treatment. Subjects will report their average pain score over the last 24 hours. Diaries will be distributed and collected from the subjects every 2 weeks to ensure compliance.

Brief Pain Inventory (BPI): is a 32-question long form questionnaire that assesses the severity of pain and its impact on specific daily functions. Cronbach's alpha reliability ranges from 0.77-0.91. The BPI long form will be administered at the Enrollment Visit, Day 30, 61, 91, and end of study visit (Day 121). The change from baseline will be captured and assessed.

Brief Fatigue Inventory (BFI): is a 4-question assessment that assesses the level of fatigue and the impact of the fatigue on daily function over the last 24 hours. A global fatigue score is collected by averaging all items on the BFI. Cronbach's alpha reliability ranges from 0.82-0.97. BFI is patient reported and collected at the Enrollment Visit, Days 30, 61, 91, and end of study visit (Day 121). The change from baseline will be captured and assessed.

Patient Global Impression of Change (PGIC): a 7-point validated categorical scale of overall change in status since initiation of treatment with the study device. PGIC allows subjects to integrate into one overall evaluation of the different aspects of their response to treatment, including pain reduction, improvement in functioning and side effects. PGIC will be collected every 7 days in the paper diary, immediately following the morning treatment. PGIC serves to anchor within-subject changes in pain over the course of treatment.

In a single question, subjects will be asked to describe their overall status compared to the start of the study ("Since the start of the study, my overall status is:"), and to score it as either very much worse, much worse, minimally worse, no change, minimally improved, much improved or very much improved (Appendix C). "Much Improved" and "Very Much Improved" are considered clinically meaningful results.¹ PGIC will be collected in the paper diary every 7 days immediately following the morning treatment during the 120-day treatment period. PGIC serves to anchor within-subject changes in pain over the course of treatment.

Hospital Anxiety and Depression Scale (HADS): is a patient reported assessment that detects states of depression and anxiety. The subscales within the assessment assess the severity of the emotional disorder connected to having diabetic peripheral neuropathy. Subjects will complete the assessment at the Enrollment Visit, Days 30, 61, 91, and end of study visit (Day 121).

NeuroQoL: is a validated measure that measures the effects of diabetic peripheral neuropathy and its complications on an individual's quality of life. The questionnaire will be completed by the subject at the Enrollment Visit and end of study visit (Day 121).

3. Exploratory Efficacy Assessment

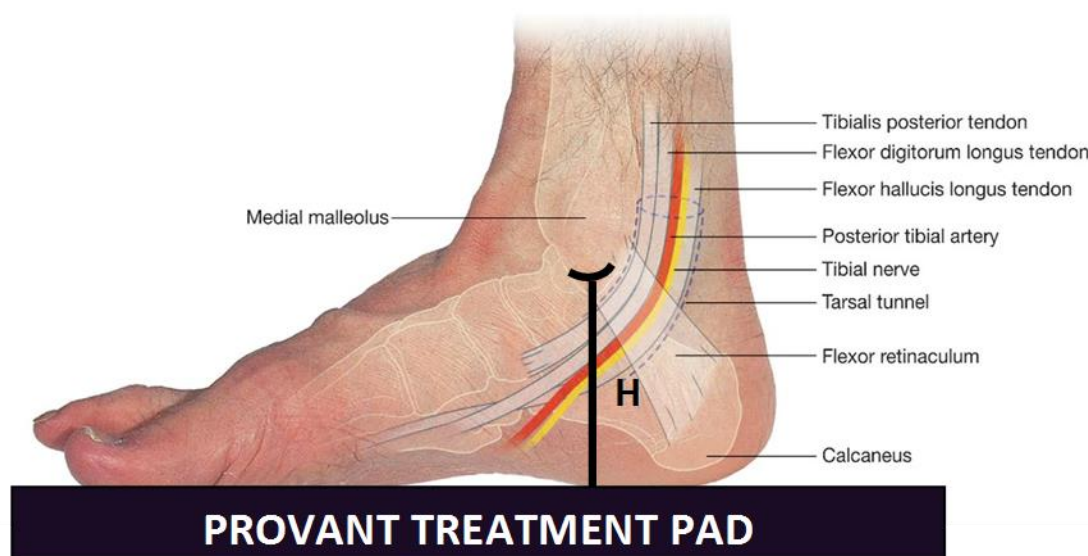
Biopsy: To assess c-fiber nerve density when treatment with Provant is administered. Biopsies will be taken from subjects that consent to them being taken. At least 2 subjects per pain phase category will be consented. One biopsy will be obtained at the distal leg, 10cm above the lateral malleolus on the right leg. A second biopsy will be obtained at the distal thigh, 10cm above the superior margin of the patella on the right leg. Both biopsies will be taken at the Enrollment Visit. The biopsies will be shipped overnight to the central lab. At the Day 121 Visit, a second set of biopsies will be obtained to the right of the baseline biopsies on the same subjects that consented at enrollment and shipped overnight to the central lab. At the end of the study, the biopsies will be compared to assess nerve fiber density.

4. Additional Study Assessments

Measurement of Ankle-Brachial Index (ABI): Subject is in a supine position, with the arms and legs at the same level as the heart for a minimum of 10 minutes before measurement to obtain the ABI measurement. ABI will be measured at the Screening Visit and the end of study visit (Day 121) on both legs. At Day 121, for those subjects who will have biopsies performed, ABI will be completed prior. The change from baseline will be captured and assessed.

Measurement of Foot Thickness: The depth of the foot (H) will be measured from the most inferior aspect of the medial malleolus to the plantar aspect of the foot when residing

on the treatment pad (see diagram below). The depth should not be more than 8cm for inclusion in the trial.



Hemoglobin A1c (HbA1c) Test: provides the average level of glucose in the blood over the past 2 to 3 months. For this test, the A1C Now[®] System will be used, subjects will have a finger stick to collect 5µL of blood to obtain the A1c value at the Screening Visit to obtain eligibility (and baseline). At the end of the study visit (Day 121) the A1c will be collected and compared to the baseline value. Each subject will have a A1C Now[®] System assigned to them. The change from baseline will be captured and assessed.

Blood Glucose: measures the amount of sugar in the blood at the time of collection. A TRUE METRIX[®] PRO Professional Monitoring Blood Glucose System will be assigned to each subject for the course of the study. Subjects will have a finger stick to collect 5µL of blood to measure their glucose value at the Enrollment Visit and on Days 30, 61, 91, and 121. The American Diabetes Association's goals for blood glucose control in patients with diabetes is 70 to 130 mg/dL before meals and less than 180mg/dL after meals.

Subject adherence: compliance with twice daily treatment with the study device will be assessed verbally during the Day 3 telephone call, at the interim visits and upon completion of the study. At each of the interim visits, subjects will be required to bring in their devices to ensure compliance by recording the usage meter reading on the side of the study device control panel.

Treatment Satisfaction: will be obtained at Days 15, 30, 45, 61, 75, 91, 105, and end of study visit to assess the patients level of satisfaction with the treatment. Once subjects are

randomized, they will also be asked which device (active or sham) they believe they were randomized to at Day 121 (blinding assessment).

5. Safety Assessments

Safety will be assessed through review of AE reports and concomitant treatments and medications. All concomitant drug or non-drug treatments used during the study will be recorded. Safety outcomes will be assessed at the interim visits and the Day 121 visit.

IV. STUDY PROCEDURES

The study procedures are summarized in the Schedule of Events (Appendix A) and described immediately following:

A. Visit 1 – Screening Visit (Day -14 to 0)

The Screening Visit will take place no more than 14 days prior to the Enrollment Visit. If a successfully screened subject falls out of the 14-day limit, the subject will require another screening to participate in the trial. The following procedures will be performed:

1. Informed consent review and signature
2. Review Inclusion and Exclusion criteria
3. Collect subject demography data (including age, weight, height, gender, race/ethnicity)
4. Collect Medical and Surgical History
5. Collect depth of the foot measurement from right foot
6. Conduct directed physical exam
7. Obtain Ankle-Brachial Index
8. Assess venous insufficiency
9. Measure HbA1c
10. Review and record all concomitant medications
11. Perform a urine pregnancy test for females of child bearing potential
12. Obtain patient completed Michigan Neuropathy Screening Instrument
13. Administer a urine drug screen
14. Assess Pain Phase (at least 10 subjects in each pain phase)
15. If the subject meets the eligibility criteria, continue to Enrollment Visit.

If the subject does not require any washout for prohibited medications or procedures, the Screening and the Enrollment Visits can be conducted concurrently.

All subjects will provide a urine sample for a urine drug screen. The test is intended to identify methamphetamine, cocaine and heroin for purposes of excluding subjects who are abusing illicit drugs, and hydrocodone, oxycodone and methadone for purposes of confirming the use of prescribed opioids. The urine drug screen test kit, Reveal 7 Panel Cup, from American Screening Corporation, will be provided by the sponsor to the investigative site for use at point-of-collection.

B. Visit 2 – Enrollment Visit (Day 0)

The following procedures will be performed:

1. Review Inclusion/Exclusion criteria (if visits not combined)
2. Review and record any changes in medical history and study eligibility criteria since screening (if visits not combined)
3. Collect Baseline Health Economics
4. Review and record adverse events (if visits not combined)
5. Review and record any changes in concomitant medications (if visits not combined)
6. Conduct VPT
7. Conduct Quantitative Sensory Testing (QST) of Heat and Cold
8. Conduct NCV
9. Collect subject's average pain score
10. Measure blood glucose
11. Collect BPI, BFI, HADS, NeuroQoL
12. Conduct SPP
13. Collect Biopsy of from consented subjects (at least 2 subjects per pain phase category)
14. If the subject continues to meet eligibility criteria, dispense active study devices
15. Introduce and train the subject on the use of the PROVANT[®] Therapy System, including instructions for proper positioning and operation of the devices.
16. Distribute the diary and instruct subject how to complete.

During this visit, eligible subjects will receive two active PEMF devices and 120 Disposable Applicator Covers per device (4 packs of 30) and the subject will be instructed to administer treatment on both feet twice daily at 8am and 8pm (\pm 2 hours) for 60 days.

C. Day 3 Phone Call (Day 3 +2 Days)

A telephone call follow-up will be performed and the following will be assessed:

1. Review and record adverse events
2. Review and record all concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion

D. Day 15 Interim Visit (Day 15 + 3 Days)

Subjects will return to the clinic on Day 15 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Collect diary and dispense a new diary for the next two weeks
4. Review and record adverse events
5. Review and record all concomitant medications
6. Assess adherence to PEMF treatment regimen by monitoring the usage meter
7. Assess treatment satisfaction

E. Day 30 Interim Visit (Day 30 + 3 Days)

Subjects will return to the clinic on Day 30 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Measure blood glucose
4. Collect BPI, BFI, HADS
5. Collect diary and dispense a new diary for the next two weeks
6. Review and record adverse events
7. Review and record all concomitant medications
8. Assess adherence to PEMF treatment regimen by monitoring the usage meter
9. Assess treatment satisfaction

F. Day 45 Interim Visit (Day 45 + 3 Days)

Subjects will return to the clinic on Day 45 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Collect diary and dispense a new diary for the next two weeks
4. Review and record adverse events
5. Review and record all concomitant medications
6. Assess adherence to PEMF treatment regimen by monitoring the usage meter
7. Assess treatment satisfaction

G. Day 61 Visit (Day 61 +3 Days)

Subjects will return to the clinic on Day 61 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Measure blood glucose
4. Conduct SPP
5. Collect BPI, BFI, HADS
6. Collect subject's average pain score
7. Collect diary and dispense a new diary for the next two weeks
8. Review and record adverse events
9. Review and record all concomitant medications
10. Assess adherence to PEMF treatment regimen by monitoring the usage meter
11. Assess treatment satisfaction
12. Assess response
 - If a subject is determined to be a responder (based upon a 1-point decrease in average pain score over the last 24 hours using the NPRS) return the active devices and randomize the subject per the schedule.
 - If the subject is determined to be a non-responder, instruct the subject to continue treating with the active devices and dispense additional DACs.

H. Day 75 Interim Visit (Day 75 + 3 Days)

Subjects will return to the clinic on Day 75 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Collect subject's average pain score (if non-responder at Day 61)
4. Collect diary and dispense a new diary for the next two weeks
5. Review and record adverse events
6. Review and record all concomitant medications
7. Assess adherence to PEMF treatment regimen by monitoring the usage meter
8. Assess treatment satisfaction
9. Assess response for non-responders at Day 61
 - If a subject is determined to be a responder (based upon a 1-point decrease in average pain score over the last 24 hours using the NPRS) return the active devices and randomize the subject per the schedule.
 - If the subject is determined to be a non-responder, instruct the subject to continue treating with the active devices and dispense additional DACs.

I. Day 91 Visit (Day 91 +3 Days)

Subjects will return to the clinic on Day 91 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Measure blood glucose
4. Collect BPI, BFI, HADS
5. Collect subject's average pain score (if non-responder at Day 61 or 75)
6. Collect diary
7. Review and record adverse events
8. Review and record all concomitant medications
9. Assess adherence to PEMF treatment regimen by monitoring the usage meter
10. Assess treatment satisfaction
11. Assess response for non-responders at Day 75

- If a subject is determined to be a responder (based upon a 1-point decrease in average pain score over the last 24 hours using the NPRS) return the active devices and randomize the subject per the schedule.
 - If the subject is determined to be a non-responder, complete the Day 121 end of study visit procedures and return the devices and unused DACs.
12. Dispense a new diary for the next two weeks to Responders only and additional DAC packs as needed.

J. Day 105 Interim Visit (Day 105 + 3 Days)

Subjects will return to the clinic on Day 105 with their devices. At this visit, the following procedures will be performed:

1. Conduct VPT
2. Conduct QST
3. Collect diary and dispense a new diary for the next two weeks
4. Review and record adverse events
5. Review and record all concomitant medications
6. Assess adherence to PEMF treatment regimen by monitoring the usage meter
7. Assess treatment satisfaction
8. Dispense additional DAC packs as needed.

K. Day 121 Visit (Day 121 + 3 Days)

Subjects will return to the clinic on Day 121 for the end of study visit. At this visit, the following procedures will be performed:

1. Collect subjects weight
2. Obtain Ankle-Brachial Index
3. Assess venous insufficiency
4. Conduct VPT
5. Conduct QST
6. Conduct NCV
7. Measure blood glucose
8. Measure HbA1c
9. Collect BPI, BFI, HADS, NeuroQoL

10. Conduct SPP
11. Collect diary
12. Conduct Blinding Assessment
13. Assess adherence to PEMF treatment regimen by monitoring the usage meter
14. Assess treatment satisfaction
15. Obtain skin biopsy from subjects that had a biopsy at baseline
16. Review and record adverse events
17. Review and record all concomitant medications
18. Return of study device and unused DACs

L. Treatment adherence/study compliance

Subject adherence (compliance with twice daily treatment with the study device) will be assessed during the interim visits by viewing the usage meter on each device, and upon completion of the treatment period at the Day 121 visit by the research staff reading and recording the number displayed on the study device usage meter. The usage meter will read 0.0 at Enrollment and upon randomization and will increase by 0.5 for each complete 30-minute treatment. A subject with complete adherence will be expected to have a usage meter reading based upon their response date.

Subjects will be instructed to return all unused DACs at the end of treatment visit. Each treatment session requires one new DAC, thus in the course of 120 days of treatment, the subject will utilize up to 240 DACs. If a subject is determined to be a non-responder at Day 91, they will utilize 180 DACs per PEMF device (360 total).

M. Protocol Adherence

Strict adherence to all specifications laid down in this protocol is required for all aspects of the study conduct. If protocol modifications are necessary, all alterations that are not solely of an administrative nature require a formal protocol amendment.

If an investigator has deviated from the protocol in order to eliminate an immediate hazard to subjects or for other inevitable medical reasons, the investigator shall document all such deviations, including the reasons thereof, and immediately submit the documentation to the sponsor and to the IRB if required.

N. Concomitant Medications

All concomitant drug and non-drug treatments as well as the frequency of administration and indication for the treatment will be recorded in the subject's chart. Additions to the subject's therapeutic regimen (agent, dose, frequency of administration) for treatment of diabetic peripheral neuropathy (other than the introduction of PEMF therapy) will not be

allowed through Day 121 of the study. Subjects will be allowed to continue administration of prn medications on an *ad lib* basis. Subjects may choose to reduce or discontinue opioid or other drug therapies during the treatment period of the study.

It is important to record the reason why each analgesic is being taken by the subject, specifically analgesics taken for treatment of pain associated with diabetic neuropathy. Analgesics taken for other reasons, e.g., headache, will be collected through recording of concomitant medications in the subject's chart.

1. Allowed Medications

Subjects will be allowed to continue their regimen of analgesic medications from the time of the Screening Visit through and including the Day 121 visit. In this context, "analgesic medications" refers to medications prescribed and administered for the treatment of pain, and includes but is not limited to anticonvulsants, opioids, nonsteroidal anti-inflammatory agents, anti-depressants and muscle relaxants. As such, this includes medications taken on an "as needed" (prn) basis as well as those medications taken on a regular schedule. Subjects may continue to take prn medications on an *ad lib* basis in response to their pain experience. Subjects who experience increased pain during the study will be instructed to increase the self-administration of their prescribed prn analgesic(s). Subjects may choose to reduce or discontinue prn opioid or other analgesic drug therapies during the treatment period of the study, and will be specifically instructed to do so by the investigator if their pain remits.

Medications prescribed for other indications are allowed and will be recorded as concomitant medications. Low dose aspirin (acetylsalicylic acid) 81 mg is allowed if taken for cardiac or vascular prophylaxis.

2. Prohibited Medications/Treatments

The following medications and therapeutics are prohibited throughout the study:

- Systemic steroids or topical steroids on the lower extremities
- Transcutaneous electrical neurostimulators (TENS units)
- Implanted neurostimulators
- Local injections
- Intrathecal infusion
- Acupuncture
- Surgery

V. WITHDRAWAL PROCEDURES

If a subject is withdrawn from study participation, the subject's enrollment in the study will terminate, study device application will be discontinued and no further data will be collected on the subject. Efforts will be made to perform all assessments scheduled for the Day 121 Visit prior to subject withdrawal.

A subject may be withdrawn from further study participation under the following circumstances:

- At the subject's request.
- Noncompliance with the protocol by the subject.
- Non-Responder at Day 91
- Adverse Event (decision to be removed from study made by either the investigator or subject). The investigator must notify the sponsor immediately if a subject is withdrawn because of an AE.
- Decision by the investigator or sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an AE.
- Request for withdrawal by the subject for reasons other than an intolerable AE.
- Lost to follow-up, as determined by failure to respond to at least 2 telephone calls followed by certified letter sent to the subject's last known address. All attempts to contact the subject must be documented in the subject's source documents.

VI. STATISTICAL CONSIDERATIONS

The statistical analysis of the study is described in detail in a separate version-controlled prospective Statistical Analysis Plan (SAP). However, the statistical methodology described in this section of the protocol will be the basis for the detailed SAP.

This bi-phasic design includes 2 sequential periods: the *Induction Phase* and *Randomized Withdraw Phase*. All safety analyses will be performed on the *Safety Analysis Set*, defined as all subjects who were enrolled into the study and issued study devices during the *Induction Phase* and followed through the *Randomization Withdraw Phase* or until they withdraw. Once a subject is determined to be eligible, the subject will be issued active treatment devices and the subject will be formally enrolled into the study and become part of the *Safety Analysis Set*. Where not otherwise specified, the last pre-treatment observation will be used as baseline for calculating post-treatment changes from baseline.

A. Induction Phase / Baseline Evaluations

Prior to study treatment, subjects will complete the baseline health economic questions, including the Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), Hospital Anxiety and Depression Scale (HADS), and the NeuroQoL. Vibration Perception Threshold (VPT), Quantitative Sensory Test (QST) and Nerve Conduction Velocity (NCV) will be completed. Skin Perfusion Pressure

(SPP) will be performed to obtain a baseline value of the plantar and dorsal aspect of the right foot. Once the subject is determined to be eligible, the subject will be issued active treatment devices and the subject will be formally enrolled into the study and become part of the *Safety Analysis Set*.

Subjects in the *Safety Analysis Set* will be instructed in the use of the devices for 60 days in the home environment. At Days 15 and 45, subjects will return to the clinic to have the VPT and QST conducted. Subjects will return to the clinic at days 30 and 61 for evaluation and complete questionnaires.

B. Randomized Withdraw Phase

Randomization of subjects can occur at different times, depending on when the subject is determined to be a responder. Once a subject is determined to be a responder (based upon a 1-point decrease in average pain score over the last 24 hours using the NPRS), the subject will return the active devices and be randomized 1:1 to receive active treatment or inactive sham devices and be instructed to treat through study day 120. If a subject is determined to not be a responder at Day 91, i.e., their final chance to be randomized, the subject will be terminated from the study at the end of the Day 91 visit.

C. Summarization of Results

The tabulations will be based on the paired results for the change from the baseline to study day 120 for patients who are randomized, and separately for the last observation. Supportive subject data listings will be sorted and presented by subject number, visit date and relative study day. Listings will also include the number of days relative to the initiation of treatment. Two sets of analyses will be generated; summary tabulations for all randomized subjects who complete the baseline and study day 120 evaluations (*Completers Analysis Set*), and all randomized subjects using the baseline and last recorded set of evaluations (*End of Study Evaluation Set*). This latter set should include all subjects who were randomized and complete at least one set of evaluations after randomization.

Specific algorithms will be described in the Statistical Analysis Plan for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data will be flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived / analysis datasets.

The total duration for a subject *on-study* will be calculated as the difference between the date of initial study treatment in the *Induction Phase* and the last day of observation plus 1 day. All calculations for defining the duration on-study will follow the algorithm $\text{DURATION} = [\text{STUDY COMPLETION OR WITHDRAW DATE} - \text{INITIAL TREATMENT DATE} + 1]$.

Summary statistics will consist of the count and percentage in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables. All mean and median values will be formatted to one more decimal place

than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. The number and percentage of responses will be presented in the form XX (XX.X%). Pairwise differences between the treatment groups will be calculated and 95% confidence intervals constructed.

While no formal hypothesis testing is planned, probability values may be generated to determine the magnitude of the difference between subject groups for an endpoint. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'. P-values <0.05 will be discussed as being statistically significant.

All summary tables will include the analysis population sample size (i.e., number of subjects). Study Day 1 is defined as the day the subject receives their initial exposure to the active study device. All *study days* are determined relative to the day of initial treatment with the study device. Baseline values will be defined as those values recorded closest to, but prior to, the first active study treatment during the initial phase of the study. Date variables will be formatted as DDMMYY for presentation. Where appropriate, only the measurements from the right foot will be used in the calculations.

D. Adverse Events

All summaries of adverse events will be based on treatment-emergent adverse events. Adverse events will be provided in a listing. The number and percentage of subjects experiencing adverse events will be summarized. Summaries by maximum severity and relationship to the study device (active or sham) will also be provided. Serious adverse events and adverse events leading to discontinuation from the study will be presented. Treatment-related adverse events will be defined as adverse events with investigator assessment of related or possibly related. In summaries of adverse events by severity and relationship to study device, patients reporting multiple episodes will be counted once under the worst severity and the strongest relationship, respectively. Serious adverse events will also be presented by relationship to treatment. The number of patients with at least one adverse event will be tabulated for each treatment group. The number of adverse events for each treatment group will also be tabulated.

E. Sample Size

This is a proof of concept study with no formal hypothesis testing planned and therefore there is no power associated with this study. The sample size of 40 patients is a sample of convenience for this study.

VII. INFORMED CONSENT

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or

to withdraw from it at any time for any reason. Appropriate IRB-approved forms for obtaining written informed consent will be provided by the investigator or by Regenesis Biomedical, Inc. or their designee.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects (including those already being treated) will be informed of the new information, given a copy of the revised form and be re-consented to continue in the study.

VIII. INSTITUTIONAL REVIEW BOARD

This protocol, the informed consent form and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the subject, will be submitted by the investigator or investigator's designee to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the date on which the IRB met and granted the approval.

IX. TERMINATION OF THE INVESTIGATION

As the study sponsor, Regenesis Biomedical, Inc. reserves the right to terminate the study at any time. Should early termination be necessary, Regenesis Biomedical, Inc. and the investigator will consult and make sure that adequate consideration is given to the protection of subjects' interests.

Additionally, all clinical investigational data will be reviewed by the sponsor on a regular basis. Reports of all data will be made available to the Institutional Review Boards and to the FDA as required. Unanticipated adverse device events will be evaluated and reported in accordance with 21 CFR Part 812 requirements and as required by the governing IRB.

The clinical investigation will be suspended if the investigator or the sponsor, upon review and evaluation of the clinical data, finds the severity or incidence of single or total adverse events unacceptable for continuation of the investigation.

X. ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

A. Adverse Events

An adverse event is defined as follows: Any untoward medical occurrence in a patient or clinical investigation patient administered a medical device treatment which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study device treatment, whether or not considered related to the study device.

All AEs occurring after signing of the consent form will be recorded. AEs arising subsequent to the time of initiation of first treatment with study device will be considered treatment emergent AEs.

At each contact with the subject, the investigator or designee must seek information on AEs by non-leading specific questioning and, as appropriate, by examination. All observed or volunteered AEs, regardless of suspected causal relationship to study device, must be recorded in the patient's chart.

Any events involving illnesses or injuries with onset during the study or any events involving exacerbations of pre-existing illnesses should be recorded. All clearly related signs and symptoms should be grouped together and recorded as a single diagnosis in the patient's chart. A pre-existing condition must not be reported as an AE unless the condition worsens during the trial.

Each AE will be independently judged by the investigator in terms of causality. The following definitions will be used for these causality assessments.

- | | |
|--------------------------|--|
| Related: | This causal relationship is assigned when the AE: <ul style="list-style-type: none"> • starts a reasonable time after study device administration, • cannot be reasonably explained by the subject's clinical state. |
| Possibly Related: | This causal relationship is assigned when the AE: <ul style="list-style-type: none"> • starts a reasonable time after study device administration, but • could have been produced by the subject's clinical state or other modes of therapy administered to the subject. |
| Unrelated: | This causal relationship is assigned when the AE: <ul style="list-style-type: none"> • is definitely not associated with the study device administered and is readily explained by other events or diagnoses. |

Each AE will also be independently judged by the investigator in terms of severity. The following definitions will be used for these severity assessments.

- | | |
|------------------|--|
| Mild: | The event is transient (<48 hours) or causes mild discomfort; no medical intervention/therapy is required |
| Moderate: | The event results in mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy is required |
| Severe: | The event results in marked limitation in activity, assistance is usually required; medical intervention/therapy is required and hospitalization is possible |

Each AE will also be independently judged by the investigator in terms of seriousness. A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death, or
- Is life-threatening,

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in permanent impairment of a body function or permanent damage to a body structure,
- Is a congenital anomaly/birth defect,
- Necessitates medical or surgical intervention to preclude any one of the outcomes listed in this definition.

All SAEs must be reported *immediately* (within 24 hours of knowledge of the event) by telephone and fax to the following:

Sponsor Medical Contact – Adrienne P.S. (Patti) Smith, MD; Regenesys Biomedical Inc.

Mobile: (480) 848-8671; Fax: (480) 718-8702; patti.smith@regenesysbio.com

The investigator will follow up with a written description of the SAE submitted to the sponsor within 3 days, including the results of the SAE investigation and any treatment(s) provided.

All adverse events will be followed until resolution or until the investigator assesses the subject’s status has returned to normal.

B. Anticipated Adverse Device Effects Associated with Provant Therapy System

Anticipated adverse events associated with PROVANT[®] Therapy System ² and the procedures and medicines used in the study are as follows:

- Device fails to operate
- Warmth or burning at treatment site
- Skin reaction at treatment site (tingling, pins-and-needles, rash, blisters, swelling, dry skin, redness, numbness)
- Increased bleeding at surgical site
- Chilliness
- Headache
- Malaise
- Nausea
- Abdominal or chest wall discomfort
- Muscle cramps
- Excessive menstruation
- Failure to reduce pain or an increase in pain

² Reported at least once since market launch in 2004.

C. Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect means 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 protocol or informed consent form, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects. The protocol will contain all of the anticipated Adverse Events that could be associated with the study.

All UADEs must be reported *immediately* (within 24 hours of knowledge of the event) by telephone and fax to the following:

Sponsor Medical Contact – Adrienne P.S. (Patti) Smith, MD; Regenesis Biomedical Inc.;
Mobile: (480) 848-8671; Fax: (480) 718-8702; patti.smith@regenesisbio.com

The investigator will follow up with a written description of the UADE submitted to the sponsor within 3 days, including the results of the UADE investigation and any treatment(s) provided.

Any UADE occurring up to the date of the final Follow-up Visit will be followed until it resolves, the investigator assesses the subject's status to have returned to baseline, or until the investigator feels that the event is stable and chronic.

The investigator shall submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible in accordance with the IRB submission guidelines, but in no event later than 10 working days after the investigator first learns of the effect.

XI. INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) Subject clinical source documents. The Investigator's Study File will contain the protocol/amendments, data collection forms, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, device records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence. All records defined in 21 CFR 312.140 will be kept on file.

Subject clinical source documents include subject hospital/clinic records, physician's and nurse's notes, appointment book, original lab reports, special assessment reports, signed informed consent forms, subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least 2 years after the latest of the following: completion, discontinuation of the study, or the regulatory submission for which the study is being performed is no longer under review. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, Regenesis Biomedical, Inc. must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Regenesis Biomedical, Inc. to store these in a sealed container(s) off-site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

A. Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when data requires clarification. In case of special problems/and or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

All forms should be typed or filled out using indelible ink, and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate.

B. Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Regenesis Biomedical, Inc. Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the data must be by direct inspection of source documents and patient charts.

XII. MONITORING THE STUDY

It is understood that the responsible Regenesis Biomedical, Inc. monitor (or designee) will contact and visit the investigator regularly and will be allowed, upon request, to inspect the various records of the trial (source documents and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the patient charts at regular intervals throughout the study to verify the adherence to the protocol and the completeness, consistency and accuracy of the data. The monitor should have access to laboratory test reports and other subject records needed. The investigator (or his/her designee) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

XIII. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a

subject enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Regenesis Biomedical, Inc., e.g., subjects' written consent forms, in strict confidence.

XIV. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Regenesis Biomedical, Inc. at least 30 days prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Regenesis Biomedical, Inc. will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement. Any formal publication of the study in which input of Regenesis Biomedical, Inc. personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Regenesis Biomedical, Inc. personnel. Authorship will be determined by mutual agreement.

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APPENDIX A - TIME AND EVENTS SCHEDULE

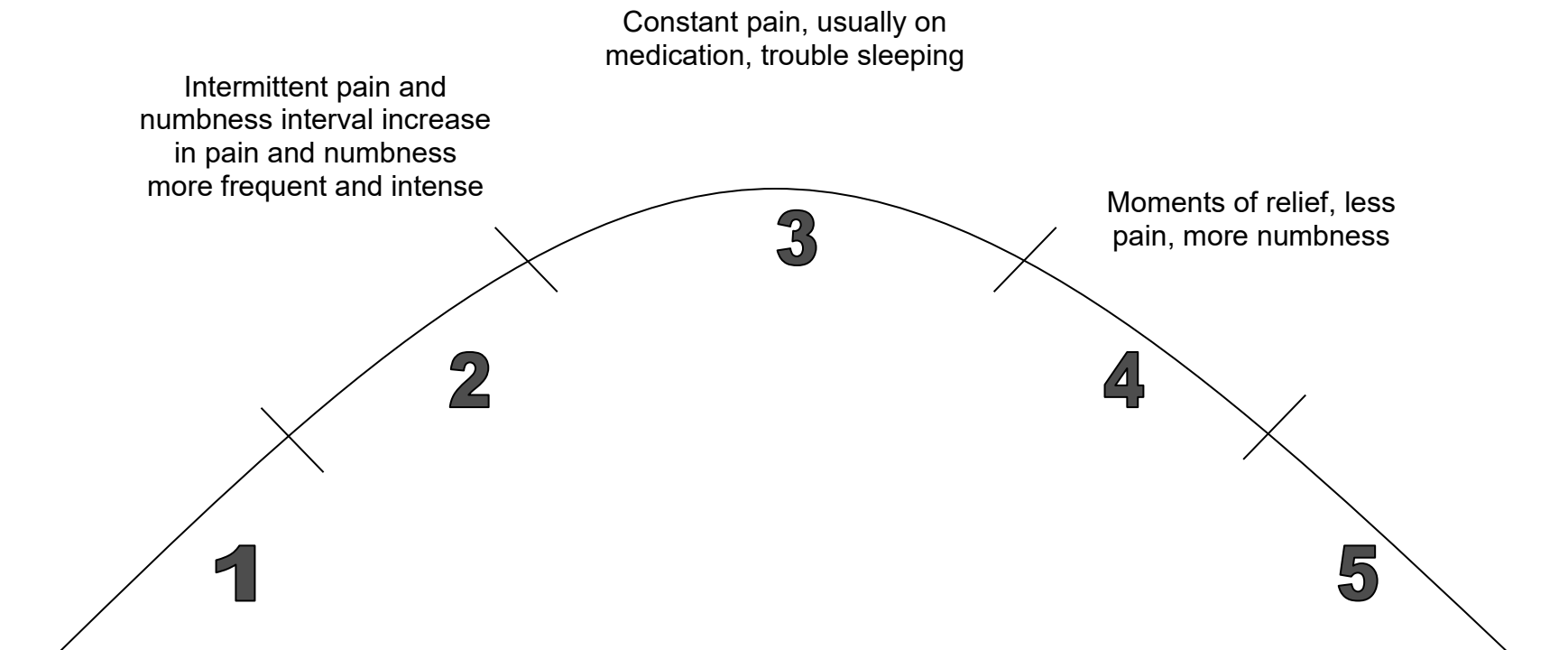
Period	Screening Visit	Enrollment (Baseline) Visit	Day 3 Phone Call	Day 15 Visit	Day 30 Visit	Day 45 Visit	Day 61 Visit	Day 75 Visit	Day 91 Visit	Day 105 Visit	Day 121 Visit
Study Day	-14 - 0	0	3 (+2)	15 (+3)	30 (+3)	45 (+3)	61 (+3)	75 (+3)	91 (+3)	105 (+3)	121 (+3)
Informed Consent	X										
Demographic Information	X										
Medical/Surgical History/Physical Exam	X										
Inclusion/Exclusion Criteria	X	X ¹									
Baseline Health Economics		X									
Pain Score Assessment (NPRS)	X	X					X	X ¹⁴	X ⁴		
Michigan Neuropathy Screening Instrument	X										
Pain Phase Assessment	X										
Urine Drug Screen	X										
Urine Pregnancy Test	X ²										
Height and Weight	X										X ⁷
Measurement of Foot Thickness	X										
Obtain Ankle-Brachial Index (ABI) & Assess Venous Insufficiency	X										X ³
Vibration Perception Threshold (VPT)		X		X	X	X	X	X	X	X	X
Quantitative Sensory Test (QST)		X		X	X	X	X	X	X	X	X
Sural Nerve Conduction Velocity (NCV)		X									X
Measure Blood Glucose		X			X		X		X		X
Measure HbA1c	X										X
Brief Pain Inventory (BPI)		X			X		X		X		X
Skin Perfusion Pressure (SPP)		X					X				X
Brief Fatigue Inventory (BFI)		X			X		X		X		X
Hospital Anxiety and Depression Scale (HADS)		X			X		X		X		X
NeuroQoL		X									X
Dispense Active Study Device		X									
Study Device Training		X									
Randomize and Dispense Study Device							X ⁵	X ⁹	X ¹⁰		
Distribute Diary (NPRS, PGIC) ⁶		X		X	X	X	X	X	X ¹¹	X	
Collect Diary				X	X	X	X	X	X	X	X
Study Device Blinding Assessment											X
Response Assessment							X ⁵	X ¹⁴	X ⁴		
Assess Adverse Events	X ⁸	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Assess Subject Adherence to Treatment			X	X	X	X	X	X	X	X	X
Treatment Satisfaction				X	X	X	X	X	X	X	X
Return Study Device and Unused DACs									X ¹³		X
3mm Skin Punch Biopsy at distal leg and distal thigh		X ¹²									X ¹²

1. The Screening Visit and the Enrollment Visit may occur on the same day in which I/E criteria will not need to be reviewed.

2. Urine pregnancy test will be performed on women of child-bearing potential.
3. ABI and Venous Insufficiency will be obtained at Day 121 for those subjects who were responders completing treatment through Day 120.
4. Only subjects determined to be non-responders at Day 75 will be assessed. Subjects determined to be non-responders at Day 91 will be terminated from the study.
5. Non-responders at Day 61 will continue treating with the Active device. Response will again be assessed at Day 75.
6. Numeric pain scores along with weekly PGIC will be recorded by the subject on the diary each day immediately after the morning treatment.
7. Collect only weight at end of study visit.
8. Assessment of adverse events will be conducted after the signing of the Informed Consent.
9. Subjects determined to be responders at Day 75 will be randomized to active or sham and continue treating through Day 120.
10. Subjects determined to be responders at Day 91 will be randomized to active or sham and continue treating through Day 120.
11. A new diary is dispensed only to subjects who are responders.
12. A 3mm skin punch biopsy will be obtained from at least 2 subjects in each pain phase category at the Enrollment Visit and at Day 121.
13. Only subjects determined to be non-responders will return their study devices and unused DACs at Day 91.
14. Only subjects determined to be non-responders at Day 61 will be assessed. Non-responders at Day 75 will continue treating with the Active device. Response will again be assessed at Day 91.

APPENDIX B - PAIN PHASE ASSESSMENT SCALE

Phasing of Neuropathy



APPENDIX C – SUBJECT DIARY FOR DAILY PAIN SCORE AND WEEKLY GLOBAL IMPRESSION OF CHANGE

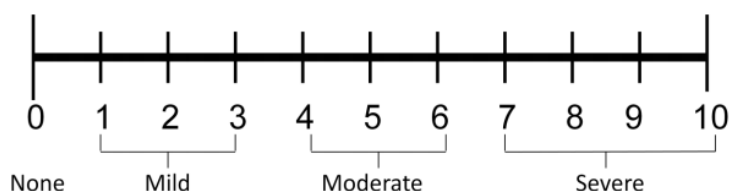
PATIENT: _____

Week Start Date: _____

Treat Both Feet, Simultaneously, Twice Daily for 30 minutes, 8am +/- 2 hours and 8pm +/- 2hours.

Circle the Pain Score which represents your average Pain over the last 24 hours after completing your Morning (am) treatment.

On the scale below, a score of 0 represents No Pain whereas a score of 10 represents the Worst Possible Pain. Every 7 days, mark your overall status compared to the start of the study.



	No Pain										Worst Possible Pain
Date: _____	0	1	2	3	4	5	6	7	8	9	10
Date: _____	0	1	2	3	4	5	6	7	8	9	10
Date: _____	0	1	2	3	4	5	6	7	8	9	10
Date: _____	0	1	2	3	4	5	6	7	8	9	10
Date: _____	0	1	2	3	4	5	6	7	8	9	10
Date: _____	0	1	2	3	4	5	6	7	8	9	10

Since the start of the study, my overall status is:
(check one box only)

- ☐ Very Much Worse
 ☐ Much Worse
 ☐ Minimally Worse
 ☐ No Change
☐ Minimally Improved
 ☐ Much Improved
 ☐ Very Much Improved

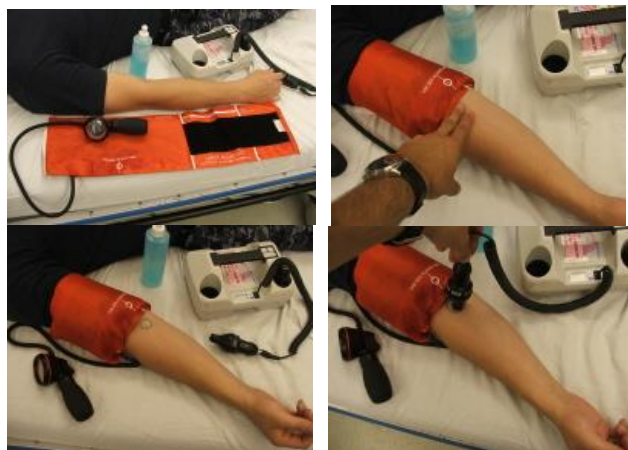
APPENDIX D – INSTRUCTIONS FOR OBTAINING ANKLE-BRACHIAL INDEX

Measurement of Ankle-Brachial Index

1. Place the patient in the supine position, with the arms and legs at the same level as the heart, for a minimum of 10 minutes before measurement.
2. Select an appropriately sized blood pressure cuff for both the ankle and the arms (see the images below); the cuff width should be, at a minimum, 20% greater than the diameter of the extremity.
 - a. For the brachial systolic pressure, make sure you have appropriately sized upper-extremity cuff.
 - b. For the ankle systolic pressures, make sure that cuff completely encircles lower extremity. The ankle cuff should go on the leg between the malleolus and the calf. Enough room should be left below both cuffs to permit placement of the ultrasound gel, so that the Doppler device can adequately detect the brachial, dorsalis pedis (DP), and posterior tibial pulses (PT).
3. Obtain the brachial systolic pressures of both arms (see the images below), and choose the higher of the 2 values as the brachial systolic pressure (the difference between them should be less than 10 mm Hg). The brachial pulse is best appreciated on the medial side of the antecubital fossa.
4. Obtain the anterior tibial and posterior tibial systolic pressures of the extremity in question (see the images below), and select the higher of the 2 values as the ankle pressure measurement. The posterior tibial pulse is best appreciated just dorsal and inferior to the medial malleolus. The dorsalis pedis pulse is best appreciated on the dorsum of the foot between the proximal section of the first and second metatarsals, usually above the navicular bone. Palpate artery. Dorsalis pedis is palpated by hand before Doppler device is used. Place small amount of ultrasound transmission gel at landmark where the artery was located. Locate artery with Doppler device. Posterior tibial artery is located and marked with gel. Identify artery with Doppler device. Upon application of Doppler probe, arterial pulsations should be audible. If they are not, reposition probe until appropriate sound is obtained.
5. Do not obscure artery with cuff; you will need to be able to palpate artery and/or locate it with Doppler device. As with each appropriately identified arterial site, mark site with ultrasound transmission gel after palpation. Locate artery with device. Typically, Doppler probe must be positioned at 45-60 degrees, not at 90 degrees as shown.
6. Finally, divide the ankle pressure by the brachial artery pressure; the result is the ABI.

Obtained from: <http://emedicine.medscape.com/article/1839449-overview#aw2aab6b4>

Brachial Systolic Pressure



Anterior Tibial and Posterior Tibial Systolic Pressures



APPENDIX E – GRADING SYSTEM FOR VENOUS INSUFFICIENCY

VENOUS INSUFFICIENCY CLASSIFICATION SYSTEM (CEAP)

For the initial assessment of a patient with venous insufficiency, the clinical severity is established by observation (without any specialized testing). The classification system increases in severity from C0-C6 as noted below.

Patients with C3-6 disease demonstrate an increasing severity of chronic venous insufficiency with chronic irreversible functional abnormality of the venous system. Patients with foot edema that typically resolves overnight is generally classified as a C2 (as long as they do not also meet criterion for C5 or C6). Patients with persistent ankle edema, gaiter lipodermatosclerosis, and history of a healed ulcer or current open ulcer will be excluded from the trial as a consequence of their increased risk of developing a chronic non-healing venous ulcer after biopsy.

Grade	Description
C 0	No evidence of venous disease.
C 1	Superficial spider veins (reticular veins) only
C 2	Simple varicose veins only
C 3	Ankle edema of venous origin (not foot edema)
C 4	Skin pigmentation in the gaiter area (lipodermatosclerosis)
C 5	A healed venous ulcer
C 6	An open venous ulcer