CLINICAL STUDY PROTOCOL

Study Title:	**A Multi-Center, Double-Blind, Sham-Controlled, Randomized Trial of Dual Field PEMF Therapy [Provant® Therapy System] in Lower Extremity Painful Diabetic Distal Symmetric Peripheral Neuropathy (DSPN) (The RELIEF Trial)**
Protocol Number:	RBI.2017.002
Version:	C
Phase:	III
Principal Investigator:	Leslie J. Klaff, M.D., Ph.D., FRCP (Edin), FACE
Sponsor:	Regenesis Biomedical, Inc. 5301 N. Pima Road, Suite 150 Scottsdale, AZ 85250
Final Protocol:	July 17, 2018

PROTOCOL SIGNATURE PAGE – SPONSOR

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The undersigned acknowledges that he/she has received and read Protocol RBI.2017.002, Version C, dated 17JUL2018.

Sponsor Representatives	Signature	Date
Scott Brooks Chief Executive Officer		
Jamie Muhlenfeld Director of Clinical Research		

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

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Investigator Name (printed)	Signature	Date

DOCUMENT REVISION HISTORY		
	Date	Summary of changes
Version A	06FEB2018	Original document
Version B	02APR2018	Clarification on Exclusion Criteria #15. Removing screening -14 days and replacing with -15 days window. Clarification to Exclusion #13 to add "chronic" use of systemic corticosteroids. Removal of "Simultaneous bilateral testing can be done" from SPP and ABI sections. Clarification of Screening Visit Window. Change to foot measurement process to allow measuring from floor. Addition of Venous Insufficiency Classification Scale.
Version C	17JUL2018	Two-month open label extension period updated to an 8-month open label extension period. Additional phone calls and clinic visits added to visit schedule.

Study Synopsis

Study Title	**A Multi-Center, Double-Blind, Sham-Controlled, Randomized Trial of Dual Field PEMF Therapy [Provant® Therapy System] in Lower Extremity Painful Diabetic Distal Symmetric Peripheral Neuropathy (DSPN) (The RELIEF Trial)**
Protocol Number	RBI.2017.002
Name of Study Device	PROVANT® Therapy System
Phase of Development	III
Objective	To demonstrate the analgesic efficacy of PEMF treatment compared to sham treatment in patients with painful diabetic distal symmetric peripheral neuropathy (DSPN) when treatment is administered 30 minutes twice daily through a 120-day period (4 months) (Part A). An 8-month open-label active treatment extension period is included to collect longer-term data on pain, medication use, quality of life and safety (Part B).
Study Design	Part A of this trial is a multi-center, prospective, double-blinded, sham-controlled, randomized clinical trial conducted on subjects with painful diabetic distal symmetric peripheral neuropathy. Part B of this trial is an 8-month single-arm, open-label, active treatment extension period upon completion of Part A. Eligible subjects will include those between 22 and 80 years of age with documented Type 1 or Type 2 diabetes having persistent pain related to diabetic neuropathy in the lower extremities, despite previous treatment(s). Subjects will be assessed with the Toronto Clinical Neuropathy Score at screening, to evaluate the severity of peripheral neuropathy for inclusion. Eligible subjects will be entered into a 14-day ePRO diary run-in period to collect average baseline pain scores related to their diabetic neuropathy in the lower extremities, diary compliance, and analgesic consumption (maintenance and prn prescribed peripheral neuropathic pain medication pill counts). Subjects will collect electronic patient-reported outcome (ePRO) data each morning around the same time during the run-in period. Only those subjects having a mean pain intensity in the lower extremities of ≥4 and <9 on an 11-point numeric pain rating scale (NPRS) and a diary compliance score of ≥ 70% during the 14-day run-in period will be eligible. Subjects will return to the clinic at Baseline (Day 0) for review of eligibility, diary compliance, average baseline diabetic

	neuropathic pain score of ≥4 and <9 (calculated as the average of the last 7 days preceding the enrollment visit), and review of stable analgesic pain consumption profile during the 14-day run-in period. Qualified subjects based on diary compliance and average pain score will be randomized 1:1 (active: sham) and will be instructed to self-treat twice daily (morning and evening; 8am ± 2 hours and 8pm ± 2 hours) for 120 days. Subjects will record electronic patient-reported outcome (ePRO) data following each morning treatment for 120 days. Subjects consenting to distal thigh and distal leg skin biopsies during the Screening visit will have biopsies collected and sent to the central laboratory for assessment. All subjects will have a baseline Skin Perfusion Pressure (SPP), Sural Nerve Conduction Studies (NCS), Quantitative Sensory Testing (QST), and will complete the Work Productivity and Activity Impairment Questionnaire (WPAIQ), and NeuroQoL. Subjects will receive a telephone call at Day 7 to ensure compliance to treatment and diary completion, provide follow-up information on the biopsy sites (if applicable), complete a blinding assessment as well as be assessed for safety and concomitant medication changes. At **Month 1** subjects will return to the clinic for evaluation of safety, concomitant medication changes, review device usage (reports will be supplied to the site) and ePRO diary completion, and Patient Global Impression (PGI). Treatment satisfaction will also be assessed. At **Month 2** subjects will return to the clinic for evaluation of safety, concomitant medication changes, treatment satisfaction, review of device usage (reports will be supplied to the site) and ePRO diary completion, quality of life outcomes (WPAIQ and NeuroQoL), Patient Global Impression (PGI), and interim visit measurements of SPP. At **Month 3**, subjects will return to the clinic for evaluation of safety, concomitant medication changes, review device usage (reports will be supplied to the site) and ePRO diary completion, and Patient Global Impression (PGI). Treatment satisfaction will also be assessed. At **Month 4** (end of Part A / start of Part B), subjects will return to the clinic for evaluation of safety, treatment satisfaction, review of device usage (reports will be supplied to the site), HbA1c, concomitant medication changes, weight, quality of life

	outcomes (WPAIQ and NeuroQoL), PGI, final measurements of SPP, NCS, QST and be assessed to determine their Toronto Clinical Neuropathy Score. Those subjects who consented and had biopsies collected at the Enrollment visit, will have their 4-month study biopsies during this visit and samples sent directly to the central laboratory for assessment. Subjects will return the study device and complete a blinding assessment. Subjects that complete Part A will continue into the open-label extension period (Part B). All subjects will be reconsented if not completed at a prior visit and given an open-label active device. Subjects will record ePRO data for one week prior to the Month 6, 8, 10, and 12 visits following each morning treatment. Subjects will be reminded of the150-day (Month 5) phone call. At **Month 5**, subjects will receive a telephone call to ensure compliance to treatment, and to be assessed for safety and concomitant medication changes. Subjects will be reminded to record ePRO data for one week prior to the 180-day (Month 6) phone call. At **Month 6**, subjects will receive a telephone call to ensure treatment compliance and collection of diary data, and to assess safety and concomitant medication changes. Subjects will be reminded of the 210-day (Month 7) phone call. At **Month 7**, subjects will receive a telephone call to ensure treatment compliance, and to assess safety and concomitant medication changes. Subjects will be reminded to record ePRO data for one week prior to the 240-day (Month 8) visit. At **Month 8**, subjects will return to the clinic for evaluation of safety, measure QST, treatment satisfaction, review of device usage (reports will be supplied to the site) and collection of diary data, concomitant medication changes, quality of life outcomes (NeuroQoL), and PGI. Subjects will be reminded of the 270-day (Month 9) phone call. At **Month 9**, subjects will receive a telephone call to ensure treatment compliance, and to assess safety and concomitant medication changes. Subjects will be reminded to record ePRO data for one week prior to the 300-day (Month 10) phone call.

	At **Month 10**, subjects will receive a telephone call to ensure treatment compliance and collection of diary data, and to assess safety and concomitant medication changes. Subjects will be reminded to record ePRO data for one week prior to the 330-day (Month 11) phone call. At **Month 11**, subjects will receive a telephone call to ensure treatment compliance, and to assess safety and concomitant medication changes. Subjects will be reminded to record ePRO data for one week prior to the 361-day (Month 12) end of study visit. At **Month 12** (end of open-label treatment extension), subjects will return to the clinic for evaluation of safety, weight, QST, NCS, TCNSS, PGI, treatment satisfaction, review of device usage (reports will be supplied to the site) and collection of diary data, concomitant medication changes, quality of life outcomes (NeuroQoL), and will return the study device. Subjects who consented and had biopsies collected at the 4 Month visit, will have their end of study biopsies performed during this visit. Biopsy samples will be sent directly to the central laboratory for assessment.
Sample Size	The anticipated enrollment in this study is 170 subjects. The estimate of 85 patients per arm is based on results from a previous trial of PEMF therapy in this patient population.
Study Locations	Up to 20 sites in the United States
Indication	Adjunctive treatment of diabetic neuropathic pain and discomfort.
Visit Schedule	This study includes a total of 8 clinic visits and 7 telephone calls. The visit schedule is as follows: • Screening Visit (Day -15) • Enrollment Visit (Day 0) • Day 7 phone call (+2 days) • Month 1 (± 3 days) • Month 2 (± 3 days) • Month 3 (± 3 days) • Month 4 (± 3 days) (end of Part A / start of Part B) • Month 5 phone call (± 3 days)

	• Month 6 phone call (± 3 days) • Month 7 phone call (± 3 days) • Month 8 Visit (± 3 days) • Month 9 phone call (± 3 days) • Month 10 phone call (± 3 days) • Month 11 phone call (± 3 days) • Month 12 Visit (end of Part B) (± 3 days)
Treatment Arms	**Part A - 1:1 Randomization (PEMF 42 µs : Sham)** **Part B – open-label PEMF 42 µs treatment**
Efficacy Endpoints	**Primary Endpoint:** • Absolute change from baseline in pain intensity as measured by the 11-point, numerical pain rating scale (NPRS) (0-10; where 0=no pain, to 10=worst possible pain) through 4 months. **Secondary Endpoints:** • Percentage of patients who have either a 2 point or 30% reduction in NPRS at 4 Months. • Time to 30% or 2-point reduction in NPRS, whichever comes first at 4 Months. • Change in neuropathy related quality of life (NeuroQoL) between baseline and end of treatment at 4 Months. • Changes in Skin Perfusion Pressure from baseline to end of treatment at 4 Months. • Changes in Nerve Conduction Studies of Velocity and/or Amplitude between baseline and end of treatment at 4 Months. • Changes in Quantitative Sensory Testing between baseline and end of treatment at 4 Months. • Change in Patient Global Impression at 4 Months. **Exploratory Endpoints:** • Changes in WPAIQ • Changes in intraepidermal nerve fiber density (IENFD) at the distal thigh. • Changes in IENFD at the distal leg. • Evaluation of the NPRS, NCS and NeuroQoL during Part B will be considered exploratory
Safety Endpoints	• Adverse events, serious adverse events • Unanticipated adverse device effects

Study Device	The study device is the PROVANT® Therapy System. The active device will deliver dual field pulsed electromagnetic field energy in the radiofrequency range. 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.
Inclusion/Exclusion	**Inclusion Criteria** 1. Subject has documented Type 1 or Type 2 diabetes mellitus according to the ADA criteria (Appendix B).[33] 2. Subject has daily pain attributed to symmetrical lower extremity diabetic peripheral neuropathy for at least 6 months prior to screening, as confirmed by score of ≥ 6 on the Toronto Clinical Neuropathy Scoring System. 3. Subjects' average lower extremity pain related to diabetic peripheral neuropathy over the preceding 24 hours is ≥4 and <9 based on the 11-point NPRS (0-10) at the Screening Visit. 4. Subject age is greater than or equal to 22 years and less than 80 years of age. 5. Subject is on stable diabetes treatment which should include medication and/or diet and exercise for at least 3 months prior to Screening. 6. Subject has an HbA1c ≤10% at Screening or within 3 months of Screening. 7. Subject has not changed their analgesic prescriptions in the preceding one month. 8. Subject has an ankle-brachial index (ABI) of ≥0.8 to ≤1.3. If the subject has incompressible vessels, a toe brachial index of 0.8 to 1.3 is required. These adequate lower extremity studies are with no documented intermittent claudication. 9. Subject walks independently with or without assistive devices, and does not require a wheel chair.

	10. Subject is willing and able to give written informed consent and to comply with all parts of the study protocol. 11. Female subjects must be post-menopausal, surgically sterile, abstinent, or, if of child-bearing potential, practicing (or agreeing 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. 12. Subject can access an internet browser in the home environment or through a smart phone. **Enrollment Visit Inclusion Criteria** 1. Average diabetic peripheral neuropathic pain intensity (NPRS score) is ≥ 4 and < 9 calculated as the mean of the daily NPRS scores for neuropathic pain in the lower extremities over the 7 days preceding the visit. 2. Subject has completed a minimum of 70% of the ePRO assessments during the run-in period. **Exclusion Criteria** 1. Subject has an active, open ulcer on either lower extremity. 2. Subject has significant peripheral vascular disease defined as absence of more than one-foot pulse per foot and/or ABI <0.7 and >1.3 and/or history of angioplasty, peripheral bypass surgery, or claudication within 6 months of the Screening Visit. 3. Subject has venous insufficiency with an active ulcer as classified by the Venous Insufficiency Classification System of grade C6. 4. Subject has a history of previous solid organ transplant or severe renal disease (i.e. estimated creatinine clearance ≤30 mL/min). 5. Subject has been diagnosed with a non-diabetic cause of chronic neuropathy (e.g. end stage renal disease, infectious etiology, chemotherapy, drug etiology, alcohol abuse, ingestion of toxic substance, nerve decompression

	surgery (related to lower extremity symptoms), or connective tissue disease) within the past 10 years. 6. Subject has previous or current history of primary or tertiary hyperparathyroidism, hypercalcemia, psychiatric disorder, alcohol dependency, Hepatitis B or C, or HIV infection. 7. According to the judgement of the Investigator, subject has clinically significant cardiovascular disease within 6 months prior to screening (unstable or poorly controlled hypertension, transient ischemic attack, myocardial infarction, unstable angina, arrhythmia, cardiac surgery, stent placement or angioplasty, or congestive heart failure). 8. Subject has a history of any uncontrolled medical illness that, in the investigators judgment, places the subject at unacceptable risk for enrollment in a research trial with pulsed electromagnetic field therapy. 9. Subject requires or anticipates the need for surgery (other than minor day surgical procedures such as dental or minor cosmetic procedures not involving the lower extremities and not requiring extended use of analgesics) or extended travel during the treatment period. 10. 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. 11. Subject has received any investigational drug or device within 30 days prior to the Screening Visit. 12. Subject has received long acting lidocaine, marcaine or bupivacaine injection products or other agents for nerve blocks within 6 weeks prior to the Screening Visit. 13. Subject has used chronic systemic corticosteroid treatment within 3 months of the Screening Visit. 14. Subject has a history of malignancy within the past 5 years in the treatment area. 15. Subject has severe mental health or psychiatric disorder of sufficient severity that would interfere with study performance and/or assessments in the opinion of the Investigator. 16. Subject is receiving prn narcotic medications. 17. Subject has a known history of drug or alcohol abuse 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 to become pregnant prior to Day 180. 20. Treatment of the lower extremity with PROVANT® Therapy System. 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 Neuroarthropathy or Talipes Equinovarus). 24. Subject has been diagnosed with mononeuropathy in the distal lower extremities. 25. Subject has a skin condition that could alter their peripheral sensation (i.e. exfoliating skin conditions, dermatitis, bruises, weeping skin, skin lesions, infected skin, or necrotic skin) on the feet. 26. Subject has had previous surgery to the spine or lower extremity with residual symptoms of pain or difficulty with movement. 27. Subject has clinically significant arthropathy (i.e. rheumatoid arthritis, osteoarthritis, gout) that contributes to pain during casual walking or stair climbing.
Statistical Considerations	All safety analyses will be performed on the intent to treat population from Part A of the study, defined as all subjects who were enrolled into the study and issued a study device when randomized. Once a subject is determined to be eligible, after completion of the run-in period, the subject will be enrolled and randomized into the study and become part of the ITT population. 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 121, and separately for the change from baseline to the last recorded set of evaluations. The latter should include all subjects who were randomized and completed at least one set of evaluations after randomization.

	A pre-specified sub-group analysis will be performed on subjects with pain scores ≥ 5 as well as subjects with A1C above and below 8.5. All hypothesis tests comparing active and sham treatment will be two-sided and conducted at the 5% significance level based on Part A of the study. The primary population for assessing efficacy and safety will be the ITT population from Part A. A secondary analysis of the individual efficacy endpoints will be conducted using the Per-Protocol population from Part A. All summary tables will be presented by treatment group and over all patients in the analysis population being summarized. Continuous variables will be summarized using the following descriptive statistics: n, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Percentages presented will be calculated using all patients in the analysis population being summarized (with randomized or received treatment as/if appropriate) as the denominator. To compare the absolute change in pain from baseline to 4-months, the intra-patient change will be calculated and serve as the dependent variable in the analysis. The baseline pain score will be introduced in the model as a covariate. Clinical site will be added to the model to assess poolability of the data across sites. Interaction between clinical site and treatment will be evaluated using a type 1 error rate of 10%. Treatment-emergent adverse events will be summarized by study part, type, frequency, severity, and relationship to the study device. Adverse events will be provided in a listing. SAS® Version 9.4 or later will be used to produce all statistical tables, listings and figures to be contained in the integrated statistical/clinical report.

Table of Contents

LIST OF ABBREVIATIONS

ABI	Ankle Brachial Index
AE	Adverse Event
AGE	Advanced Glycation End Products
CAN	Cardiovascular Neuropathy
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
DFU	Diabetic Foot Ulcerations
DSPN	Diabetic Distal Symmetric Peripheral Neuropathy
DTR	Deep Tendon Reflexes
ePRO	electronic Patient Reported Outcomes
E-STIM	Electrical Nerve Stimulation
FCC	Federal Communication Commission
FDA	Food & Drug Administration
HIV	Human Immunodeficiency Virus
IENFD	Intraepidermal Nerve Fiber Density
IRB	Institutional Review Board
ITT	Intent to Treat
LCD	Liquid Crystal Display
LOPS	Loss of the Protective Sensation
LSA	Laser Sensor Assembly
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Nerve Conduction Studies
NeuroQoL	Neuropathy and foot ulcer specific quality of life instrument
NOS	Nitric Oxide Synthase
NPRS	Numeric Pain Rating Scale
PAD	Peripheral Arterial Disease
PEMF	Pulsed Electromagnetic Field
PGI	Patient Global Impression
PRFE	Pulsed Radio Frequency Energy

PRN	As Needed
PT	Physical Therapy
QA	Quality Assurance
QC	Quality Control
QST	Quantitative Sensory Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPP	Skin Perfusion Pressure
SSRI	Selective Serotonin Reuptake Inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitors
TCA	Tricyclic Antidepressants
UADE	Unanticipated Adverse Device Effect

1. INTRODUCTION AND BACKGROUND

In 2015 the Centers for Disease Control and Prevention (CDC) had estimated that 30.3 million people have diabetes (9.4% of the United States population), of which 23.1 million are diagnosed and 7.2 million are undiagnosed.[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] Diabetic neuropathies are the most prominent chronic complications of diabetes.[3] While symptomatic or asymptomatic neuropathy can be diagnosed at any time during the course of the disease, there tends to be an increased association with increased age and disease duration.[4] The maintenance of stable glycemic control has been associated with improvement in neuropathic pain for people with type 1 and type 2 diabetes. However, people with type 2 diabetes, despite adequate control, have a higher prevalence for developing diabetic distal symmetric peripheral neuropathy (DSPN).[3]

Clinical neuropathy syndromes associated with diabetes mellitus are categorized according to their neurologic distribution. While overlap in presentation exists the categories are as follows: [3]

Table 1. Classification for diabetic neuropathies

<table>
<tr>
<td rowspan="3">A. Diffuse neuropathy
DSPN
• Primarily small-fiber neuropathy
• Primarily large-fiber neuropathy
• Mixed small- and large-fiber neuropathy (most common)
Autonomic
Cardiovascular
• Reduced HRV
• Resting tachycardia
• Orthostatic hypotension
• Sudden death (malignant arrhythmia)
Gastrointestinal
• Diabetic gastroparesis (gastropathy)
• Diabetic enteropathy (diarrhea)
• Colonic hypomotility (constipation)
Urogenital
• Diabetic cystopathy (neurogenic bladder)
• Erectile dysfunction
• Female sexual dysfunction
Sudomotor Dysfunction
• Distal hypohydrosis/anhidrosis,
• Gustatory sweating
Hypoglycemia Unawareness
Abnormal Pupillary Function</td>
<td>B. Mononeuropathy (mononeuritis multiplex) (atypical forms)
• Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
• Mononeuritis multiplex (if confluent may resemble polyneuropathy)</td>
</tr>
<tr>
<td>C. Radiculopathy or polyradiculopathy (atypical forms)
• Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)
• Thoracic radiculopathy</td>
</tr>
<tr>
<td>Nondiabetic neuropathies common in diabetes
• Pressure palsies
• Chronic inflammatory demyelinating polyneuropathy
• Radiculoplexus neuropathy
• Acute painful small-fiber neuropathies (treatment-induced)</td>
</tr>
</table>

Diabetic distal symmetric peripheral neuropathy (DSPN) is the most common form of diabetic neuropathy and accounts for approximately 75% of diabetic neuropathies.[3] 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 the 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.

The clinical presentation of DSPN initially involves the feet. DSPN leads to balance issues, causing fall and fractures. Initially affects smaller unmyelinated fibers which convey pain and unpleasant temperature sensations. With progression, larger myelinated fibers are affected and can be the cause of numbness, tingling, and insensate feet leading to diabetic foot ulceration (Table 2).[3]

Table 2. Symptoms and Signs of DSPN*

Large myelinated nerve fibers	**Small myelinated nerve fibers**
Numbness	Pain:
Tingling	burning
Poor balance	electric shocks
	stabbing

*Adapted from Pop-Busui, R, Boulton, AJ. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017 Jan; 40(1):139 [3]

Diabetic neuropathy is a major cause of foot ulceration which is a complication that arises in late stages of DSPN which can lead to amputations and increased health economic costs.[3] 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 may 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 Charcot neuroarthropathy.[6.7,10] Combined with ischemia and infection, LOPS may culminate 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.[8]

The pathophysiology for DSPN, as noted above, is complex and involves multiple mechanistic pathways. 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 and reduction

of nitric oxide synthase (NOS) levels, leading to small vascular vasoconstriction, larger vascular calcifications and constriction, which ultimately result in nerve ischemia.[6,7, 8]

Therapeutic intervention for the prevention and treatment of DSPN includes optimized glycemic control, dietary and lifestyle based counselling, antioxidant-rich nutrition, weight management, moderate exercise, routine foot screening, proper foot wear, and avoidance of alcohol and tobacco. Other than tight glycemic control, there are no effective treatments that target the pathophysiology of DSPN. In addition to glycemic control, diabetic neuropathy management has focused predominantly on symptomatic pharmaceutical pain control with analgesics and medications such as pregabalin and duloxetine (FDA approved for the treatment of neuropathic pain from diabetes).[3] Pharmacologic agents prescribed for pain from DSPN are listed in Table 3.

Table 3. Pharmacologic interventions for the treatment of pain associated with DSPN [3,4]

Drug Class	Agent	Effective Dose
Anticonvulsants	Pregabalin Gabapentin	300-600 mg/day 900-3,600 mg/day
Antidepressants (Serotonin-norepinephrine reuptake inhibitors)	Duloxetine Venlafaxine	60-120 mg/day 75-225 mg/day
Tricyclic antidepressants (TCA)	Amitriptyline Desipramine Nortriptyline	25-100 mg/day
Opioids	Tramadol Tapentadol	210 mg/day Immediate Release: day 1: 700mg; day 2 60 mg/day Extended Release: 50 mg, twice daily

*Adapted from Pop-Busui, R, Boulton, AJ. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017 Jan; 40(1):141-142 [3]

While TCAs are the most studied agents used for neuropathic pain, the use of such agents has occurred in the absence of regulatory approval from the Food and Drug Administration (FDA). Duloxetine (Cymbalta®) and pregabalin (Lyrica®) are medications approved by the FDA specifically for the treatment of painful peripheral diabetic neuropathy. Patients may 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.[11]

Potential Therapeutic Value of Pulsed Electromagnetic Energy Fields (PEMF) for DSPN

Provant® Therapy System is a medical device manufactured by Regenesis 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. Life Science laboratory research led to Provant Therapy's energetic settings, which have been associated with reductions in post-operative chronic pain in a clinical trial. Provant Therapy is dual-field electromagnetic energy (i.e. high electric and magnetic fields). High energy electric and magnetic fields in combination have been associated with changes in gene expression which are involved in pain and inflammation pathways in laboratory studies.[23,32] 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 the Provant® Therapy System can reduce pain, promote healing, and promote restored range of motion following reparative surgery in wounded extremities.[19,21] As an analgesic, it is non-addictive and does not alter the mental state of the user. Regenesis Biomedical, Inc., has marketed the device since 2004 and has treated over 15,000 patients within the U.S. Over two million individual treatments have been administered with rare adverse events reported.[15] In addition, the safety of PEMF has been well documented. The 2012 meta-analysis by Guo et al[20] of 25 clinical trials of PEMF in the 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,[12,14,16,23,25,27] and chronic pain. [13,15,26]

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),[20,21,24] and can promote cell proliferation.[17] Regenesis 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.[21,22] 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-1ß levels in post-operative wound exudates.[24] Together, these findings suggest that PEMF therapy reduces pain both by modulating inflammation and by activating peripheral endogenous opioids.

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.

An exploratory prospective randomized, sham-controlled study was recently conducted at two sites using the Provant® Therapy System to (a) evaluate small fiber nerve growth and function in subjects with painful peripheral diabetic neuropathy and to (b) determine the safety and feasibility of Provant in such subjects. 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 with persistent numbness, tingling, or burning in at least one foot despite standard of care treatment.

Nineteen 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 velocity, although no consistent changes were observed in self-reported pain scores based on paper diaries. The twice daily application of PEMF was determined to be feasible and safe in subjects with DSPN.

The purpose of the current study is to evaluate the efficacy and safety of PEMF treatment with the Provant® Therapy System. The current study focuses on pain relief and self-reported functional improvement as well as objective measures that may further elucidate the basic mechanisms of the intervention. The current study will use electronic diaries rather than paper diaries and include a larger sample size to improve the reliability and precision of the result.

2. STUDY OBJECTIVES

This study is designed to evaluate the efficacy of dual field PEMF Therapy [Provant® Therapy System] compared to sham treatment in patients with painful diabetic distal symmetric peripheral neuropathy (DSPN) when treatment is administered, 30 minutes twice daily through a 120-day period (4 months).

3. STUDY DESIGN

3.1 Study Design

Part A of the study is a double-blind, sham-controlled, randomized trial of the safety and efficacy of dual field PEMF therapy in subjects with bilateral symmetrical painful diabetic distal symmetric peripheral neuropathy (DSPN). A graphic presentation of the study design for Part A is shown in Figure 1. Part B of the study is an 8-month open-label active treatment extension period. A graphic presentation of the study design is shown in Figure 2.

Figure 1. Part A Study Flow Schematic

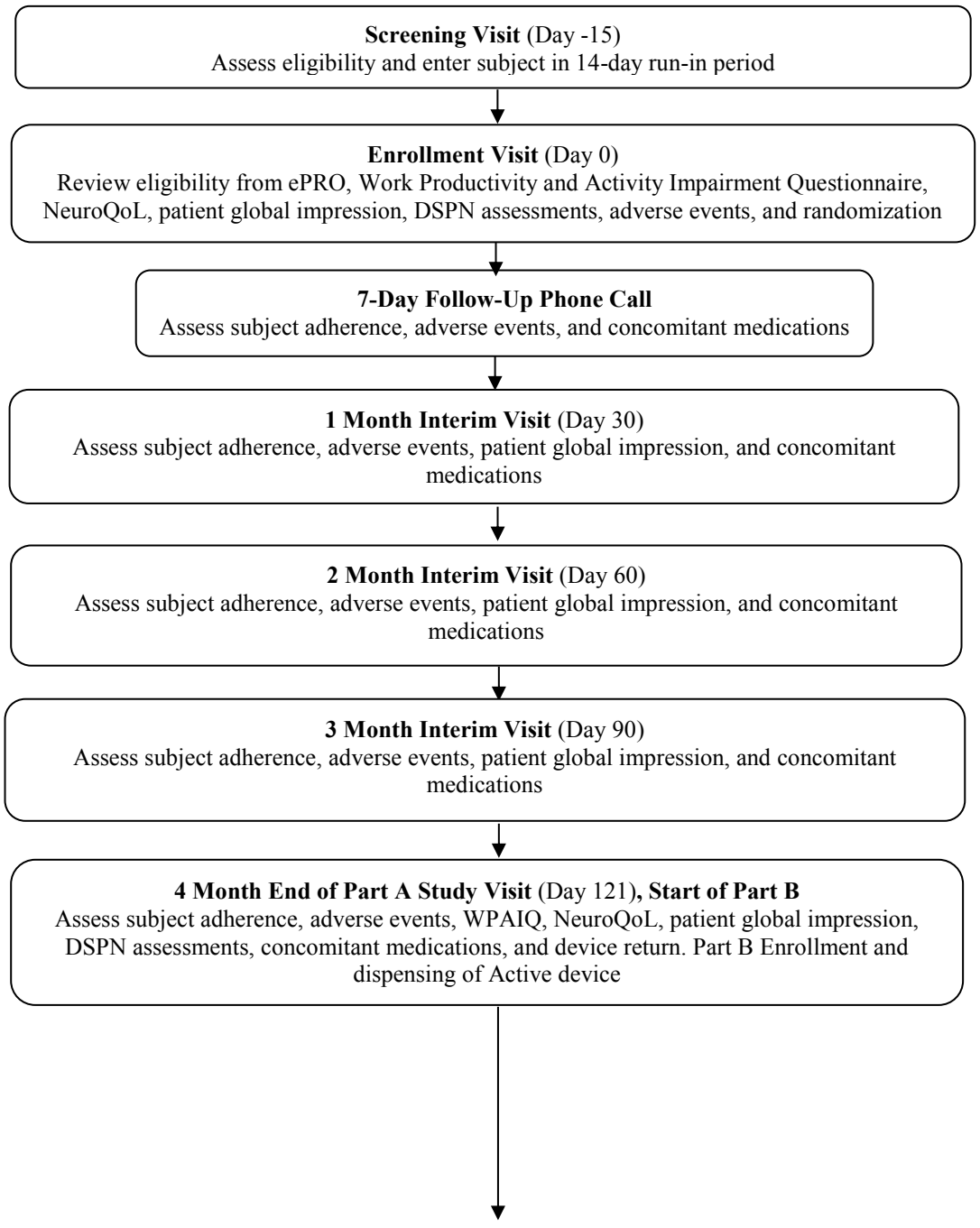
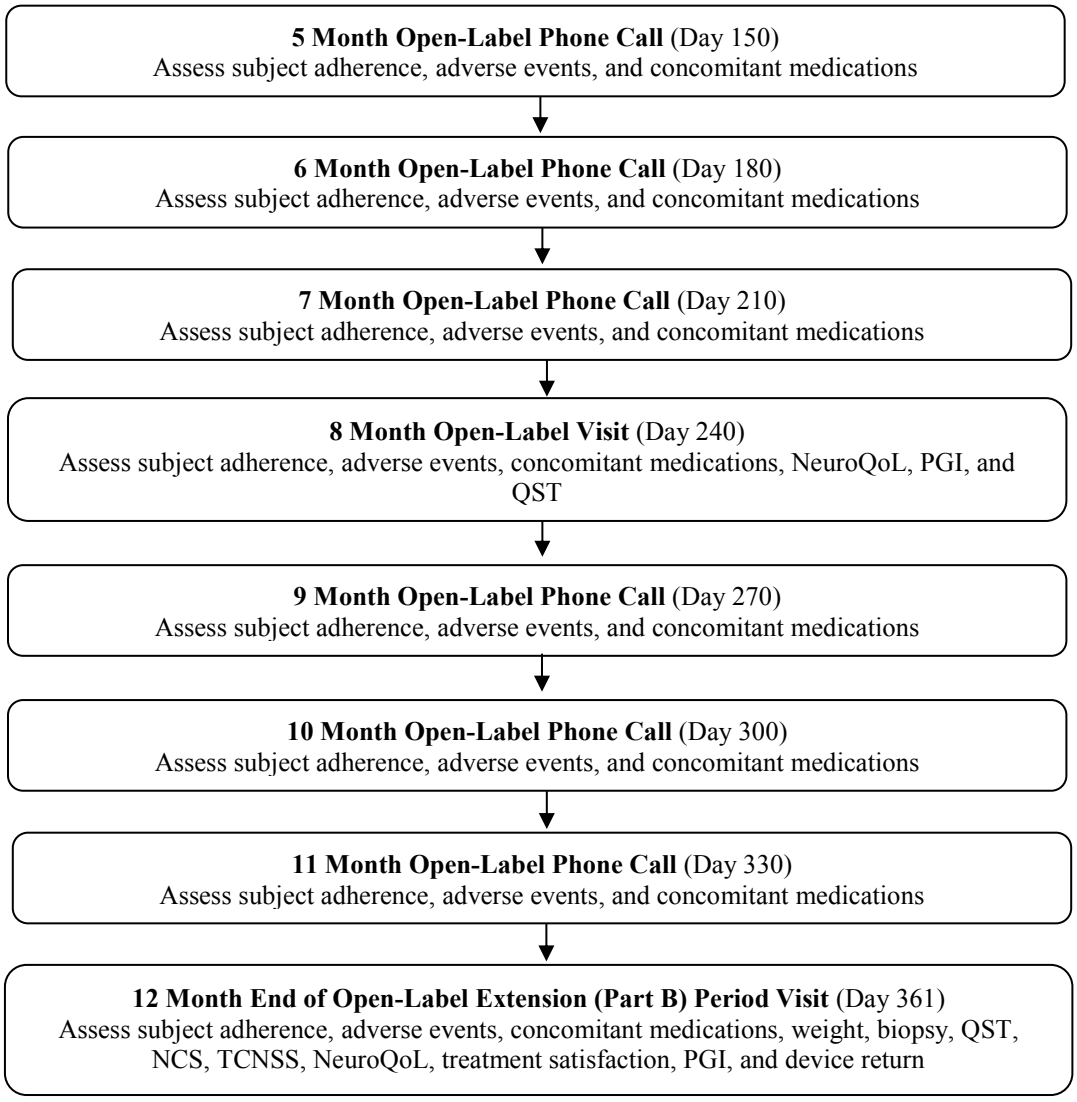


Figure 2. Part B Study Flow Schematic



3.2. Efficacy Endpoints

This study will evaluate the changes in NPRS, skin perfusion pressure (SPP), Sural Nerve Conduction Studies (NCS), WPAIQ, NeuroQoL, Patient Global Impression (PGI), thermal sensory perception (QST), and change in nerve density at the distal thigh and distal leg from baseline to 120 days (4 months).

3.3 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.

3.4 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.

Inclusion Criteria

1. Subject has documented Type 1 or Type 2 diabetes mellitus according to the ADA criteria (Appendix B).[33]

2. Subject has daily pain attributed to symmetrical lower extremity diabetic peripheral neuropathy for at least 6 months prior to screening. Confirmed by score of ≥ 6 on the Toronto Clinical Neuropathy Scoring System.

3. Subjects' average lower extremity pain related to diabetic peripheral neuropathy over the preceding 24 hours is ≥4 and <9 based on the 11-point NPRS (0-10) at the Screening Visit.

4. Subject age is greater than or equal to 22 years and less than 80 years of age.

5. Subject is on stable diabetes treatment which should include medication and/or diet and exercise for at least 3 months prior to Screening.

6. Subject has an HbA1c ≤10% at Screening or within 3 months of Screening.

7. Subject has not changed their analgesic prescriptions in the preceding one month.

8. Subject has an ankle-brachial index (ABI) of ≥0.8 to ≤1.3. If the subject has incompressible vessels, a toe brachial index of 0.8 to 1.3 is required. These adequate lower extremity studies are with no documented intermittent claudication.

9. Subject walks independently with or without assistive devices, and does not require a wheel chair.

10. Subject is willing and able to give written informed consent and to comply with all parts of the study protocol.

11. Female subjects must be post-menopausal, surgically sterile, abstinent, or, if of child-bearing potential, practicing (or agreeing 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.

12. Subject can access an internet browser in the home environment or through a smart phone.

Enrollment Visit Inclusion Criteria

1. Average diabetic peripheral neuropathic pain intensity (NPRS score) is ≥ 4 and < 9 calculated as the mean of the daily NPRS scores for neuropathic pain in the lower extremities over the 7 days preceding the visit.

2. Subject has completed a minimum of 70% of the ePRO assessments during the run-in period.

Exclusion Criteria

1. Subject has an active, open ulcer on either lower extremity.
2. Subject has significant peripheral vascular disease defined as absence of more than one-foot pulse per foot and/or ABI <0.7 and >1.3 and/or history of angioplasty, peripheral bypass surgery, or claudication within 6 months of the Screening Visit.
3. Subject has venous insufficiency with an active ulcer as classified by the Venous Insufficiency Classification System of grade C6.
4. Subject has a history of previous solid organ transplant or severe renal disease (i.e. estimated creatinine clearance ≤30 mL/min).
5. Subject has been diagnosed with a non-diabetic cause of chronic neuropathy (e.g. end stage renal disease, infectious etiology, chemotherapy, drug etiology, alcohol abuse, ingestion of toxic substance, nerve decompression surgery (related to lower extremity symptoms), or connective tissue disease) within the past 10 years.
6. Subject has previous or current history of primary or tertiary hyperparathyroidism, hypercalcemia, psychiatric disorder, alcohol dependency, Hepatitis B or C, or HIV infection.
7. According to the judgement of the Investigator, subject has clinically significant cardiovascular disease within 6 months prior to screening (unstable or poorly controlled

hypertension, transient ischemic attack, myocardial infarction, unstable angina, arrhythmia, cardiac surgery, stent placement or angioplasty, or congestive heart failure).

8. Subject has a history of any uncontrolled medical illness that, in the investigators judgment, places the subject at unacceptable risk for enrollment in a research trial with pulsed electromagnetic field therapy.
9. Subject requires or anticipates the need for surgery (other than minor day surgical procedures such as dental or minor cosmetic procedures not involving the lower extremities and not requiring extended use of analgesics) or extended travel during the treatment period.
10. 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.
11. Subject has received any investigational drug or device within 30 days prior to the Screening Visit.
12. Subject has received long acting lidocaine, marcaine or bupivacaine injection products or other agents for nerve blocks within 6 weeks prior to the Screening Visit.
13. Subject has used chronic systemic corticosteroid treatment within 3 months of the Screening Visit.
14. Subject has a history of malignancy within the past 5 years in the treatment area.
15. Subject has severe mental health or psychiatric disorder of sufficient severity that would interfere with study performance and/or assessments, in the opinion of the Investigator.
16. Subject is receiving prn narcotic medications.
17. Subject has a known history of drug or alcohol abuse 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 to become pregnant prior to Day 180.
20. Treatment of the lower extremity with PROVANT® Therapy System.
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 Neuroarthropathy or Talipes Equinovarus).
24. Subject has been diagnosed with mononeuropathy in the lower extremities.
25. Subject has a skin condition that could alter their peripheral sensation (i.e. exfoliating skin conditions, dermatitis, bruises, weeping skin, skin lesions, infected skin, or necrotic skin) on the feet.
26. Subject has had previous surgery to the spine or lower extremity with residual symptoms of pain or difficulty with movement.
27. Subject has clinically significant arthropathy (i.e. rheumatoid arthritis, osteoarthritis, gout) that contributes to pain during casual walking or stair climbing.

3.5 Enrollment

Subjects are considered enrolled in this study when all the following have occurred:

1. Written informed consent is obtained
2. All inclusion criteria and no exclusion criteria have been met
3. All screening evaluations are complete as outlined in section 4.1

3.6 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. Randomization will be stratified by each site. The randomization schedule will randomize in a 1:1 ratio (42 μs : 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.

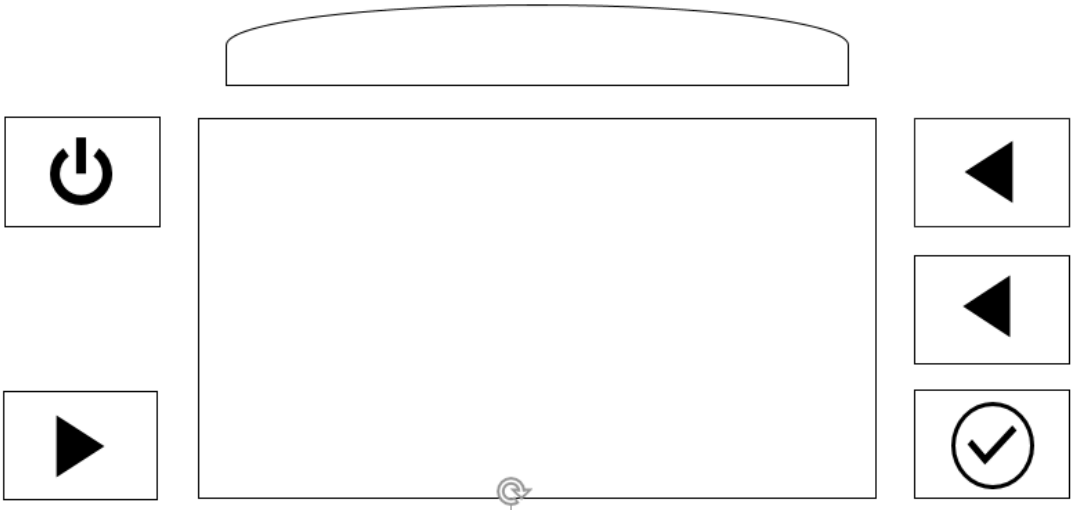
3.7 Device Description

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(s) that generate and deliver the shortwave RF energy. Key functions and features of these components are as follows:

3.7.1 Control Unit

The control unit contains the main electronics, software, and user interface of the system. The control panel (Figure below) has an LCD display which is located on the front of the control panel with an indicator light above the display and buttons to either side of

the LCD screen. The indicator light changes color to inform the patient along with the LCD verbiage. The five (5) buttons are located to the right and left sides of the LCD (2 on the left, 3 on the right) and light up when needed. The top left button serves as a power on/off switch and bottom left serves as a start/stop therapy switch. The top right button serves as a pause/resume therapy during treatment. The middle right and bottom right buttons are for future use and will be not be active.



When the system is plugged in, the Provant Therapy System enters a "soft power" mode, waiting for the user to press the power on/off button. Once the power on/off button is depressed, the system enters an active mode, performs some internal diagnostics to assure functionality, then proceeds to inform the patient to place the midfoot of each foot over each treatment applicator and press the start button to initiate therapy.

Pressing the start button initiates a preset, thirty (30)-minute therapy session and treatment sequence described in greater detail below. Once therapy is initiated, the LCD screen will indicate the remaining time as well as the number of minutes completed. Pressing either the power on/off button, the therapy start/stop button or the therapy pause/resume button after a therapy session has started will stop the RF energy generation. The power on/off button will initiate a power down of the system. The therapy start/stop button will initiate termination of the current therapy session. The therapy pause/resume button will allow for pausing and continuation of a therapy session. All buttons have a tactile resistance and emit a small chirp when pressed.

When the thirty-minute therapy session is concluded, the generation of RF energy is automatically terminated and an audible tone is generated to alert the user that the treatment is finished. The LCD screen then instructs the user to press the power on/off button to power down the system. The patient can either store the unit or leave plugged in until the next use.

The Provant® Therapy system also has additional functions, independent of the user interface. The system logs internally any errors encountered, start and stop times of treatment, as well as feedback from the treatment applicator at predefined intervals. This data is stored on an internally mounted SD card (no external access) and the data can be read upon return of the device or can also be relayed back to the Sponsor's engineering technicians through the device's cellular module.

In this study, the subject will treat both feet for 30 minutes, twice a day for 120 days. Subjects will be instructed to treat barefooted, placing each bare foot on a treatment applicator and treating for the full 30 minutes, twice a day.

3.7.2 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 load capacitance. In this way, the correct energy output is constantly monitored, regulated, and maintained at the preset therapy dose levels.

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.

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 a "Service Required" message will be displayed on the LCD screen. 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.

3.8 Logistics and Device Accountability

The study device 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 delegate 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 devices 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.

3.9 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.

3.10 Preparation and Administration

Each subject will receive one device with two applicator pads to use during the study. Each treatment session with the study device 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 device 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, remove shoes and socks, and place one foot on each treatment applicator of the PEMF device, 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 (± 2 hours) and 8pm (± 2 hours) up to Day 120 (4 months).

Prior to initiation of each treatment session, the subject will place the midfoot of each foot over the starburst of each applicator pad. Further directions for use for the PEMF system are found in the Instruction Manual. Upon completion of the treatment session, the subject will store the PEMF device until the time of the next scheduled treatment session.

3.11 Blinding

This is a randomized, double-blind, sham-controlled study. The sham devices will be Provant devices that are de-activated such that no RF energy is generated or delivered when the device is started. All other functions, including the start sequence, display lights, audible start-beep and operation of the sham devices are identical to that of the active Provant devices. Sham devices are indistinguishable from the active Provant devices being used in the study. The subjects and research personnel will be fully blinded to the randomization assignment and unable to differentiate active and sham devices. All research personnel at the investigative sites and sponsor will be blinded.

3.12 Study Assessments

All efficacy outcome measures will be assessed in order to allow for characterization of the response to PEMF therapy.

3.12.1 Primary Efficacy Assessment

Pain Intensity (PI)

The primary outcome measure is the absolute change in pain intensity as measured by patient reported numeric pain rating scale (NPRS) evaluations. The NPRS is a validated 11-point numerical rating scale for pain (0=no pain to 10=worst possible pain) collected as patient-reported outcomes in an electronic diary. The NPRS will be scored daily (8am ± 2 hours) during the 14-day run-in period in order to establish a baseline for purposes of eligibility assessment. During the subsequent 4-month (120-day) treatment period, NPRS will be scored immediately after each morning treatment session (8am ± 2 hours).

Subjects will be instructed to "Select the one number that best indicates the average intensity of pain you have had over the last 24 hours in your legs".

The primary endpoint is the absolute change from baseline in the NPRS Pain score through Month 4 (Day 120) comparing the PEMF group to the sham group. For purposes of statistical analysis, the baseline NPRS will be the average NPRS during the 7 days preceding the start of treatment with the study device. For subsequent time points, including the primary endpoint at Day 120, NPRS will be calculated as 7-day rolling averages during the treatment period.

During Part B of the protocol (through Month 12 (day 360)), NPRS will be scored immediately after each morning treatment session (8am ± 2 hours) for one week prior to Months 6, 8, 10, and 12. Evaluation of the NPRS during Part B of the protocol will be considered an exploratory endpoint.

3.12.2 Secondary Efficacy Assessments

NeuroQoL

The NeuroQoL is a validated 29 question assessment tool that measures the effects of diabetic peripheral neuropathy and its complications on an individual's quality of life. Subjects are asked about the effect their foot problems may have on their daily life and well-being in the past 4 weeks, with "foot problems" meaning lost or reduced feeling in the lower extremities, pain discomfort, and in some cases unsteadiness while walking or standing. The questionnaire will be completed by the

subject at the Enrollment Visit, Month 2, Month 4, Month 8, and Month 12 visit (Day 361).

Skin Perfusion Pressure

Vasamed Sensilase PAD-IQ measures the perfusion pressure (in mmHg) of microcirculation using a laser Doppler sensor. SPP uses the reactive hyperemia to assess capillary health in specific angiosomes. Two previous trials were conducted in patients with painful peripheral diabetic neuropathy showing an increase in circulation (pressure) from baseline.

The 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 on the foot. 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. Skin Perfusion Pressure- SPP is the pressure required for restoring microcirculatory blood flow following release of carefully controlled occlusion. Two measurements are obtained per foot; one on the dorsal aspect of each foot in the distribution of the dorsalis pedis artery angiosome and on the plantar aspect of each foot in the distribution of the lateral plantar artery angiosome. SPP will be conducted at the Enrollment Visit to obtain a baseline value and at months 2, and 4. An increase in SPP would be considered clinically meaningful.

Sural Nerve Conduction Studies (NCS)

Sural Nerve Conduction Studies (NCS) assess large myelinated axons. Using the NC-stat® DPNCheck®, the subject will assume a comfortable position so that their right or left 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 lateral malleolar (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 on either side of the calf. The sural nerve conduction velocity and amplitude will be recorded. The test will then be repeated on the opposite leg. NCS will be collected at the Enrollment Visit to obtain a baseline value and at Days 121 (month 4) and 361 (month 12). An increase in velocity and/or an increase in amplitude would suggest DPN improvement.

Quantitative Sensory Testing (QST)

Quantitative Sensory Testing (QST) for thermal sensation assesses small diameter unmyelinated and lightly myelinated axons. QST is a noninvasive technique providing an easy to use, validated measure of warm, cool, and heat pain thermal sensory thresholds.

The Thermal Stimulator is placed on the surface of the skin on the dorsal aspect of the foot. The Thermal Stimulator is held in place on the foot by a Velcro strap, which wraps around the subject's foot.

Contact thermal stimulation will be delivered using the Medoc Ltd. Q-Sense system. A Thermal Stimulator probe ("thermode") is placed on the surface of the skin on the dorsal aspect of the foot in the distribution of the superficial branch of the distal fibular (peroneal) nerve. The probe is held in place by a Velcro strap, which wraps around the subject's foot. Using a Patient Response Unit (PRU), the subject presses a button to identify their response to the delivered thermal stimulation. This is done by successful trials to assess cool sensation threshold (CS), warm sensation threshold (WS) and heat pain threshold (HP) modalities using the method of Limits. Within the cool and warm sensation modalities, the trial is repeated 4 times on each foot and 3 times on each foot for heat pain threshold modality. The cool thermal testing should be conducted prior to the warm and heat pain thermal testing.

Heat-Pain threshold tests a subject's ability to determine when a stimulus begins to feel painful, not hot, in order to develop a pain perception profile. At any point during testing, the subject can choose to discontinue further testing of the heating stimuli. The entire study will last between 5-10 minutes.

QST will be performed at the Enrollment Visit to obtain a baseline value and at the Day 121 Visit (Month 4), Day 240 Visit (Month 8), and Day 361 Visit (Month 12).

Patient Global Impression (PGI)

PGI is a 3-question questionnaire assessing the subject's interpretation of their painful diabetic neuropathy as well as overall health on an 11-point numerical rating scale (NRS). PGI allows subjects to integrate, into three questions their overall evaluation of their status, the different aspects of their overall diabetic neuropathy in their legs, overall health, and overall status compared to the start of the study. It is important to note that an 11-point global scale is common and considered a valid

approach; however, the specific wording for the questionnaire in this trial has not been validated.

In the first question, subjects will be asked to circle the number on an 11-point scale that best describes their overall status of their diabetic neuropathy in their legs over the past week ("How would you rate the overall status of your diabetic neuropathy in your legs over the past week?"). Subjects are then asked to circle the number on an 11-point scale that best describes their overall health over the past week ("How was your overall health over the past week?"). The third question assesses change since the start of the study on a 7-point scale ("Since the start of the study, how has your diabetic neuropathy in your legs changed?"), and to score it as either very much worse, much worse, minimally worse, no change, minimally improved, much improved or very much improved. PGI will be collected in the clinic at Months 1, 2, 3, and 4 during the 120-day treatment period and at Months 8 and 12 during the open label extension period. PGI serves to anchor within-subject changes in overall status during the course of treatment.

3.12.3 Exploratory Efficacy Assessment

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The Work Productivity and Activity Impairment Questionnaire (WPAIQ) is a validated 6 question assessment tool that measures time missed from work, impairment of work and regular activities due to their health problem. Subjects are asked about the effect their diabetic neuropathy has on their ability to work and perform regular activities in the past 7 days. The questionnaire will be completed by the subject at the Enrollment Visit, Month 2, and Month 4.

Biopsy

Two 3 mm punch skin biopsies will be performed at baseline and end of treatment to assess IENFD. At the Enrollment Visit, one biopsy will be obtained at the distal leg, 10 cm above the lateral malleolus on the right leg and a second biopsy will be obtained at the distal thigh, 10 cm above the superior margin of the patella on the lateral right leg. The biopsies will be shipped overnight to the University of Utah Cutaneous Nerve Laboratory. At the end of Part A study visit Month 4 (Day 121), a second set of biopsies will be obtained lateral to the baseline biopsies and shipped overnight to the central lab. Subjects who do not consent to skin biopsies may still be enrolled in the study. Subjects that did not consent to or have biopsies at the Baseline Visit may still have biopsies collected at Month 4 as they enter into the open label extension period. At the end of Part B study visit Month 12 (Day

361), a final set of biopsies will be obtained lateral to the Month 4 biopsies and shipped overnight to the central lab.

NOTE: Skin biopsies will not be performed in subjects receiving anticoagulants. Biopsies may be performed on subjects receiving anti-platelet therapy (i.e. non-steroidal anti-inflammatory medications, clopidogrel) according to clinical judgment.

3.12.4 Additional Study Assessments

Measurement of Ankle-Brachial Index (ABI)

Ankle Brachial Index (ABI) compares pressures in the brachial arteries to lower extremity pressures in the posterior tibial and dorsalis pedis arteries as measured with doppler ultrasound. The ratio between these pressures is the ABI. Subjects should be in a supine position, with the arms and legs at the same level as the heart for a minimum of 10 minutes before obtaining the ABI measurement. ABI will be measured at the Screening Visit on both sides. For subjects that consented to having biopsies collected, ABI measurements will be taken before the biopsies are collected.

Venous Insufficiency

Venous insufficiency will be graded by the Investigator at the Screening Visit using the venous insufficiency classification scale[34] below:

Grade	Description
C 0	No visible changes in the clinical examination
C 1	Reticular veins, redness of the skin around the ankles
C 2	Varicose veins
C 3	Presence of edema without skin changes
C 4	Lesions dependent of venous diseases (discoloration, blemishes, lipodermatosclerosis)
C 5	Skin changes described above with signs of healed venous ulcers
C 6	Skin lesions such as in groups C1 to C4 plus active venous ulcers

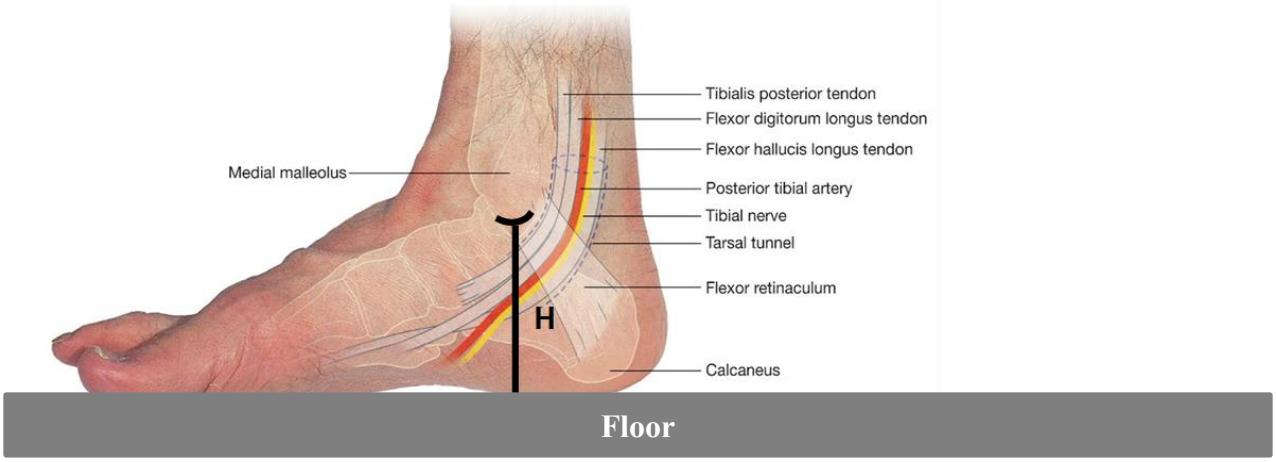
C = Clinical

Toronto Clinical Scoring System (TCSS)

The Toronto Clinical Scoring System (TCSS) is a validated and quantitative instrument to evaluate the severity of peripheral neuropathy in the lower extremities. The scoring system is broken out into 3 elements of Reflex, Symptom, and Sensory. Each patient is assessed as to the presence or absence of symptom, reflex, or sensation on each foot. The outcome, the clinical neuropathy score, is a continuous variable ranging from a minimum of 0 (no neuropathy) to a maximum of 19 points (0-5 points no neuropathy, 6-8 points mild neuropathy, 9-11 points moderate neuropathy, and 12+ severe neuropathy). The Toronto Clinical Scoring System will be used as a screening assessment for inclusion at the Screening Visit and measured at the Day 121 visit (Month 4) and Day 361 Visit (Month 12).

Measurement of Foot Thickness

The depth of the foot (H below) will be measured from the most inferior aspect of the medial malleolus to the plantar aspect of the foot when residing on the floor (see diagram below). The depth should not be more than 8cm for inclusion in the trial for optimal treatment penetration.



The width (widest portion) and length (heel to the tip of the longest toe) of the foot will also be measured in centimeters using a tape measuring device. The shoe size will be obtained using the Brannock Foot Measuring Device.

Hemoglobin A1c (HbA1c) Test

Hemoglobin A1c provides the average level of glucose in the blood over the past 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. At the end of the study, Month 4 (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.

Subject adherence

Compliance with twice daily treatment with the study device will be assessed verbally during the Day 7 telephone call, at the interim visits and upon completion of the study. Data on the usage of each device is collected in real time at Regenesis Biomedical, Inc. The report will contain the patient's device treatment information and will be sent to the site at regular intervals. The site will assess compliance based on the report and contact the patient if the subject is not complying with the treatment regimen. The site will also review compliance with the subject at each of the interim visits.

Treatment Satisfaction and Blinding Assessment

Treatment satisfaction with the device will be obtained at Months 1, 2, 3, end of Part A study visit (Month 4), and at Months 8 and 12 of Part B, to assess the patients level of satisfaction with the treatment. The subject will be asked "How satisfied are you with the Investigational Treatment?" and will choose between Very Satisfied, Satisfied, Neither Satisfied or Dissatisfied, Dissatisfied, and Very Dissatisfied.

Subjects will also be asked which device (active or sham) they believe they were randomized to at the Day 7 phone call and Month 4 (Day 121) (blinding assessment).

3.12.5 Safety Assessments

Safety will be assessed through review of adverse events including serious adverse events. Adverse events will be assessed at the enrollment visit, interim visits and the Month 4 visit.

4. STUDY PROCEDURES

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

4.1 Visit 1 – Screening Visit (Day -15)

The Screening Visit will take place 15 days prior to the Enrollment Visit. If a successfully screened subject falls more than 1 day early (earlier than day -14) or more than 2 days late (later than day -17), the subject will require another screening and run-in period to

participate in the trial. The following procedures will be performed during the Screening Visit:

1. Informed consent review and signature
2. Review Inclusion and Exclusion criteria
3. Collect Toronto Clinical Neuropathy Scoring System for Inclusion
4. Obtain baseline pain score (baseline score must be ≥ 4 and <9 for eligibility)
5. Collect subject demographic data (including age, weight, height, gender, race/ethnicity)
6. Collect baseline diabetes related health resource utilization including the regimen for their diabetic care (number of doctors' visits and history of ulcers)
7. Collect Medical and Surgical History
8. Collect depth, width, and length foot measurements and shoe size for each foot
9. Conduct directed physical exam (abnormal or normal) for General Appearance, Cardiovascular, Musculoskeletal, Extremities/Skin, Neurological, and Other
10. Obtain Ankle-Brachial Index
11. Assess venous insufficiency
12. Measure HbA1c
13. Review and record medications taken for their diabetic neuropathy pain (including over the counter PRN)
14. Review and record all additional medications
15. Perform a urine pregnancy test for females of child bearing potential
16. If the subject meets the eligibility criteria, enroll the subject in to the 14-day ePRO run in period in the ePRO system.

During this visit, the subject will be introduced to the electronic (ePRO) diary and trained in the proper use of the patient-reported-outcome (PRO) assessment tools for pain intensity and analgesic consumption for their diabetic neuropathy pain (including over the counter and prn medications). Analgesic medications taken for their diabetic neuropathy pain will be captured in the ePRO and subjects will enter the number of pills they have taken over the last 24 hours. The ePRO diary can be accessed by the subject through any device that has an internet connection and web browser.

Subjects will be instructed to utilize their prn analgesic medications prescribed prior to enrollment in the event their diabetic neuropathy pain increases during the trial, and not to introduce new medications or therapies into their analgesic treatment regimen through

Month 6 (Day 180) of the trial. In this context, "analgesic medications" includes but is not limited to nonsteroidal anti-inflammatory agents, anti-depressants and muscle relaxants, and includes medications taken on an "as needed" (prn) basis (including over the counter medications) as well as those medications taken on a regular schedule.

4.2 14-Day Run-In Period

The subject will be instructed to record NPRS scores at 8 am (± 2 hours) for 14 consecutive days beginning the day following the Screening Visit. There will be 2 questions generated on a daily basis, one question will address diabetic neuropathy pain and a separate question will ask the subject to enter consumption (number of pills/tablets/capsules) of each indicated analgesic taken for their neuropathic pain over the previous 24 hours.

4.3 Visit 2 – Enrollment Visit (Day 0)

The following procedures will be performed:

1. Review Inclusion/Exclusion criteria
2. Review and record any changes in medical history and study eligibility criteria since screening.
3. Review average baseline NPRS score collected in ePRO (mean of the preceding 7 days must be ≥4 and <9).
4. Review diary compliance (must be ≥ 70%)
5. Review analgesic pain consumption profile in ePRO
6. Review and record adverse events since signing of the Informed Consent
7. Review and record any changes in concomitant medications
8. Conduct Skin Perfusion Pressure (SPP)
9. Conduct Sural Nerve Conduction Studies (NCS)
10. Conduct Quantitative Sensory Testing (QST) of Cool, Warm, and Heat as Pain
11. Collect WPAIQ
12. Collect NeuroQoL
13. Collect Biopsies at distal thigh and distal leg from consenting subjects
14. If the subject continues to meet eligibility criteria, enroll and randomize subject
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. Remind the subject in the use of patient-reported-outcome (PRO) tools of NPRS and analgesic consumption for their diabetic neuropathic pain.
17. Enroll the subject into the treatment period in the ePRO system.

During this visit, eligible subjects will receive a randomized Provant device and will be instructed to administer treatment on both feet twice daily at 8am and 8pm (± 2 hours) for 4 months (120 days).

4.4 Day 7 Phone Call (Day 7 +2 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion
4. Conduct blinding assessment
5. Conduct follow-up on the biopsy sites (asking the patient on how the area looks, cleaning techniques, and questions on if an infection is present) (if applicable)

4.5 1 Month Interim Visit (Day 30 ± 3 Days)

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

1. Collect Patient Global Impression (PGI)
2. Assess for adverse events
3. Assess for changes in concomitant medications
4. Assess adherence to PEMF treatment regimen by reviewing the usage report provided by Regenesis Biomedical and ePRO entries
5. Assess treatment satisfaction

4.6 2 Month Interim Visit (Day 60 ± 3 Days)

Subjects will return to the clinic on Day 60. At this visit, the following procedures will be performed:

1. Collect Patient Global Impression (PGI)
2. Assess for adverse events
3. Assess for changes in concomitant medications

4. Assess adherence to PEMF treatment regimen by reviewing the usage report provided by Regenesis Biomedical and ePRO entries
5. Assess treatment satisfaction
6. Collect WPAIQ
7. Collect NeuroQoL
8. Conduct SPP

4.7 3 Month Interim Visit (Day 90 ± 3 Days)

Subjects will return to the clinic on Day 90. At this visit, the following procedures will be performed:

1. Collect Patient Global Impression (PGI)
2. Assess for adverse events
3. Assess for changes in concomitant medications
4. Assess adherence to PEMF treatment regimen by reviewing the usage report provided by Regenesis Biomedical and ePRO entries
5. Assess treatment satisfaction

4.8 4 Month End of Part A Visit (Day 121 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess treatment satisfaction
4. Collect subjects weight
5. Collect WPAIQ
6. Collect NeuroQoL
7. Collect PGI
8. Conduct SPP
9. Conduct NCS
10. Conduct QST
11. Measure HbA1c

12. Obtain skin biopsies from subjects that had biopsies at baseline, or that consent to having biopsies at Month 4 as they enter the open label extension period
13. Collect Toronto Clinical Neuropathy Scoring System
14. Conduct Blinding Assessment
15. Assess adherence to PEMF treatment regimen by reviewing the usage report provided by Regenesis Biomedical and ePRO entries
16. Return of randomized device
17. Enroll Subject in Part B / open-label part of protocol

    During this visit, subjects will receive an Active Provant device and will be instructed to administer treatment on both feet twice daily at 8am and 8pm ($\pm$ 2 hours) for 8 months (through Day 360).

4.9 Part B - 5 Month Phone Call (Day 150 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen

4.10 Part B - 6 Month Phone Call (Day 180 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion

4.11 Part B - 7 Month Phone Call (Day 210 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen

4.12 Part B - 8 Month Visit (Day 240 ± 3 Days)

Subjects will return to the clinic on Day 240 for the Month 8 visit. At this visit, the following procedures will be performed:

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion
4. Collect NeuroQoL
5. Collect PGI
6. Assess treatment satisfaction
7. Conduct QST

4.13 Part B - 9 Month Phone Call (Day 270 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen

4.14 Part B - 10 Month Phone Call (Day 300 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion

4.15 Part B - 11 Month Phone Call (Day 330 ± 3 Days)

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

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen

4.16 Part B - 12 Month End of Study Visit (Day 361 ± 3 Days)

Subjects will return to the clinic on Day 361 for the end of study visit. At this visit, the following procedures will be performed:

1. Assess for adverse events
2. Assess for changes in concomitant medications
3. Assess adherence to PEMF treatment regimen and diary completion
4. Collect NeuroQoL
5. Collect PGI
6. Collect Weight
7. Conduct NCS
8. Conduct TCNSS
9. Conduct QST
10. Assess treatment satisfaction
11. Obtain skin biopsies from subjects that consented to having biopsies
12. Return of active device

4.17 Treatment adherence/study compliance

Subject adherence (compliance with twice daily treatment with the study device) will be assessed verbally during the Day 7 telephone call, at the interim visits and upon completion of the study. Data on the usage of each device is collected in real time at Regenesis Biomedical, Inc. The report will contain information on the patient's device usage and will be sent to the site at regular intervals. The site will assess compliance based on the report and contact the patient if the subject is not complying with the treatment regimen. A subject with complete adherence will be expected to have a usage report of 120 during Part A of the study and 240 during Part B of the study.

4.18 Protocol Adherence

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.

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major". Deviations will be defined prior to un-blinding.

4.19 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 and/or changes to the subject's therapeutic regimen (agent, dose, frequency of administration) for treatment of diabetic peripheral neuropathy pain (other than the introduction of PEMF therapy) will not be allowed through Day 360 of the study. Subjects will be allowed to continue administration of prn medications if they were added and taken at least 30 days prior to Screening.

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. The analgesics taken for diabetic neuropathy will be entered in to the ePRO system for the subject to enter the number of pills taken for each one daily through 120 days, at Months 5, 6, 7, 9, 10, and 11 phone calls, during the one week of ePRO assessments prior to Months 6, 8, 10, and 12 visits, and at the Month 8 and 12 on site visits. Analgesics taken for other reasons, e.g., headache, will be collected through recording of concomitant medications in the subject's chart.

4.19.1 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 120 visit. In this context, "analgesic medications" refers to medications prescribed and administered for the treatment of pain from diabetic neuropathy, and includes but is not limited to anticonvulsants, 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. Medications identified as those taken for the subject's painful diabetic distal symmetric peripheral neuropathy will be auto populated in the subject's ePRO diary in order to capture the number of pills/capsules/tabs taken in the last 24 hours.

Medications prescribed for other indications are allowed and will be recorded as concomitant medications.

4.19.2 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

5. 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 Month 4 Visit (Day 121) prior to subject withdrawal in Part A, and Month 12 Visit (Day 361) prior to subject withdrawal in Part B.

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.
- 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.

6. RISK BENEFIT

In a prior study evaluating PEMF therapy on pain sensitivity to different qualities of experimentally induced pain in subjects with 41 subjects with painful peripheral diabetic neuropathy, treatment with Provant was well tolerated. There were no adverse events were reported in that study for either treatment group. A review of the data with the use of Provant in multiple on-label and off-label uses supports the safety of Provant when used in its labeled twice-daily frequency of administration. The anticipated adverse events were mild to moderate with none being serious in nature. Moreover, non-thermal devices similar to Provant have been found to have a favorable risk-benefit profile in clinical trials. Accordingly, Regenesis Biomedical, Inc. has reviewed all reported adverse events in clinical studies and in post-market data collection and has concluded that the use of Provant as intended in this clinical trial does not present a potential for serious risk to the health of participants. In addition, preclinical data related to diabetic neuropathy and clinical data in different indications suggest that short and long-term benefits in subjects with painful peripheral diabetic neuropathy may occur. Therefore, the risk-benefit profile for participating in the current study appears to be favorable.

7. STATISTICAL CONSIDERATIONS

The statistical analysis plan for this study will be described in detail in a separate Statistical Analysis Plan (SAP). The initial phase of this study is defined as *Part A* and represents the randomized double-blind portion of the study. Part B is the open-label extension phase where all subjects will receive active therapy.

The primary population for assessing efficacy and safety will be the *Intent to Treat (ITT) Analysis Set*, defined as all subjects who were enrolled into the study and issued a study device.

A secondary analysis of the individual efficacy endpoints will be conducted using the *Per Protocol (PP) Analysis Set*, defined as all subjects who were enrolled and completed ≥70% use in treating with the study device.

Subjects will complete a 14-day run in period to obtain an average over the last 7 days in the run-in period to obtain the NPRS score for qualification. Once the subject is determined to be eligible, the subject will be enrolled and randomized 1:1 to either an active or inactive sham device and become part of the *ITT and PP sets*.

Subjects in the *ITT and PP sets* will be instructed in the use of the devices for 120 days in the home environment. At months 1, 2, and 3 subjects will return to the clinic to complete PGI and review of adherence to treatment and diary entries. At month 3, subjects will return for completion of the WPAIQ, NeuroQoL and SPP measurements. Subjects will return to the clinic at day 121 for final evaluation and to complete the questionnaires, SPP, QST, and NCS.

7.1 Summarization of Results

The tabulations will be based on the results for the change from baseline to study day 120. 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. Summary tabulations will be created 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 and the last day of observation plus 1 day. All calculations for defining the duration on-study will follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – 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. Pairwise differences between the treatment groups will be calculated and 95% confidence intervals constructed. Time to event analysis will be determined through Kaplan Meier analysis and log-rank testing.

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 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.

The primary endpoint for the study is the change from baseline in the NPRS score at 4 months.

The primary hypothesis to be tested is presented below:

Ho: μ (Change in NPRS score at 4 months / PEMF group) = μ (Change in NPRS score at 4 months / sham group)

Ha: μ (Change in NPRS score at 4 months / PEMF group) $\neq$ μ (Change in NPRS score at 4 months / sham group)

To compare the absolute change in pain from baseline to 4-months, the intra-patient change will be calculated and serve as the dependent variable in the analysis. The baseline pain score will be introduced in the model as a covariate. Clinical site will be added to the model to assess poolability of the data across sites. Interaction between clinical site and treatment will be evaluated using a type 1 error rate of 10%.

Mixed Models with Repeated Measures (MMRM) comparing results across all time-points will also be performed, adjusted for the baseline value, week, treatment by week interaction and the effect of the patient.

Sub-group analysis will be pre-specified in the SAP and will be performed on subjects with pain scores ≥ 5 as well as subjects with A1C above and below 8.5.

Missing or Incomplete Data

If a patient reports at least 3 days with non-missing pain intensity scores within a particular week, the weekly mean pain intensity score will be derived using the non-missing scores only. This is identical to imputing the missing scores as the mean of the non-missing scores. If the patient reports less than 3 days with non-missing pain intensity scores within a particular week, the weekly mean pain intensity score will be treated as missing data.

Missing weekly mean pain intensity scores will be imputed using multiple missing data and pattern mixture methodology. Sensitivity analyses will be conducted exploring different patterns for missing data. An MMRM will be performed using only observed data without multiple imputation

and an analysis using the change from baseline to the last non-missing weekly mean pain intensity score will also be provided.

The pattern mixture model methodology will be implemented using SAS procedures MI and MIANALYZE. Specifically, the following steps will be followed:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.

Data for patients who discontinues early will be multiply imputed as follows:

- If the patient discontinues due to an AE lack of response, then missing data will be assumed to follow a distribution similar to the baseline values observed in the patient's randomized treatment.
- If the patient discontinues due to reasons other than AE or treatment response, at each time point, missing data will be assumed to follow a distribution similar to scores for patients that are still in the study and randomized to the same treatment group.

Results of the 120-day results, and the MMRM using the multiply imputed data, will be summarized using the SAS MIANALYZE procedure.

A hierarchical approach will be undertaken for the pre-specified secondary outcomes. Testing will occur in the listed sequence following testing of the primary endpoint.

7.2 Evaluating the Effect of Clinical Sites

This is a multi-center clinical study, with standardization of patient enrollment, data entry, and adverse event reporting. All clinical sites will follow the requirements of the use of the device, data collection procedures, diaries and case report forms. To present the data from this clinical study in a summarized form, a comparison of the primary endpoint results across clinical sites will be performed to determine if the response among sites is consistent. Small sites (i.e., sites that have less than 6 patients) will be identified and the following method will be used for combining the data. Data from all small sites (<6 patients) will be combined to form a single site in order to obviate non-estimable estimates in the evaluation of site and site interaction effects. Once combined, the pooled site will remain in the model for all analyses where a site effect is to be determined. If the pooled smaller sites represent a single site that has more than twice as many patients as the largest single site, however less than 3 times as many patients, the small sites will be ranked by size and divided into 2 pooled assignments using an alternating sequence (ABABAB). If the pooled smaller sites represent a site that has more than three times as many patients as the largest single site, however less than four times as many patients, the small sites will be ranked by size and divided into 3 pooled assignments using an alternating sequence (ABCABCABC).

The statistical test to evaluate poolability for binomial and multinomial variables will be a test of homogeneity comparing the proportions of patients with a positive outcome for the endpoints across clinical sites; a p-value less than 0.1 will be considered evidence of non-poolability. Even with the absence of statistical significance, sites with substantial differences in clinical outcomes will be thoroughly investigated.

7.3 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.

7.4 Sample Size

This is a Phase III study with a sample size of 170 patients (85 per treatment group). The sample size for the trial has been set at 170. Based on a previously conducted clinical trial assessing the efficacy and safety of the Provant Therapy System in a similar population, the mean ± standard deviation change in the NPRS from baseline to 60 days was 1.79 ± 1.83 units. The data are derived from the open-label, single arm part of the trial in which all subjects received PEMF. Assuming a placebo effect of 40% results in an assumed between group difference of 1.07 units. Based on alpha = 0.05 and 90% power, a sample size of 62 patients per treatment group would be needed based on a two-sided sample t-test for the NPRS. A total sample size of 162 was estimated based on an assumed premature discontinuation rate of 30%.

8. 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 all subjects prior to participating in this study. The original informed consent from will be filed in the Investigator Site File.

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.

9. 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.

10. 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.

11. ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

11.1 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:

- 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:

- 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:

- 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 study manager:

FAX: 480-907-1292

Attention: Medical Monitor

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.

11.2 Anticipated Adverse Device Effects Associated with Provant Therapy System

Anticipated adverse events associated with PROVANT® Therapy System are as follows:

- Skin Reaction in the application area (i.e. rash, erythema)
- Altered sensation in the treatment area (i.e. burning, paresthesia)
- Hyperalgesia in the application area (i.e. increased pain, hypersensitivity)

11.3 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:

Regenesis Biomedical, Inc. Fax: (480) 907-1292The 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.

12. 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 812.140 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.

12.1 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.

12.2 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.

13. 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.

14. 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.

15. 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

Part A

Part B

Period	Screening Visit	14-day Run-In	Enrollment (Baseline)	Day 7 Call	M1 Visit	M2 Visit	M3 Visit	M4 Visit	M5 Call	M6 Call	M7 Call	M8 Visit	M9 Call	M10 Call	M11 Call	M12 Visit
Study Day	**-15**		**0**	**7 (+2)**	**30 (±3)**	**60 (±3)**	**90 (±3)**	**121 (±3)**	**150 (±3)**	**180 (±3)**	**210 (±3)**	**240 (±3)**	**270 (±3)**	**300 (±3)**	**330 (±3)**	**361 (±3)**
Informed Consent	X															
Demographic Information	X															
Medical/Surgical History/Physical Exam	X		X[3]													
Inclusion/Exclusion Criteria	X		X[1]													
Baseline Health Economics	X															
Pain Score Assessment (NPRS)	X		X[2]													
Measurement of Foot Thickness, Width, and Length	X															
Height and Weight	X							X[5]								X[5]
Urine Pregnancy Test	X[4]															
Measure HbA1c	X							X								
Obtain Ankle-Brachial Index & Assess Venous Insufficiency	X															
ePRO Diary (pain scores, analgesic use)		X	X	X	X	X	X	X		X		X		X		X
Assess Adherence to treatment regimen and ePRO entries			X[7]	X	X	X	X	X	X	X[8]	X	X[8]	X	X[8]	X	X[8]
Toronto Clinical Neuropathy Scoring System	X							X								X
Randomize and Dispense Study Device			X													
3mm Skin Punch Biopsy at distal leg and distal thigh			X					X								X
WPAIQ			X			X		X								
NeuroQoL Questionnaire			X			X		X				X				X
Skin Perfusion Pressure (SPP)			X			X		X								
Quantitative Sensory Test (QST) thermal			X					X				X				X
Sural Nerve Conduction Studies (NCS)			X					X								X
Study Device Training			X													
Assess Biopsy Treatment Site				X												
Study Device Blinding Assessment				X				X								
Assess Adverse Events			X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Assess Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Impression (PGI)					X	X	X	X				X				X
Review Device Usage Report				X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Satisfaction					X	X	X	X				X				X
Return Study Device								X								X
Enroll Subject in Part B of protocol in ePRO and dispense device								X								

1. Inclusion/Exclusion criteria must be reviewed to ensure patient continues to qualify for the study.
2. Average pain score over the 7 days preceding the visit will be calculated in the EDC system and verification of inclusion pain score ≥4 and <9 and compliance of ≥70% will be determined at the Enrollment Visit.
3. Medical History will be reviewed at the Enrollment Visit for any changes.
4. Urine pregnancy test will be performed on women of child-bearing potential.
5. Weight will be measured at the end of Part A and at the end of Part B.
6. Assessment of adverse events will be conducted after the signing of the Informed Consent.
7. Adherence to ePRO entries will be assessed at the Enrollment Visit for inclusion.
8. Adherence to diary completion will be completed at the 6M, 8M, 10M, and 12M visits.

APPENDIX B: AMERICAN DIABETES ASSOCIATION CRITERIA FOR DIAGNOSIS OF DIABETES

FPG ≥ 126mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours*

OR

2-hour PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water. *

OR

A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Note. Criteria for diagnosing diabetes Table 2.2. Referenced from "Standards of Medical Care in Diabetes 2018," American Diabetes Association, 2018, The Journal of Clinical and Applied Research and Education, V41, Supplement 1, p.S15. 2018.