CLINICAL STUDY PROTOCOL

Study Title:	**An Open-Label, Non-Controlled Study to Evaluate Outcomes of Pulsed Electromagnetic Field (PEMF) Therapy in Subjects with Various Pain Etiologies**
Protocol Number:	RBI.2015.005
Version:	B
Phase:	Post-Market
Sponsor:	Regenesis Biomedical, Inc. 5301 N. Pima Road Scottsdale, AZ 85250
Medical Contact:	Adrianne P.S. Smith, M.D. Vice President, Clinical Business and Education Regenesis Biomedical, Inc.
Final Approval Date:	18 January 2017

PROTOCOL SIGNATURE PAGE – SPONSOR

Study Title: **An Open-Label, Non-Controlled Study to Evaluate Outcomes of Pulsed Electromagnetic Field (PEMF) Therapy in Subjects with Various Pain Etiologies**

Protocol Number: RBI.2015.005

Version: B

The undersigned acknowledges that he/she has received and read Protocol RBI.2015.005, Version B, dated 18 January 2017.

Sponsor Representatives	Signature	Date
Adrianne P.S. Smith, M.D. Vice President, Clinical Business and Education		
Jamie Muhlenfeld Director Clinical Research		

PROTOCOL SIGNATURE PAGE – Principal Investigator

Study Title: **An Open-Label, Non-Controlled Study to Evaluate Outcomes of Pulsed Electromagnetic Field (PEMF) Therapy in Subjects with Various Pain Etiologies**

Protocol Number: RBI.2015.005

Version: B

The undersigned acknowledges that he/she has received and read Protocol RBI.2015.005, Version B, dated 18 January 2017.

Principal Investigator	Signature	Date

DOCUMENT REVISION HISTORY		
	Date	Summary of changes
Version A	01/11/2016	Original document
Version B	1/18/2017	Updated to include the Numeric Pain Rating Scale (NPRS), Clinical Global Impression – Global Improvement (CGI-I) Scale, Patient Global Impression of Change (PGIC) and 3-Month follow-up and signature line for Dr. Smith.

Study Synopsis

Study Title	**An Open-Label, Non-Controlled Study to Evaluate Outcomes of Pulsed Electromagnetic Field (PEMF) Therapy in Subjects with Various Pain Etiologies**
Protocol Number	RBI.2015.005
Name of Study Device	Provant® Therapy System
Phase of Development	Post-Market
Objective	To obtain data on the safety and effectiveness of PEMF treatment in patients with various pain etiologies. Data from enrolled patients will contribute to a patient registry on the post-market use of Provant.
Number of Subjects	Up to 300 subjects will be enrolled.
Study Design	This is an open-label, non-controlled trial in subjects with various pain etiologies at multiple centers in the US. Eligible subjects will include those ≥ 22 years of age that have been deemed appropriate for treatment with Provant by the study investigator (prescriber). Subjects will treat based on the treatment prescribed (location, frequency, duration) by the study investigator.
Assessments	Data from assessments administered as part of standard of practice will be obtained at baseline and, at a minimum, at the end of treatment. Protocol required assessments will include baseline, interim visit / end of treatment visit and 3-month follow-up (post-treatment) pain scores using an 11-point numeric pain rating scale (NPRS), and a Clinical Global Impression – Global Improvement (CGI-I) Scale and a Patient Global Impression of Change (PGIC) Scale administered at follow-up / end of treatment visits. If the investigator administers additional assessments during the course of treatment, the data will be collected. Safety will be assessed during office visits and through review of AE reports and concomitant treatments and medications. All concomitant drug or non-drug treatments used during the study will be recorded.
Study Procedures	Subjects will be evaluated for eligibility at the Screening/Enrollment Visit. Following assessment of eligibility, subjects will be assessed using standard of practice baseline measures and the NPRS related to the location of treatment. Subjects will be instructed in the use of the device and will self-treat as prescribed by the study investigator. As part of the investigator's standard of practice, subjects may be provided with a patient reported outcome form(s) for capturing their daily pain

	scores, which may include a 11 point numerical pain score scale, or other patient-reported outcomes related to the pain etiology. Subjects will document outcomes as instructed by the site at the Enrollment Visit. The site will contact the subject via telephone or the subject will come for an interim visit at regular intervals (to be determined by the investigator based on treatment regimen and standard of practice) to assess subject adherence to treatment, completion of patient reported outcomes, NPRS, CGI-I, PGIC and any safety concerns and/or changes in concomitant treatments/medications. After up to 20 weeks of treatment, the subject will return to the clinic for a final assessment that will include the NPRS, CGI-I and PGIC. Adverse events and changes in concomitant medications will be collected. Three months post-treatment, a follow-up phone call will be made to collect the NPRS.
Study Device	The study device is the Provant® Therapy System which delivers Pulsed Electromagnetic Field (PEMF) energy therapy. Each device will be identified by a unique serial number.
Study Sample	The anticipated enrollment in this study is up to 300 subjects. The study will be conducted at multiple (up to 25) sites.
Outcome Measures	Outcome measures will be assessed in order to allow for characterization of the response to PEMF therapy. **<u>Efficacy Assessments</u>** Outcome measures of response to treatment with Provant will be determined based on the pain and/or edema being treated. The initial evaluations will include treatment of post-surgical hand edema, arterial insufficiency, diabetic peripheral neuropathy, abdominoplasty and other plastic surgeries, post-hernia surgical pain, and pelvic pain. All outcome measures used as part of the standard of practice regimen will be non-invasive assessments e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects. Protocol required assessments will include the NPRS, CGI-I and PGIC. **Subject adherence** (compliance with the prescribed treatment regimen) will be assessed verbally during follow-up and upon completion of the treatment period. A subject with complete adherence will be expected to have a usage meter reading of 1.0 for every hour that the subject treated.

Statistical Considerations	Safety summaries will be conducted on all subjects who undergo treatment. The summaries on the efficacy parameters will be conducted on subjects completing the given evaluation at that given time point. No imputation will occur. If subjects need to discontinue the study prior to the prescribed treatment duration, attempts will be made to conduct the final visit evaluations at the time of discontinuation. Demographic and subject characteristics will be summarized using descriptive statistics. Assessments that are measured on a continuous scale will be summarized descriptively using the mean, standard deviation, median, minimum, and maximum value by time. Variables that are measured on a categorical scale will be summarized as a proportion of the population. The change from baseline will be summarized for assessments in common between subjects/sites and 95% confidence intervals constructed. Adverse events will be summarized using MedDRA categories and by severity and relationship. Concomitant medications will be summarized by WHODrug categories. This is an open-label, non-controlled study with no formal hypothesis testing planned. Data will be collected through an Electronic Data Capture system as part of a registry to evaluate the use of Provant post-market.

LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Global Improvement Scale
eCRFs	Electronic Case Report Form
FBSS	Failed Back Surgery Syndrome
FDA	Food & Drug Administration
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MHz	Megahertz
NPRS	Numeric Pain Rating Scale
PEMF	Pulsed Electromagnetic Field
PGIC	Patient Global Impression of Change
PRFE	Pulsed Radio Frequency Energy
PRN	As Needed
RF	Radiofrequency
RFID	Radio Frequency Identification Device
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
WHO	World Health Organization

I. INTRODUCTION AND BACKGROUND

This study is being conducted to evaluate the effectiveness of the pulsed electromagnetic energy fields provided by the Provant® Therapy System (Provant) to treat pain and edema of multiple etiologies. Provant 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 of soft tissue." The device delivers self-administered, non-thermal, non-ionizing pulsed electromagnetic energy to the target tissue, using 27.12 MHz pulses lasting 42 microseconds and delivered 1000 times per second. The system generates an electromagnetic field that is continuously monitored and regulated to ensure consistent dosing. The therapeutic electromagnetic field is delivered by means of an applicator pad that is placed against the treatment site. The device is non-invasive and does not require placement of surface or deep electrodes, nor removal of bandages or clothing. Treatment is usually imperceptible and very well tolerated. Evidence suggests that Provant can reduce pain, promote healing, and promote restored range of motion following reparative surgery in wounded extremities. [Guo 2011, Moffett 2011] As an analgesic, it is non-addictive and does not alter the mental state of the user.

Regenesis Biomedical, Inc., has marketed Provant since 2004 and has treated over 11,500 patients within the U.S. Over two million individual treatments have been administered with rare adverse events reported. [FDA MAUDE Database 2014] In addition, the safety of PEMF has been well documented. The 2012 meta-analysis by Guo et al [Guo 2012] of 25 clinical trials of PEMF in treatment of pain, edema and wound healing identified no serious adverse events among 1,332 patients treated with PEMF. In addition, the same meta-analysis found statistically significant evidence supporting the efficacy of adjunctive PEMF therapy for pain relief, edema reduction, and wound healing promotion. Finally, adjunctive PEMF therapy has been reported effective in alleviating pain resulting from trauma, [Comorosan 1991, Foley-Nolan 1992, Wilson 1972, Barclay 1983, Pennington 1993, Shandles 2002] and chronic pain. [Foley-Nolan 1990, Wagstaff 1986, Brook 2012].

In vitro and in vivo evidence suggest PEMF functions by modulating factors involved in pain signaling and soft tissue repair. In vitro studies demonstrated that Provant treatment of cells in culture can mediate wide-spread changes in transcript levels encoding factors involved in pain and the inflammatory response (including endogenous opioids, growth factors, cytokines, and cell cycle regulating factors), [Moffett 2011, Moffett 2012, Rohde 2010] and can promote cell proliferation. [George 2002] 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. [Moffett 2012a, Moffett 2012b] These findings have led to the proposition that PEMF activates peripheral endogenous opioids which, in turn, activate an analgesic cascade via the endothelin pain axis. In a recent clinical study, PEMF usage for post-operative pain not only reduced pain levels and opioid consumption relative to sham-treated patients, but was also associated with lower IL-1ß levels in post-operative wound exudates. [Rohde 2010] Together, these

findings suggest that PEMF therapy reduces pain both by modulating inflammation and by activating peripheral endogenous opioids.

An exploratory prospective single-arm open-label IRB-approved study was recently conducted at four geographically distributed sites using the Provant device to treat persistent postoperative failed-back surgery syndrome (FBSS) pain. Thirty FBSS subjects with moderate to severe axial back and/or radicular leg pain were treated for 45 days with twice-daily Provant PEMF therapy. [Harper 2015].

Subjects were eligible for enrollment if they had a history of 1 or 2 lumbar spine surgeries with persistent axial and/or radicular leg pain 3 to 36 months (inclusive) following the most recent lumbar spine surgery, and had a mean Pain Intensity score of 4 or greater (0-10 numeric pain rating scale) for either axial or radicular pain during a 5-day run-in baseline period.

Thirty subjects in this study were evaluated for the effectiveness of the Provant Therapy System in the treatment of post-surgical pain after back surgery. Provant treatment twice daily for 45 days was associated with improved pain scores, improved overall well-being, improved physical function, and reduced analgesic consumption, especially in subjects who had undergone a discectomy.

The purpose of the current study is to confirm the findings of pain relief observed in patients receiving treatment with Provant in a “real-world”, post-market setting. Data from this study may be combined with other studies conducted in the post-market setting, i.e., in a patient registry.

II. STUDY OBJECTIVES

This study is designed to provide post-market evidence of the safety and effectiveness of the Provant Therapy System for improving pain and edema in subjects with multiple pain etiologies.

III. STUDY DESIGN

A. Study Design

The study is an open-label, non-controlled study of the safety and effectiveness of investigator determined Provant therapy in subjects with pain and/or edema from various pain etiologies.

B. Efficacy Assessments

Outcome measures of response to treatment with Provant will be determined based on the location of the subject's treatment area. Protocol required assessments will include baseline and interim / end of treatment visit and 3-month follow-up (post-treatment) pain scores using an 11-point numeric pain rating scale (NPRS), and a Clinical Global Impression – Global Improvement (CGI-I) Scale and a Patient Global Impression of Change (PGIC) Scale. All outcome measures used in the investigator's standard of practice are non-invasive assessments, e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects.

C. Safety Evaluation

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

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

D. Eligibility Criteria

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

1. Inclusion Criteria

1. Subject age is greater than or equal to 22 years.
2. Subject has pain (chronic or acute) and/or edema that the prescriber deems treatment with Provant is warranted.

3. Subject is willing and able to give written informed consent.

4. Female subjects must be post-menopausal, surgically sterile, abstinent, or practicing (or agree to practice) an effective method of birth control if they are sexually active for the duration of the study. (Effective methods of birth control include prescription hormonal contraceptives, intrauterine devices, double-barrier methods, and/or male partner sterilization).

2. Exclusion Criteria

1. Subject requires or anticipates the need for surgery of any type during the duration of treatment.

2. Subject has received any investigational drug or device within 30 days or 5 half-lives of the drug, whichever is longer, prior to the Screening Visit or is enrolled in another clinical trial.

3. Subject has used systemic corticosteroids within 2 months of the Screening Visit.

4. Subject has a history of a solid tumor that is not in complete remission for greater than 2 years other than successfully treated non-metastatic basal cell or squamous cell carcinomas of the skin in the treatment area.

5. Subject has a history of blood cancer (e.g., leukemia, lymphoma, multiple myeloma).

6. Subject has a serious psychosocial co-morbidity.

7. Subject has a history of drug or alcohol abuse within one year prior to the Screening Visit.

8. Subject has an implanted pacemaker, defibrillator, neurostimulator, spinal cord stimulator, bone stimulator, cochlear implant, or other implanted device with an implanted metal lead(s).

9. Subject is currently pregnant or planning on becoming pregnant during the treatment period.

10. Subject has been previously treated with the Provant Therapy System.

11. Subject is unwilling or unable to follow study instructions, or comply with the treatment regimen and study visits.

E. Recruitment

Study subjects will be drawn from the investigative site.

F. Randomization

This is an open-label study. No subject randomization will occur. Each Provant Therapy System will have a unique serial number that will be recorded on the eCRFs.

G. Device Description

The Provant Therapy System is a solid-state, fixed-power output radio frequency generator and transmitter designed to operate at the Federal Communication Commission authorized medical device frequency of 27.12 MHz. The Provant System's primary components are the Control Unit, the Treatment Applicator that generates and delivers the shortwave RF energy, and single-use Disposable Applicator Covers intended to minimize contagion transmission and help protect the Treatment Applicator from biological contamination. Key functions and features of these components are as follows:

1. Control Unit

The Control Unit contains the main electronics, software, and user interface of the Provant System. The Control Panel has a Therapy Start/Stop Switch and two Therapy Status Indicators, described below, which are located on the top of the Control Panel, as well as a Usage Meter on the side of Control Panel.

Pressing the Therapy Start/Stop Switch initiates a preset, thirty (30)-minute therapy session by starting the Radio Frequency Identification Device (RFID) Tag interrogation and treatment sequence described in greater detail below. Pressing the Therapy Start/Stop Switch again after a therapy session has started will stop the RF energy generation. When pressed, the therapy Start/Stop switch generates an audible tone to inform the user that therapy is being initiated or terminated.

The two Therapy Status Indicators on the Control Panel indicate when therapy is underway and the amount of time (in minutes) remaining in the therapy session. When treatment is initiated, the message "CPI RUNNING" is displayed and green bars scroll from left to right across the indicator window. When the thirty-minute therapy session is concluded, the generation of RF energy is automatically terminated, the Therapy Status Indicator windows go blank, and a brief audible beep is generated to alert the user that the treatment is finished. The user will then be instructed to turn off the Power Switch, remove the used Disposable Applicator Cover, and store the Treatment Applicator and cable until the next use.

2. Disposable Applicator Covers.

The Provant Therapy System features Disposable Applicator Covers, which are placed over the Treatment Applicator (described below) before each therapy session. The Disposable Applicator Covers of the Provant Therapy System are single-use-only and are intended to minimize contagion transmission and help protect the Treatment Applicator from biological contamination. Embedded in the Disposable Applicator

Covers is RFID reader functionality that is controlled by software in the Provant Control Unit. This software prevents the reuse of a Disposable Applicator Cover by confirming that a new Disposable Applicator Cover is in place before allowing the generation and delivery of the therapeutic RF energy. If the user attempts to reuse a cover, the device recognizes the RFID tag on the cover at start up as "used" and will generate an audible alert to inform the user to replace the used cover with a new cover. If the user attempts to use the device without a Disposable Applicator Cover in place over the Treatment Applicator, the device will generate an audible alert to remind the user to place a new cover. In either scenario, the Provant Therapy System will not initiate a therapy session until a new Disposable Applicator Cover is in place. The used Disposable Applicator Covers will be discarded as standard (not bio-hazard) waste.

3. Treatment Applicator Pad

The Provant Therapy System delivers pulsed RF energy to the desired treatment area via a spiral antenna in the Treatment Applicator Pad. The Treatment Applicator Pad 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 Pad and sends this information to the controller for the RF Generator. This feedback circuit is used to regulate the RF therapy level, as the RF circuit reactance changes due to changes in body capacitance. In this way, the correct energy output is constantly monitored, regulated, and maintained at the preset therapy dose levels.

The Provant Therapy System generates pulsed RF energy using a highly efficient Class-C RF amplifier. Subjects 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 Pad circuit board for the preset 30-minute duration of therapy.

The amount of forward RF energy emitted from the Treatment Applicator Pad is preset at 591 ± 44 V/m at a distance of 5.0 cm from the radiating surface of the Treatment Applicator Pad. The amount of radiated RF energy diminishes with increasing distance from the radiating surface of the Treatment Applicator Pad. 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 Pad detects an absent or out of range therapy dosage level, treatment will not occur and the message "Service Required" will be displayed on the LED indicator window. In such an event, the Research Center will trouble shoot the issue as instructed in the Instructions for Use which accompanies the Study Device, and if unsuccessful in resolving the matter, will contact the sponsor to access a replacement device.

H. Logistics and Device Accountability

The investigator or delegated designee will ensure that all study devices are stored in a secured area, in accordance with applicable regulatory requirements.

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

I. Labeling

The Provant Therapy System will be labelled per commercial labelling which includes the Instruction for Use Manual and product labelling with product name and serial number.

J. Preparation and Administration

Each subject will receive one device to use. All treatment sessions will be self-administered by the subject or his/her family or caregiver in the home or similar setting.

Subjects will assume a comfortable position and place the treatment applicator pad of the Provant device on the location as identified by the investigator. Treatment will be administered continuously for 30 minutes. Thereafter, subjects will self-administer treatments as prescribed by the investigator.

Prior to initiation of each treatment session, the subject will take the Treatment Applicator Pad of the study device and insert it into a new Disposable Applicator Cover. When inserted properly, the yellow starburst logo on the Treatment Applicator Pad is aligned with the same logo on the Disposable Applicator Cover, and the words “This side towards patient” will be visible through the clear window of the Disposable Applicator Cover. When applied to the treatment area, the side of the Treatment Applicator Pad with the yellow starburst logo is directed toward the treatment location. Further directions for use of the Provant Therapy System are found in the Instruction Manual. Upon completion of the treatment session, the subject will remove and discard the Disposable Applicator Cover, and store the Provant device until the time of the next scheduled treatment session. Disposable Applicator Covers may be discarded as standard waste.

K. Blinding

This is an open-label study. No blinding will occur.

L. Study Assessments

1. Efficacy Assessments

Efficacy assessments conducted during the Enrollment Visit (Day 0) and, at a minimum, at the completion of treatment will be collected.

Outcome measures of response to treatment with Provant will be determined based on the location of the subject's treatment area. Protocol required assessments will include baseline and interim / end of treatment visit and 3-month follow-up (post-treatment) pain scores using an 11-point numeric pain rating scale (NPRS), and a Clinical Global Impression – Global Improvement (CGI-I) Scale and a Patient Global Impression of Change (PGIC) Scale. All outcome measures administered as part of non-invasive standard of practice assessments will be collected, e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects.

2. Safety Assessments

Safety will be assessed through review of AE reports and concomitant treatments and medications. All concomitant drug or non-drug treatments used will be recorded. Safety outcomes will be assessed at office visits as defined by the treatment regimen.

IV. STUDY PROCEDURES

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

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

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

1. Informed consent review and signature.
2. Review Inclusion and Exclusion criteria.
3. Collect subject demography data (including age, weight, height, gender, and race/ethnicity).
4. Collect Medical and Surgical History.
5. Review and record all concomitant medications.
6. Perform a urine pregnancy test for females of child bearing potential.
7. If the subject meets the eligibility criteria, continue on to the Enrollment Visit.

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

B. Visit 2 – Enrollment Visit (Day 0)

The following procedures will be performed:

1. Review Inclusion/Exclusion criteria (if Screening/Enrollment visits not combined).

2. Review and record any changes in medical history and study eligibility criteria since screening (if Screening/Enrollment visits not combined).
3. Review and record adverse events (if Screening/Enrollment visits not combined).
4. Review and record any changes in concomitant medications (if Screening/Enrollment visits not combined).
5. Conduct baseline efficacy assessments.

   Response to treatment with Provant will be determined based on the location of the subject's treatment area. Assessments will include the NPRS and non-invasive assessments part of the investigator's standard of practice e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects.
6. If the subject continues to meet eligibility criteria, enroll subject, and dispense study device.
7. Introduce and train the subject on the use of the Provant Therapy System, including instructions for proper positioning and operation of the device.
8. If applicable, distribute a patient diary and instruct the subject on how to complete. Examples of diary collection tools are provided in Appendix B.

During this visit, eligible subjects will receive a Provant device and up to 120 Disposable Applicator Covers (packs of 30, depending on the anticipated treatment duration) and the subject will be instructed to administer treatment as prescribed by the investigator.

C. Treatment Period

Treatment may be self-administered by the subject, or with the assistance of a family member or caregiver. Subjects will assume a comfortable position and place the treatment applicator pad of the Provant device centering the applicator pad on the treatment location as instructed by the investigator. Treatment will be administered for 30 consecutive minutes.

Subjects will be asked to complete the patient reported outcome form(s) as instructed (as applicable).

D. Interim Visits

Subjects will be required to return to the clinic during the course of treatment as instructed by the investigator. Telephone follow-ups may also be performed with each subject as determined by the investigator. At these interim visits, the following will be collected if assessed:

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

4. Assess completion of the patient reported outcome form(s), as applicable
5. Conduct efficacy assessments:

   Response to treatment with Provant will be determined based on the location of the subject's treatment area. Assessments will include the NPRS, CGI-I, PGIC and non-invasive assessments part of the Investigators standard of practice e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects.

E. End of Treatment Visit

Subjects will return to the clinic after completion of treatment as required by the study investigator. At this visit, the following procedures will be performed:

1. Collect subject's weight
2. Review and record adverse events
3. Review and record all concomitant medications
4. Conduct efficacy assessments:

   Response to treatment with Provant will be determined based on the location of the subject's treatment area. Assessments will include the NPRS, CGI-I, PGIC and non-invasive assessments part of the Investigators standard of practice e.g., pain scores, SF-36, ankle-foot scales, oxygen perfusion (MOXY), and diaries with some subjects.
5. Return of study device and unused DACs
6. Return of the patient reported outcome form(s), as applicable. Examples of diary collection tools are provided in Appendix B.

F. Post-treatment Phone Call

Three months after the End of Treatment Visit, subjects will be contacted via telephone and asked to rate their pain using the NPRS.

G. Treatment adherence/study compliance

Subject adherence (compliance with the prescribed treatment regimen) will be assessed during interim visits and upon completion of the treatment period by the research staff reading and recording the number displayed on the study device usage meter. The usage meter will read 0.0 when dispensed. A subject with complete adherence will be expected to have a usage meter reading of 1.0 for each hour of treatment.

Subjects will be instructed to return any unused DACs at the End of Treatment visit. Compliance will be assessed by counting the number of returned, unused DACs, and subtracting this from the total number of DACs dispensed (120). As each treatment session requires one new DAC, compliance can be calculated based on the number of returned DACs relative to the prescribed regimen.

H. Protocol Adherence

If protocol modifications are necessary, all alterations that are not solely of an administrative nature require a formal protocol amendment.

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

I. 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. Based on the subject's pain etiology, the investigator may disallow certain concomitant medications in order to accurately assess the effect of Provant therapy. Opioid or other pain drug therapies may be reduced or discontinued during the treatment period of the study as directed by the subject's treating physician.

It is important to record the reason why each analgesic medication is being taken by the subject, specifically analgesics taken for treatment of pain/edema. In this context, "analgesic medications" refers to medications prescribed and administered for the treatment of pain, and includes but is not limited to opioids, nonsteroidal anti-inflammatory agents, anti-depressants and muscle relaxants.

Prohibited Medications/Treatments

The following medications and therapeutics are prohibited throughout the study:

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

V. WITHDRAWAL PROCEDURES

If a subject or the prescriber decides to discontinue the subject's treatment with the device, efforts will be made to perform all assessments scheduled for the End of Treatment Visit prior to subject withdrawal.

VI. STATISTICAL CONSIDERATIONS

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

Where not otherwise specified, the last pre-treatment observation will be used as baseline for calculating post-treatment changes from baseline. All confidence intervals will use a significance level of 5%.

A. Study Populations

Safety summaries will be conducted on all subjects who undergo treatment.

The effectiveness summaries will also be conducted on all subjects who undergo treatment. Subjects that do not attend the End of Treatment Visit will be excluded from the End of Treatment analyses. Subjects who complete the End of Treatment Visit will be assessed for efficacy regardless of the number of days of treatment received. No imputation of data will occur.

B. Efficacy Data Summaries

Demographic and subject characteristics will be summarized using descriptive statistics. Assessments that are measured on a continuous scale will be summarized descriptively using the mean, standard deviation, median, minimum, and maximum value by time. Variables that are measured on a categorical scale will be summarized as a proportion of the population.

The change from baseline will be summarized for effectiveness outcome assessments in common between subjects/sites and 95% confidence intervals constructed.

Adverse events will be summarized using MedDRA categories and by severity and relationship. Concomitant medications will be summarized by WHODrug categories.

C. Adverse Events

All adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Safety assessments will include treatment-emergent adverse events (TEAEs; adverse events that occur in subjects who undergo treatment). Subjects with TEAEs will be summarized with frequencies and percentages by system organ class and preferred term, severity, and relationship to treatment for each treatment group. Treatment-related adverse events will be defined as adverse events with investigator assessment of related or possibly related. In summaries of TEAEs by severity and relationship to study device, subjects 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 subjects with at least one adverse event will be tabulated. The number of adverse events will also be tabulated. The number of subjects and the number of adverse events will be tabulated by severity and relationship.

D. Sample Size

This is an open-label, non-controlled study with no formal hypothesis testing planned. It is anticipated that up to 300 subjects will be enrolled in this study. Data from this study will be included in a patient registry. The statistical analysis plan for the patient registry will fully describe the methods used to evaluate data from this study.

VII. INFORMED CONSENT

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate IRB-approved forms for obtaining written informed consent will be provided by the investigator or by Regenesis Biomedical, Inc. or their designee.

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

VIII. INSTITUTIONAL REVIEW BOARD

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

IX. TERMINATION OF THE INVESTIGATION

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

Additionally, data will be reviewed by the sponsor on a regular basis. Reports of 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.

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

X. ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

A. Adverse Events

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

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

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

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

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

Related: This causal relationship is assigned when the AE:

- 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 following:

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

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

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

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

B. Anticipated Adverse Device Effects Associated with Provant

Anticipated adverse events associated with Provant, reported at least once since market launch in 2004, are as follows:

- Device fails to operate
- Warmth or burning at treatment site
- Skin reaction at treatment site (tingling, pins-and-needles, rash, blisters, swelling, dry skin, redness, numbness, sensation of warmth)
- Increased bleeding at surgical site
- Chilliness
- Headache
- Malaise
- Nausea

- Abdominal or chest wall discomfort
- Muscle cramps
- Failure to reduce pain or an increase in pain
- Metallic taste in mouth
- Exacerbation of tinnitus
- Stiffness
- Weakness
- Dizziness/lightheadedness
- Restless leg syndrome
- Strong urine odor
- GI/upset stomach
- Excessive menstruation

C. Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or informed consent form, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

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

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

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

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

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

XI. INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

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

authorization forms and other appropriate documents/correspondence. All records defined in 21 CFR 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.

A. Source Documents and Background Data

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

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

B. Audits and Inspections

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

XII. MONITORING THE STUDY

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

If a monitoring visit is scheduled, the monitor may inspect the patient charts for completeness, consistency and accuracy of the data captured. The monitor should have access to laboratory test reports and other subject records needed. The investigator (or his/her designee) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

XIII. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Regenesis Biomedical, Inc., e.g., subjects' written consent forms, in strict confidence.

XIV. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

XV. REFERENCES

Barclay V, Collier RJ, Jones A. Treatment of various hand injuries by pulsed electromagnetic energy (Diapulse). Physiotherapy. 1983; 69: 186–188.

Brook J, Dauphinee DM, Korpinen J, Rawe IM. Pulsed Radio Frequency Electromagnetic Field Therapy: A Potential Novel Treatment of Plantar Fasciitis. J Foot Ankle Surg 2012; 51(3):312-6

Comorosan S, Pana I, Pop L, et al. The influence of pulsed high peak power electromagnetic energy (Diapulse) treatment on posttraumatic algoneurodystrophies. Rev Roum Physiol. 1991; 28:77–81.

FDA MAUDE and MDR databases searched on June 15, 2014 reveals 5 medical device reports related to PEMF in any indication.

Foley-Nolan D, et al. Pulsed high frequency (27MHz) electromagnetic therapy for persistent neck pain. A double blind, placebo-controlled study of 20 patients. Orthopedics 1990; 13(4): 445-51.

Foley-Nolan D, Moore K, Codd M, and et al. Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries: a double blind randomized controlled study. Scand J Rehabil Med. 1992; 24(1): 51-9.

George FR, Lukas RJ, Moffett J, Ritz MC. In vitro mechanisms of cell proliferation induction: a novel bioactive treatment for accelerating wound healing. Wounds 2002; 14(3):107-115.

Guo L, Kubat NJ, Isenberg RA. Pulsed radio frequency energy (PRFE) use in human medical applications. Electromagn Biol Med 2011; 30(1):21-45.

Guo L, Kubat NJ, Nelson TR, Isenberg RA. Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment. Ann Surg 2012;255(3):457-67.

Harper WL, Schmidt WK, Kubat NJ, Isenberg RA. An open-label pilot study of pulsed electromagnetic field therapy in the treatment of failed back surgery syndrome. International Medical Case Reports Journal 2015;8:13-22

Moffett J, Kubat NJ, Isenberg RA. Pulsed radio frequency energy as an effective pain treatment. Practical Pain Management 2011; 11(3):71-73.

Moffett J, Fray L. Cellular and molecular mechanisms of peripheral pain inhibition by treatment with pulsed radio frequency energy: the role of endogenous opioid induction in human fibroblasts and keratinocytes. J Pain 2012; 13(4) Suppl: S42.

Moffett J, Fray L, Kubat N. Activation of Endogenous Opioid Gene Expression in Human Keratinocytes and Fibroblasts by Pulsed Radio Frequency Energy Fields. Journal of Pain Research 2012; 5:347-357.

Pennington G.M., et al., Pulsed, non-thermal, high-frequency electromagnetic energy (DIAPULSE) in the treatment of grade I and grade II ankle sprains. Mil Med, 1993. 158(2): p. 101-4.

Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA. Effects of pulsed electromagnetic fields on interleukin-1beta and post-operative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. Plast Reconstr Surg 2010;125(6):1620-27.

Shandles I.D., Pruchniewski J., Reynolds K.L., Heel Neuroma: the enigma of recalcitrant heel pain and an innovative approach highlighting sixty surgical cases and a review of two hundred and fifty

seven symptomatic but non-surgical cases. The Foot, 2002. 12: 10-20.

Wagstaff P., Wagstaff S., Downey M., A pilot study to compare the efficacy of continuous and pulsed magnetic energy [shortwave diathermy] on the relief of low back pain. Physiotherapy, 1986. **72**: p. 563-566.

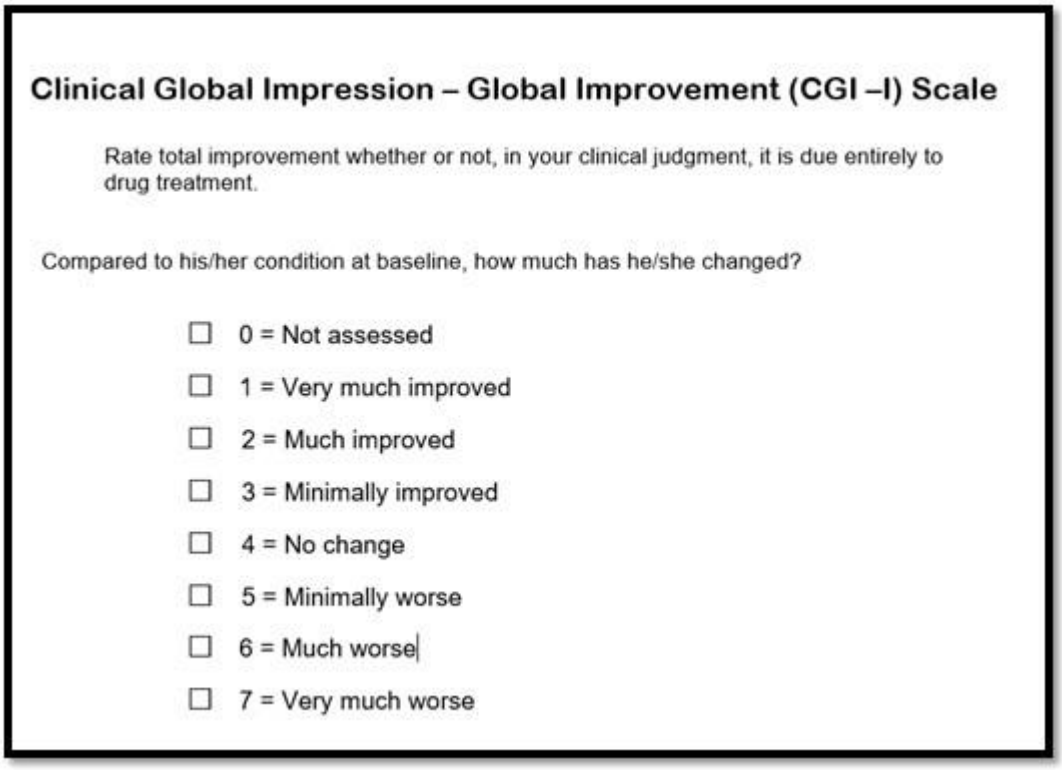
Wilson DH. Treatment of soft-tissue injuries by pulsed electrical energy. Br Med J 1972; 2: 269–270.

APPENDIX A - TIME AND EVENTS SCHEDULE

Period	Screening Visit	Enrollment (Baseline) Visit[1]	Treatment Period	Interim Visits	End of Treatment Visit	Follow-up Phone Call
Study Day	**-14 to 0**	**0**	**As Prescribed**	**As Prescribed**	**As Prescribed**	**3 months post-treatment**
Informed Consent	X					
Demographic Information	X					
Medical/Surgical History	X					
Urine Pregnancy Test[2]	X					
Height and Weight	X				X[7]	
Inclusion/Exclusion Criteria	X	X				
Efficacy Outcomes Assessments (Including NPRS, CGI-I and PGIC)		X[3]		X[3]	X[3]	X[3]
Study Device Training		X[4]				
Dispense Study Device		X				
Distribute Diary Collection Tool(s)		X[5]				
Study Device Treatment			X[6]			
Assess Adverse Events and Concomitant Medications	X[8]	X		X	X	
Assess Subject Adherence to Treatment				X	X	
Collect Diary Collection Tool(s)				X	X	
Return Study Device and Unused DACs					X[9]	

1. The Screening Visit and the Enrollment Visit may occur on the same day in which case none of the screening tests need to be repeated.
2. Urine pregnancy test will be performed on women of child-bearing potential.
3. The CGI-I and PGIC will not be conducted at the Enrollment (Baseline) Visit. Only the NPRS will be captured at the Follow-up phone call.
4. Introduction to and training on the study device will be completed during the Enrollment Visit.
5. Distribution of a diary collection tool will occur if the investigator decides to use this as a means for capturing patient reported outcomes. Completion of the forms will occur as instructed by the investigative site, as applicable.
6. The subject will self-administer treatments as prescribed by the investigator.
7. Collect only weight at End of Treatment Visit.
8. Assessment of adverse events will be conducted after the signing of the Informed Consent.
9. At the End of Treatment Visit subjects will return the study device and all unused Disposable Applicator Covers (DACs).

APPENDIX B – CLINICAL GLOBAL IMPRESSION -GLOBAL IMPROVEMENT (CGI-I) SCALE



Clinical Global Impression – Global Improvement (CGI –I) Scale

Rate total improvement whether or not, in your clinical judgment, it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has he/she changed?

- ☐ 0 = Not assessed
- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

APPENDIX C – PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

PATIENT GLOBAL IMPRESSION OF CHANGE

Since the start of the study, the subject reports their overall status as: (check one box only)

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

APPENDIX D – EXAMPLES OF DIARY COLLECTION TOOLS

Response to Study Device Form

Day 1 - Day ____

Subject #: ____ ____ - ____ ____ ____ Subject Initials: ____ ____ ____

Instructions: Enter the date as instructed by your study investigator and select the one number that best indicates the average intensity of pain you have had over the last 24 hours in the area you are treating.

Day 1 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day 2 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day 3 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day 4 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day 5 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day 6 - Date: _____

Pain Intensity Assessment (NPRS) Questionnaire										
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Day ___ Date: _______________

Pain Intensity Assessment (NPRS) Questionnaire										
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

You have completed your Day 1 - Day ___ Forms. Please return this packet to the clinic staff at your next Visit.

Medication Consumption

Day 1 - Day ____

Subject #: ____ ____ - ____ ____ ____ Subject Initials: ____ ____ ____

Instructions: Enter the date as instructed by your study investigator and list the medication(s) taken for your pain in the provided field(s) along with the number of pills you have taken over the last 24 hours.

Day 1 - Date: _____

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day 2 - Date: _____

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day 3 - Date: _____

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day 4 - Date: _____

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	

Day ____ - Date: _______________

Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	
Medication Name:		Number of Pills Taken:	