STATISTICAL ANALYSIS PLAN

PRODUCT UNDER INVESTIGATION:

PROVANT® Therapy System

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

STUDY SPONSOR
Regenesis Biomedical, Inc.
5301 N. Pima Road, Suite 150
Scottsdale, AZ 85250

PREPARED BY
Bruce C. Stouch, Ph.D.
571 Coconut Palm Terrace
Plantation, FL 33324

DATE AND VERSION
November 7, 2018 (Version 3.0)
(Based on the protocol dated July 17, 2018 – version C)

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DOCUMENT NUMBER: RBI.2017.002–SAP-003

TITLE

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APPROVALS

Name and Title	Signature	Date
Scott Brooks CEO Regenesis Biomedical, Inc.		
Bruce C. Stouch, Ph.D. Biostatistician		

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1. LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ABI	Ankle-Brachial Index
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRA	Clinical Research Assistant / Associate
CSR	Clinical Study Report
DSPN	Diabetic Distal Symmetric Peripheral Neuropathy
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
FCC	Federal Communication Commission
FDA	Food & Drug Administration
Ha	Alternative hypothesis
Ho	Null hypothesis
ICH	International Conference on Harmonization
IENFD	Intraepidermal Nerve Fiber Density
IQR	Inter-Quartile Range
IRB	Institutional Review Board
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
NeuroQoL	Neuropathy Quality of Life Questionnaire
NCS	Nerve Conduction Studies
NPRS	Numeric Pain Rating Scale
PEMF	Pulsed Electromagnetic Field
PGI	Patient Global Impression
PP	Per Protocol
PRFE	Pulsed Radio Frequency Energy
PRN	As Needed
QA	Quality Assurance
QC	Quality Control
QST	Quantitative Sensory Testing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPP	Skin Perfusion Pressure
TCNSS	Toronto Clinical Neuropathy Scoring System
TMF	Trial Master File
WHO Drug	World Health Organization Drug Dictionary
WPAIQ	Work Productivity and Activity Impairment Questionnaire

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to prospectively outline the types of analyses and presentations of the data that will form the basis for conclusions regarding this clinical investigation. The analyses defined in this plan should answer the safety and effectiveness objectives outlined in the protocol, and explain in detail how the data will be handled or analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry.

This document contains information to support the generation of a Clinical Study Report (CSR) for Clinical Protocol RBI.2017.002, including detailed descriptions of the statistical methods to be applied, as well as the analysis summary tables and figures and subject data listings intended to present the analysis results.

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.

The planned analyses identified in this SAP may be included in regulatory submissions, medical presentations and manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the CSR. The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and the International Conference on Harmonization (ICH) Guidance on Statistical Principles for Clinical Trials.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The primary objective of this study is to demonstrate the analgesic efficacy of PEMF treatment compared to sham treatment in patients with painful diabetic distal symmetric peripheral neuropathy (DSPN).

3.1.1. Efficacy Assessments and Endpoints

There will be 11 total endpoints from Part A of the protocol (Part B analysis is in a separate SAP); the interest will be in the change from baseline and the differences between active Provant therapy vs. sham.

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 Endpoint 1: Percentage of patients who have either a 2 point or 30% reduction in NPRS at 4 Months.
Secondary Endpoint 2: Time to 30% or 2-point reduction in NPRS, whichever comes first at 4 Months.
Secondary Endpoint 3: Change in neuropathy related quality of life (NeuroQoL) between baseline and end of treatment at 4 Months.
Secondary Endpoint 4: Changes in Skin Perfusion Pressure (SPP) from baseline to end of treatment at 4 Months.
Secondary Endpoint 5: Changes in Nerve Conduction Studies (NCS) of Velocity and/or Amplitude between baseline and end of treatment at 4 Months.
Secondary Endpoint 6: Changes in Quantitative Sensory Testing (QST) between baseline and end of treatment at 4 Months.
Secondary Endpoint 7: Change in Patient Global Impression (PGI) at 4 Months.

Exploratory Endpoint 1: Change in Work Productivity and Impairment Questionnaire (WPAIQ)
Exploratory Endpoint 2: Changes in intraepidermal nerve fiber density (IENFD) at the distal thigh.
Exploratory Endpoint 3: Changes in IENFD at the distal leg.

3.1.2. Safety Endpoints

Safety will be assessed through review of Adverse Event (AE) reports and unanticipated adverse device effects. Safety outcomes will be assessed at the interim visits and the end of study visit.

4. STUDY OVERVIEW

4.1. 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 a 8-month single-arm, open-label, active treatment extension period upon completion of Part A (the SAP for Part B is laid out in a separate document).

Eligible subjects will include those between 22 and 79 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 electronic patient-reported outcome (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 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 also complete the Work Productivity and Activity Impairment Questionnaire (WPAIQ) and NeuroQoL.

4.2. Study Treatment

The study device is the PROVANT® Therapy System (aka Dual Pad DPN Therapy). 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.

4.3. Sample Size Justification

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 enrolling 1.3 times the target sample size of 124 patients (124 * 1.3 = ~162).

4.4. Estimated Duration of Subject Participation, Withdraw and Follow-up

Subjects will be on study for approximately 12 months (4 months in Part A and 8 months in Part B). 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.

5. SCHEDULE OF ASSESSMENTS

The schedule of assessments is presented in Appendix A of the protocol.

6. ANALYSIS POPULATIONS

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 their compliance for using the study device was ≥70%. For the specific tables of the individual efficacy endpoints generated based on the PP analysis dataset, an *x* will be added to the table number for differentiation.

7. ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The header of each table and listing will include the sponsor's name and the study number. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation.
2. SAS® program name, including the path that generates the output.
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all subjects combined. Row entries in tables are made only if data exist for at least one subject (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data. Tables, listings, and figures will provide the units of measurement, unless not applicable.

Results recorded at single times during the study will be presented using the *Level 1* display for the *ITT population*; the example structure is presented below.

Baseline Parameters	Active Provant Treatment	Sham Provant Treatment	Overall
Age ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values			
Gender ● Male (N [%]) ● Female (N [%])			

The *Level 2* display will be used for summarizing the incidence of AEs. An example of the layout for AEs by severity is presented below.

Adverse Events	Active Provant Treatment	Sham Provant Treatment	Overall
Reported Term			
Severity			

The *Level 3* display will be used for summarizing the parameters recorded multiple times during *Part A* of the study. An example of the layout is presented below; rows will be repeated for visits conducted at each month.

Parameters	Observation Time	Active Provant Treatment	Sham Provant Treatment
● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values	Enrollment (Baseline) Visit		
● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values	Month 4 Visit		
● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values	Month 4 Visit Minus Baseline		

The Level 3 displays will report the paired results for the change from the baseline through Month 4. For example, if 18 subjects complete the baseline evaluation and 16 subjects complete the Month 4 visit, the difference (Month 4 minus Baseline) will contain 16 subjects.

Supportive individual subject data listings will be sorted and presented by subject number and visit date, if applicable. Listings will also include the number of days relative to the initial study treatment (active or sham).

Specific algorithms are discussed 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 (active or sham) 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].

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the count and percentage in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places

than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).
- All probability values will be rounded to four decimal places. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'. P-values <0.05 will be considered to be statistically significant.
- All summary tables will include the analysis population sample size (i.e., number of subjects).
- Study Day 1 is defined as the day the subject receives their initial exposure to the active study device. All *study days* are determined relative to the day of initial treatment with the study device.
- Baseline values will be defined as those values recorded closest to, but prior to, the first active study treatment.
- Change from baseline will be calculated as follows:
  - Change = Post-baseline value – baseline value.
- Date variables will be formatted as DDMMMYYYY for presentation.
- Tables, figures, and listings will be presented in landscape orientation.
- SAS® Version 9.2 or higher will be the statistical software package used for all data analyses.
- All data from this study will be presented in listings. All listings will be sorted by subject number and visit date, as applicable.
- Table and listing numbering will follow ICH guidelines for post-text table and listing numbering.

7.1. Adjustments for Covariates

The analyses will be adjusted using the baseline results that are found to differ between the randomized treatment groups to increase the precision of the model; the underlying assumption for inclusion of a covariate or covariates will be examined. Unadjusted analyses will also be conducted and reported as the first set of analyses presented.

Small sites (i.e., sites that have less than 2 patients for any of the treatment arms) will be identified and the following method will be used for combining the data. Data from all small sites will be combined to form a single site in order to obviate non-estimable situations (i.e., at least 2 observations are needed to estimate variance) in the evaluation of the performance of the

device by site. Once combined, the pooled site will remain as such for all analyses for which a site interaction effect is 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 4 times as many patients, the small sites will be ranked by size and divided into 3 pooled assignments using an alternating sequence (ABCABCABC). This methodology will be applied, based on the initial pooling of the smaller sites.

7.2. Handling of Dropouts or Missing Data

Missing data may have an impact upon the interpretation of the trial data. Values for missing data will not be imputed, however a methodology is defined for missing dates. All available data for subjects who do not complete the study will be included in the data listings. **An analysis of the last recorded observation will be conducted to facilitate a comparison predicated on the ITT population.**

Safety Data

Missing or incomplete data will not be imputed. For patients who withdraw from the study prematurely, the last recorded observation will serve as final observation.

7.3. Multiple Comparison/Multiplicity

No adjustment for multiplicity will be applied to the type 1 error rate in the analysis of the endpoints from this study.

7.4. Examination of Subgroups

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.

8. SUBJECT ACCOUNTING AND STUDY DISPOSITION

A complete accounting of subject participation in the study will be presented in Table 14.1.1 entitled *Subject Accounting and Final Study Disposition*. The Level 1 table layout will be used to present these results. The purpose of this table is to provide an accounting of subjects from their entrance into the study through the final visit and to account for subject evaluation in major analyses of safety and efficacy, including reasons for early study termination. The table will display the number and percentage of subjects who:

- were consented
- were screened
- were run-in failures
- are included in the *ITT Population*
- are included in the *Per protocol Population*
- completed the study

In addition, the reason for early study termination will be summarized separately using the number and percentage of subjects within each table column for each reason.

Listing 16.2.1 entitled *Subject Disposition* supports Table 14.1.1. This listing will be sorted by subject number and will contain the reason for discontinuation (if applicable), along with the date and last study visit attended.

Listing 16.2.2.1 entitled *Inclusion Criteria* displays the data from the Inclusion Criteria case report form (CRF). The data will be displayed for each subject and for each inclusion criterion. The listing will be sorted by subject number.

9. BASELINE SUBJECT DATA

9.1. Baseline Demographic Factors

All subjects in the *ITT Population* will be included in Table 14.1.2 entitled *Summary of Baseline Demographics and Subject Characteristics*. The Level 1 table layout will be used to present these results. This table summarizes the subject population with respect to gender, age in years at the time of entry into the study, race, ethnicity, height (cm), weight (lbs), calculated body mass index (BMI), total foot thickness (plantar surface to mid-dorsal surface on the right and left foot) [cm], venous insufficiency classification, diabetes type, HbA1c, foot length (cm), foot width (cm), and shoe size. Data collected using a continuous scale will be summarized using descriptive statistics. Data collected using a categorical scale will be presented using counts and percentages. The supportive data for Table 14.1.2 will be presented in Listing 16.2.4.1 entitled *Subject Demographics and Subject Characteristics.* This listing will be sorted by subject number.

9.2. Screening and Baseline Assessments

The purpose of these assessments is to determine the severity of the disease for each subject. Outcomes may be assessed on baseline disease severity by adding these results as a covariate to the model for analysis. The parameters to be summarized are listed below; the method of summarization will be predicated on the scale used for each parameter (continuous or categorical). Results will be presented using the *Level 1* display for the *ITT Population*.

- Pain Score Assessment (NPRS)
- Toronto Clinical Neuropathy Scoring System (TCNSS)
- Ankle-Brachial Index & Assess Venous Insufficiency
- Quantitative Sensory Test (QST)
- Sural Nerve Conduction Velocity and Amplitude (NCS)
- Measure HbA1c
- Work Productivity and Activity Impairment Questionnaire (WPAIQ)
- Skin Perfusion Pressure (SPP)
- NeuroQoL Questionnaire
- Biopsy measurements

All subjects in the ITT / Safety population will be included in Table 14.1.3 entitled *Summary of Screening and Baseline Assessments* (ITT / Safety population). The supportive data for Table 14.1.3 will be presented in Listing 16.2.4.2 entitled *Screening and Baseline Assessments*. This listing will be sorted by patient number.

Screening assessments will be presented in the following tables:
Table 14.1.2 *Summary of Baseline Demographics and Subject Characteristics*
Table 14.1.3 *Summary of Screening and Baseline Assessments*

9.3. Physical Examination

There will be 5 body systems assessed as either normal or abnormal in the physical examination:

- General Appearance
  - Normal Abnormal
- Cardiovascular
  - Normal Abnormal
- Musculoskeletal
  - Normal Abnormal
- Extremities/Skin
  - Normal Abnormal
- Neurological
  - Normal Abnormal (Other abnormalities other than DPN will be noted)

o Other, specify:

Results will be presented using the *Level 1* display for the *ITT Population*. Results will be summarized in Table 14.1.4 entitled *Summary of the Physical Examination Results*. The supportive data for this table will be presented in Listing 16.2.4.3 entitled *Physical Examination Results.* This listing will be sorted by subject.

9.4. Medical and Surgical History

The medical and surgical history will be coded for each subject. Results will be presented based on the reported history using the *Level 1* display for the *ITT Population*. Results will be summarized based on the body system description and presented in Table 14.1.5 entitled *Summary of Medical and Surgical History*. The subjects will be summarized using counts and percentages for those subjects who had a pre-study medical history. The supportive data for this table will be presented in Listing 16.2.4.4 entitled *Medical and Surgical History.* This listing will be sorted by subject.

10. STUDY DEVICE ACCOUNTABILITY AND TREATMENT

This section will describe the summarization and analysis of the administration of the treatment with the Provant device (active and sham).

10.1. Treatment Administration and Accountability

A summary of treatment sessions with the study device will be presented in Table 14.2.1 entitled *Summary of Treatment with the Study Device (Active and Sham)* and Table 14.2.2 entitled *Summary of Compliance with the Study Device (Active and Sham)*. The number and percentage of subjects who undergo treatment will be calculated and summarized using counts and percentages. The number of completed treatment sessions, and the number of treatment sessions initiated but not completed will be calculated and summarized using counts and percentages. Percent compliance will be calculated, including the number of subjects with >=70% compliance. Listing 16.2.5.1 entitled *Study Device – Application and Accountability* will contain all of the recorded treatment information; this listing will be sorted by subject number and relative study day.

11. EFFICACY EVALUATIONS

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) ≠ 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%. A Mixed Models with Repeated Measures (MMRM) analysis 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.

The primary efficacy endpoint will be summarized and reported using the Level 3 table design. Results will be presented in Table 14.4.1.1 entitled *Summary of the Pain Intensity by Randomized Treatment Assignment and Time* (*ITT Population*)

Listing 16.2.8.1 entitled *Pain Intensity by Randomized Treatment Assignment and Time* will contain all of the recorded information; this listing will be sorted by subject number and relative study day.

A list of additional summary tables is presented in the table below.

Table	Description
14.4.1.1.1	*Kaplan-Meier Estimates for the First Week where a Mean Reduction of 2 Points or a 30% Reduction from Baseline in the NPRS is Observed*
14.4.1.1.2	*Summary of the Pain Intensity Categorized by Success (>=30% reduction from baseline) by Randomized Treatment Assignment and Time*
14.4.1.1.3	*Summary of the Pain Intensity Categorized by Success (>=2 point reduction from baseline) by Randomized Treatment Assignment and Time*
14.4.1.1.4	*Summary of the Pain Intensity Categorized by Success (>=2 point reduction or 30% reduction from baseline) by Randomized Treatment Assignment and Time*

Table	Description
14.4.1.2	*Summary of the NeuroQoL Results by Question, Randomized Treatment Assignment and Time*
14.4.1.2.1	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 1: Pain*
14.4.1.2.1a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 1: Pain*
14.4.1.2.2	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 2: Lost/reduced feeling*
14.4.1.2.2a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 2: Lost/reduced feeling*
14.4.1.2.3	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 3: Diffuse sensory-motor symptoms*
14.4.1.2.3a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 3: Diffuse sensory-motor symptoms*
14.4.1.2.4	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 4: Restrictions in activities of daily living*
14.4.1.2.4a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 4: Restrictions in activities of daily living*
14.4.1.2.5	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 5: Disruptions in social relationships*
14.4.1.2.5a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 5: Disruptions in social relationships*
14.4.1.2.6	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Weighted) Domain 6: Emotional distress*
14.4.1.2.6a	*Summary of the Efficacy Endpoints by Randomized Treatment Assignment and Time - NeuroQol (Unweighted) Domain 6: Emotional distress*
14.4.1.3	*Summary of the Skin Perfusion Pressure Results by Randomized Treatment Assignment and Time*
14.4.1.4	*Summary of the Nerve Conduction Results by Randomized Treatment Assignment and Time*
14.4.1.5	*Summary of the QST Results by Randomized Treatment Assignment and Time*
14.4.1.6	*Summary of the Work Productivity and Activity Impairment Questionnaire (WPAIQ) by Visit and Randomized Treatment Assignment*
14.4.1.7	*Summary of the Patient Global Impression (PGI) by Visit and Randomized Treatment Assignment*
14.4.1.8	*Summary of Treatment Satisfaction by Visit and Randomized Treatment Assignment*
14.4.1.10	*Summary of the Toronto Clinical Neurpathy Scoring System by Randomized Treatment Assignment and Time*

12. SAFETY

The following sections describe how the safety endpoints will be analyzed.

12.1. Adverse Events

12.1.1. Missing and Partial Adverse Event Dates

The start dates for AEs are important for the:

1. Treatment emergent algorithm.
2. The designation of unique AE occurrences.

Completely missing or partially missing adverse event onset dates will be imputed as follows after due diligence to obtain accurate adverse event information has failed.

If the AE start date is completely missing then the AE will be considered treatment-emergent unless it can be determined that the AE end date occurred prior to the start of the study. If this is the case, the AE will not be considered treatment-emergent.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the start of the study, then the AE will be considered treatment-emergent unless it can be determined that the AE end date occurred prior to the start of the study.

12.1.2. Summaries of Adverse Events

All summaries of AEs will be based on treatment-emergent AEs and presented using the Level 2 table designs. Adverse events will be coded using the system organ class and preferred term. The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to the study device (active or sham) will also be provided. Serious adverse events and AEs leading to discontinuation from the study will be presented by reported adverse event term.

12.1.2.1. Summary of Adverse Events by Reported Adverse Event Term

Table 14.3.1.1 entitled *Summary of Adverse Events by Randomized Treatment Assignment, System Organ Class, and Preferred Term* will contain the primary presentation of the AE data. This table will be prepared without regard to causality or relationship to the study device. The number and percentage of subjects experiencing an adverse event will be displayed by treatment (active or sham). Reported adverse event terms will be displayed alphabetically. The incidence of AEs will be summarized using counts and percentages.

12.1.2.2. Assessment of Severity

Table 14.3.1.2 entitled *Summary of Adverse Events by Reported Adverse Event Term and Severity* will provide the presentation of AEs with respect to the severity or intensity of the event using the scale presented in the protocol. Subjects with multiple occurrences of the same reported adverse event term within the same period will be summarized at the maximum severity

reported for that AE. The number and percentage of subjects experiencing AEs for each coded adverse event term will be displayed by study device (active or sham).

12.1.2.3. Assessment of Relationship to the Study Device

Table 14.3.1.3 entitled *Summary of Adverse Events by Randomized Treatment Assignment and Relationship to the Study Device* will present the adverse events by the relationship to the study device. The categories for assessment of the relationship to the study device are defined in the protocol. Subjects with multiple occurrences of the same coded adverse event term will be summarized using the event with the strongest relationship to the study device (active or sham). The number and percentage of subjects experiencing each reported adverse event term will be displayed by study device (active or sham).

Listing 16.2.7.1 entitled *Adverse Events* will provide supportive data for Tables 14.3.1.1 through 14.3.1.3 and will be sorted by subject number and relative day.

12.1.2.4. Summary of Adverse Events Leading to Discontinuation

Results will be presented in Table 14.3.1.4 entitled *Summary of Adverse Events Leading to Discontinuation of Treatment with the Study Device* by the coded adverse event term. The structure of the table will follow Table 14.3.1.1. Listing 16.2.7.3 entitled *Adverse Events Leading to Discontinuation of Treatment* will display all treatment-emergent AEs resulting in an action taken of "Discontinued".

12.1.2.5. Summary of Serious Adverse Events

Results will be presented in Table 14.3.2 entitled *Summary of Serious Adverse Events by Randomized Treatment Assignment, System Organ Class, and Preferred Term.* The structure of the table will follow Table 14.3.1.1. Listing 16.2.7.2 entitled *Serious Adverse Events* will present the AEs coded as *serious*. The format of Listing 16.2.7.2 will be similar to that of Listing 16.2.7.1 with the exception that the column indicating whether or not the AE was serious will be removed as all AEs in this listing will be SAEs.

A complete list of the safety summary tables is presented in the table below.

Table	Description
14.3.1.1	*Summary of Adverse Events by Randomized Treatment Assignment, System Organ Class, and Preferred Term*
14.3.1.2	*Summary of Adverse Events by Reported Adverse Event Term and Severity*
14.3.1.3	*Summary of Adverse Events by Randomized Treatment Assignment and Relationship to the Study Device*
14.3.1.4	*Summary of Adverse Events Leading to Discontinuation from the Study*
14.3.2	*Summary of Serious Adverse Events by Randomized Treatment Assignment, System Organ Class, and Preferred Term*

12.2. Concomitant Medications

Listing 16.2.6 entitled *Concomitant Medications* will be presented by subject and include all of the information recoded on the concomitant medication form. This listing will be sorted by

subject number and the name of the concomitant medication; the date may not be complete for all patients and medications and may not be used as an index variable for sorting.

Listing 16.2.6.1 entitled *Analgesic Medications* will be presented by subject and include all of the information recoded on the concomitant medication form for analgesic medications taken for DSPN. This listing will be sorted by subject number and the name of the analgesic medication; the date may not be complete for all patients and medications and may not be used as an index variable for sorting.

Total dose by patient will be summarized and reported in Table 14.1.13 entitled *Summary of the Dose of Analgesic Medication Taken for DSPN by Randomized Treatment Assignment and Time.* Total rescue medication dose by patient will be summarized and reported in Table 14.1.14 entitled *Summary of the Dose of Rescue Medication by Randomized Treatment Assignment and Time.*

12.3. Additional Tabulations

The following additional tables will be generated.

14.4.1.9	*Summary of the Blinding Assessment by Randomized Treatment Assignment and Time*
14.4.1.10	*Summary of the Toronto Clinical Neurpathy Scoring System by Randomized Treatment Assignment and Time*
14.4.1.11	*Summary of HbA1c by Randomized Treatment Assignment and Time*
14.4.1.12	*Summary of the Treatment the Subjects Believe they are Receiving by Randomized Treatment Assignment and Time*

13. PROGRAMMING SPECIFICATIONS FOR STATISTICAL ANALYSES AND SUMMARY TABLES

13.1. Summary tables

• All tables and data listings will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
• Figures will be presented in Landscape Orientation.
• Legends will be used for all figures with more than one variable or item displayed.
• Figures will be in black and white. Symbols on figures will not be filled. Lines should be wide enough to see the line after being copied.

- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.

• Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
• All titles will be centered on a page. The first title line will be the number of the table, figure, or data listing. The second (and if required, third) line will be the description of the table, figure, or data listing.
• All footnotes will be left justified at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
• Missing values for both numeric and character variables will be presented as blanks in a table or data listing.
• All date values will be presented as DDMMMYYYY (e.g., 29AUG2013) format. A four-digit year is preferred for all dates.
• All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
• Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
• All tables, figure, and data listings will have the name of the program and a date/time stamp on the bottom of each output.
• Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
• Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
• All population summaries for categorical variables will include categories that the patients had a response in these categories.
• All percentages are rounded and reported to a single decimal point (xx.x%).

• Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

13.2. SAS Code for Generic Statistical Procedures

Note: Not all procedures may be required for the presentation of the results from this study. Information provided for procedures not directly referenced in this SAP may be used in supportive analyses.

1) SAS code for Kaplan-Meier analyses

```
PROC LIFETEST PLOT=(S) DATA = thedataset;
TIME DAY*CENS(1);
STRATA group;
```

CENS: Censoring variable: CENS=1 if censored, 0 otherwise.
DAYS: Time to event or censoring.
group: group to test for differences.

Note: Survival probabilities are determined from the SURVIVAL variable in the PRODUCTLIMITESTIMATES ODS data set. Survival probabilities are determined at the observed values of the time variable. Survival probabilities at other days can be determined as the last survival probability up to the specified day.

2) SAS code for Cox analyses

Dummy variables must be constructed for center and treatment. If there are C centers, construct C-1 dummy variables as

```
CENTER_2 = (CENTER = second center number);
…
CENTER_C = (CENTER=last center number);
```

Note that one arbitrarily chosen center is not accorded a dummy variable.

For treatment, construct a dummy variable XXX treatment groups:

```
XXX = (TREAT="XXX");
```

The control group is not accorded a dummy variable. Note: the coding of interactions must be determined.

The SAS code for the full model is then (replacing … with full list of variables):

```
PROC PHREG DATA=input-data-set;
MODEL DAY*CENS(1) = TREATMENT  CENTER_2 ... CENTER_C  BASELINE ;
OVERALL_CENTER: TEST CENTER_2,... ,CENTER_C;
```

CENS: Censoring variable: CENS=1 if censored, 0 otherwise. The observation will be censored if the patient finishes the study or discontinues without responding.

DAY: Time to event or censoring.
CSTRATUM: Study center (stratum).
TREAT: Treatment.

Note: Survival probabilities are determined from the SURVIVAL variable in the output file. Survival probabilities are determined at the observed values of the DAY variable. Survival probabilities at unobserved days can be determined as the last survival probability at the observed day before the desired day. In this study it is likely (but not certain) that the median times will occur on an observed day.

Calculation of confidence intervals for the hazard ratio

The 95% confidence interval on the hazard ratio is calculated with the following formula:

(exp(estimate-SE*1.96), exp(estimate+SE*1.96)).

3) SAS (version 9.2) code for the ANOVA models for analyzing efficacy parameters

```
PROC GLM DATA=inputdataset;
CLASS TREATMENT CENTER;
MODEL variable = TREATMENT CENTER BASELINE;
** differences with CONTROL;
ESTIMATE "ACTIVE-CONTROL" TREATMENT -1 1 / cl alpha=.05;
```

The values are obtained from ODS data sets as shown in the next table:

Statistical Quantity	ODS Data Set	Record Identifier in ODS	Variable
Estimates by treatment	LSMEANS	TREAT=1 etc.	LSMEAN
Estimates of treatment difference	ESTIMATES	LABEL='TREATMENT-CONTROL'	ESTIMATE
CI on treatment difference	ESTIMATES	LABEL='TREATMENT-CONTROL'	LOWER, UPPER
P-value for treatment difference	ESTIMATES	LABEL='TREATMENT - CONTROL'	PROBT

For subgroup analyses including a discrete covariate such as gender, include the term as follows:

```
PROC GLM DATA=inputdataset;
CLASS TREATMENT CENTER GENDER;
MODEL variable = TREATMENT CENTER GENDER BASELINE;

PROC GLM DATA=inputdataset;
CLASS TREATMENT CENTER GENDER;
MODEL variable = TREATMENT CENTER GENDER TREATMENT*GENDER BASELINE;
```

4) SAS (version 9.2) code for the confidence intervals on means

```
PROC UNIVARIATE DATA=inputdataset CIBASIC;
VAR value;
```

where VALUE is the analysis variable. Confidence intervals are obtained from the BASICINTERVALS ODS data set. The confidence interval is from the LOWERCL and UPPERCL variables on the record where UPCASE(VARNAME) EQ 'MEAN'.

5) SAS code for analyses using PROC FREQ

```
PROC FREQ DATA = thedataset;
TABLES response*group / CHISQ;
```

The p-value comparing GROUPs is taken from the PROB variable in the ODS EXACT dataset. The record for the Fisher's exact test is the record for which
UPCASE(STATISTIC) EQ "FISHER".

6) SAS code for CMH analyses

```
PROC FREQ DATA = the dataset;
TABLES strata*treatment*response / CMH;
```

The following table shows the sources of the values obtained from the Output Delivery System data sets.

Statistical Quantity	ODS Data Set	Record Identifier in ODS	Variable
P-value for treatment	CMH	UPCASE(ALTHYPOTHESIS) =ROW MEAN SCORES DIFFER	PROBF

where RESPONSE is the variable being analyzed, and strata is the variable being controlled for (e.g., CENTER).

7) SAS code for Cochran-Mantel-Haenszel (CMH) analyses with ordered response (Van Elteren test)

```
PROC FREQ DATA = thedataset;
TABLES strata* treatment*response / CMH SCORES=MODRIDIT;
```

8) SAS code for 2-sample Wilcoxon test

```
PROC NPAR1WAY WILCOXON DATA=inputdataset;
CLASS TREATMENT;
VAR analysis_variable;
```

Statistical Quantity	ODS Data Set	Record Identifier in ODS	Variable
P-value for treatment difference	WILCOXONTEST	(UPCASE(LABEL1) EQ "TWO-SIDED PR > |Z|) AND UPCASE(NAME1) EQ "PT2_WIL"	NVALUE1

14. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.

15. TABLE, LISTINGS, AND FIGURES

The index of tables and listings is contained in the file entitled RBI2017-002-SAP-INDEX-V1-6NOV2018.xls.