STATISTICAL ANALYSIS PLAN

PRODUCT UNDER INVESTIGATION:

PROVANT® Therapy System

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 and RBI.2016.001

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

PREPARED BY
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DATE AND VERSION
August 30, 2016 (Version 1.0)
(Based on the protocol dated January 11, 2016)

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DOCUMENT NUMBER: RBI-REGISTRY-SAP-001

TITLE

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APPROVALS

Name and Title	Signature	Date
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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
EDC	Electronic Data Capture
FCC	Federal Communication Commission
FDA	Food & Drug Administration
IQR	Inter-Quartile Range
IRB	Institutional Review Board
LSA	Laser Sensor Assembly
MedDRA	Medical Dictionary for Regulatory Activities
NCV	Nerve Conduction Velocity
PEMF	Pulsed Electromagnetic Field
PPDN	Painful Peripheral Diabetic Neuropathy
PRFE	Pulsed Radio Frequency Energy
PRN	As Needed
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMET	Submaximal Effort Tourniquet Test
SPP	Skin Perfusion Pressure
SSR	Sympathetic Skin Response
TMF	Trial Master File

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.2015.005, 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 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.

This study will determine the extent to which Pulsed Electromagnetic Field (PEMF) therapy contributes to the management of various pain etiologies in a real-world setting.

3.2. Endpoints and Study Assessments

3.2.1. Baseline Assessments

Outcome Assessments

Outcome measures used as part of the standard practice regimen

Pain Sensation

- Dull Pressure
- Ache
- Spasm
- Sharp
- Sting
- Burning
- Shooting
- Stabbing
- Squeezing
- Bloating
- Cramping
- Trying
- Exhausting
- Depressing
- Annoying
- Aggravating
- Punishing
- Tolerable
- Unrelenting
- Intolerable

Pain Radiation (yes or no; if yes, the location is added as a verbatim field)
Pain Intensity Assessment (0-10 scale)
Temporal/Timing

- Constant
- Unprovoked

- Wax/Wanes
- Intermittent
- Onset: Sudden or Gradual

Aggravates or Worsens the Pain

- Walking/Running
- Stooping
- Flexing
- Extending
- Pivoting
- Deep Massage
- Exercise/Movement/ Exertion
- Reclining
- Bending
- Sitting
- Lifting
- Medication (specific medications will be included in a listing)
- Energy Based (specific information will be included in a listing)
- Carrying
- Chewing
- Talking
- Lights/Flashing
- Noise/Sound
- Smells
- Motion
- Heat
- Cold
- Light Touch

Alleviates or Reduces the Pain – Medications

- Opioid
- Antidepressant
- Anticonvulsant
- Serotonin Inhibitor (SSRI)
- Anesthetic
- NSAID
- Other (specific information will be included in a listing)

Topical Agents and Medications

- Anesthetic
- Counter Irritant
- Capsaicin
- Other (specific information will be included in a listing)

Energetic Therapy:

- Provant
- Other PEMF
- TENS
- Acupuncture
- US
- Light Therapy
- Infrared
- PUVA
- Other (specific information will be included in a listing)

Adjunctive Therapy

- Massage
- Heat
- Cold
- Exercise/Movement
- Rest/Relaxation
- Dietary
- Compression/Stockings
- Behavior Feedback
- Other (specific information will be included in a listing)

Baseline Edema Assessment

Edema Evaluation at treatment site

- Amount: Mild, Moderate, Severe
- Pitting: Non-pitting, 1+, 2+, 3+, 4+, Lymphedema

Baseline Wound Assessment

Total number of wounds (actual number will be tabulated)
Wound Assessment:

- Postoperative
- Laminectomy
- Post-Surgical Debridement
- S/P Surgical Revision
- Post Procedure
- Thoracotomy
- S/P Amputation
- Joint Replacement
- Joint Revision
- Other (specific information will be included in a listing)

Amputation Site

- TMA
- BKA
- AKA
- Forearm

- Upper Arm
- Other (specific information will be included in a listing)

Provant Treatment Regimen

Frequency of Treatment:

- Q.D. (every day)
- B.I.D (twice daily)
- PRN (as needed)
- Other (specific information will be included in a listing)

Length of individual Treatment Session:

- 30 minutes (default)
- 15 minutes
- 1 hour (two 30 minute sessions)
- Other (specific information will be included in a listing)

Weight

3.2.2. Interim and End of Treatment Visit Assessments

Outcome Assessments

Outcome measures used as part of the standard practice regimen

Pain Intensity Assessment (Average)

Single pain score of the average intensity over the past 7 days

Assessment of Compliance and DC packs
Compliance (Yes or No)
Total number of pack provided
Provant Device Return (End of Treatment Visit)

Edema Evaluation at treatment site

- Mild, Moderate, Severe
- Pitting: Non-pitting, 1+, 2+, 3+, 4+, Lymphedema

Weight (End of Treatment Visit)

3.2.3. Safety Endpoints

The safety endpoints include the following parameters:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Condition/Diagnosis of AE

Start and stop date of the event
Serious event (yes or no)
Elements of the serious adverse events

- Results in Death
- Requires or prolongs Hospitalization
- Life-Threatening
- Congenital Anomaly/Birth Defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude any one of the outcomes listed above

Severity of the event

- Mild
- Moderate
- Severe

Relationship to the study device

- Related
- Possibly Related
- Unrelated

Action taken

- None
- Treatment Stopped
- Treatment interrupted
- Unknown
- Concomitant Medication

Frequency

- Single, continuous episode
- Recurrent / Intermittent

Outcome of the Event

- Recovered
- Resolved with residual effects
- Death
- Unknown
- Ongoing at study end

Concomitant medications

- Medication Name
- Indication / Reason for Use (verbatim)
- Start date
- Stop date
- CM for AE
- Dose
- Units

- Frequency
- Route
- Ongoing

4. STUDY OVERVIEW

4.1. Study Design

This is an open-label, non-controlled trial in subjects with various pain etiologies at multiple centers in the US. Up to 200 subjects will be enrolled. 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. Data from assessments administered as part of standard of practice will be obtained at baseline and, at a minimum, at the end of treatment. 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.

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 10 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.

After up to 20 weeks of treatment, the subject will return to the clinic for a final assessment. Adverse events and changes in concomitant medications will be collected.

4.2. 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.

4.3. Sample Size Justification

There is no formal basis for the sample size of 200 subjects. The intent of this clinical investigation is to record real-world use and the practice pattern of this approved medical device.

4.4. Estimated Duration of Subject Participation and Follow-up

Subjects will for followed for up to 20 weeks (including the screening period). If a subject completes the study with an ongoing AE, the site will continue to follow up with the subject for 30 days from the study completion date, until resolution is reached and documented. If, after 30 days, the AE is still continuing but not assessed as serious, the outcome will be recorded as ongoing and no further follow-up will be necessary. If a subject completes the study with an ongoing SAE, the subject will be followed until resolution or stabilization (i.e., the AE returns to baseline, can be attributed to agents other than the study device, or to factors unrelated to the study conduct; or no further follow-up is deemed necessary by the Investigator or it becomes unlikely that any additional information can be obtained).

4.5. Interim Analysis

An administrative extract of the data on September 2, 2016 will be used to tabulate the data for the post-operative patients. This tabulation is being prepared for a regulatory filing and does not constitute a formal analysis.

5. SCHEDULE OF ASSESSMENTS

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

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. Introduction to and training on the study device will be completed during the Enrollment Visit.
4. 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.
5. The subject will self-administer treatments as prescribed by the investigator.
6. Collect only weight at End of Treatment Visit.
7. Assessment of adverse events will be conducted after the signing of the Informed Consent.
8. At the End of Treatment Visit subjects will return the study device and all unused Disposable Applicator Covers (DACs).

6. ANALYSIS POPULATIONS

The results from this study will be presented using a single population.

- **ITT / Safety Population:** All subjects who are consented and treatment with the study device is initiated, independent of the treatment being successful implemented.

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.

Quantitative results recorded multiple times over the course of the study will be presented using the *Level 1* display.

Baseline Parameters	**Reason for Study Enrollment: Pain**	**Reason for Study Enrollment: Edema**	**Reason for Study Enrollment: Pain and Edema**	**Overall**
Age ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Gender ● Male (N [%]) ● Female (N [%])				

The *Level 2* display will be used for summarizing response by Reason for Study Enrollment (Pain, Edema or Pain and Edema). An example of the layout is presented below.

Evaluation Time Point	Reason for Study Enrollment: Pain	Reason for Study Enrollment: Edema	Reason for Study Enrollment: Pain and Edema	Overall
Baseline Pain Score ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Pain Score During the First 4 weeks on Study (Study Day 1 through Study Day 28) ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Pain Score During the First 4 weeks on Study (Study Day 1 through Study Day 28) minus Baseline ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Pain Score During the Study ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Pain Score During the Study (Final Score) minus Baseline ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Outcome Assessment Score ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Outcome Assessment				

Score During the First 4 weeks on Study (Study Day 1 through Study Day 28) ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Outcome Assessment Score During the First 4 weeks on Study (Study Day 1 through Study Day 28) minus Baseline ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Outcome Assessment Score During the Study ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				
Last Recorded Outcome Assessment Score During the Study (Final Score) minus Baseline ● N ● Mean ● Standard Deviation ● Median ● Minimum, Maximum Values ● Inter-Quartile Range (IRQ)				

The *Level 3* display will be used for summarizing the adverse events recorded through the course of the study. An example of the layout is presented below.

Adverse Events	**Reason for Study Enrollment: Chronic or Acute Pain**	**Reason for Study Enrollment: Edema**	**Reason for Study Enrollment: Chronic or Acute Pain and Edema**	**Overall**
System Organ Class				
Preferred Term				
Severity				

Supportive individual subject data listings will be sorted and presented by subject number and visit or diary entry date. Listings will also include the number of days relative to the initial study device treatment.

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 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%).

- No formal hypothesis tests are planned for this clinical investigation. Probability values may be derived for informational purposes. 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 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 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 to increase the precision of the estimates; the underlying assumption for inclusion of the covariate will be examined. Unadjusted analyses will also be conducted and reported.

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 tabulation of the last recorded observations will be performed. All available data for subjects who do not complete the study will be included in data listings.

7.3. Multiple Comparison/Multiplicity

No adjustment for multiplicity will be applied, given there is no formal hypothesis that will be tested.

7.4. Examination of Subgroups

Results will be evaluated relative to the condition the subject is using the study device to treat.

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 tolerability, including reasons for early study termination. The table will display the number of subjects who were screened and the number and percentage of subjects who:

- were enrolled
- are included in the Safety / ITT population
- completed the study
- discontinued the study

Listing 16.2.1 entitled *Subject Disposition* supports Table 14.1.1. This listing will be sorted by subject number and will contain the last study visit attended.

9. BASELINE SUBJECT DATA

9.1. Baseline Demographic Factors

All subjects in the Safety population will be included in Table 14.1.2 entitled *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) and calculated body mass index (BMI). Age, height, weight, and BMI will be summarized using descriptive statistics. The number and percent of each gender, race, and ethnicity category will be presented using counts and percentages. The supportive data for Table 14.1.2 will be presented in Listing 16.2.2 entitled *Subject Demographics*. This listing will be sorted by subject number.

9.2. Medical History

The medical history for each subject and summarized in Table 14.1.3 entitled *Summary of Medical History*. The Level 1 table layout will be used to present these results. 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 16.2.3 entitled *Medical History*. This listing will be sorted by subject.

9.3. Outcome Assessments

The data recorded on the Outcome Assessments case report form will be summarized in Table 14.1.4 entitled *Summary of Baseline Outcome Assessments*. The Level 1 table layout will be used to present these results. The subjects will be summarized using counts and percentages for each qualitative question. The supportive data for this table will be presented in Listing 16.2.4 entitled *Baseline Outcome Assessments.* This listing will be sorted by subject.

9.4. Baseline Pain Site Assessment

The data recorded on the Baseline Pain Assessment case report form will be summarized in Table 14.1.5 entitled *Summary of Baseline Pain Assessment*. The Level 1 table layout will be used to present these results. The subjects will be summarized using counts and percentages for each qualitative question. The supportive data for this table will be presented in Listing 16.2.5 entitled *Baseline Pain Assessment.* This listing will be sorted by subject.

9.5. Baseline Edema Assessment

The data recorded on the Baseline Edema Assessment case report form will be summarized in Table 14.1.6 entitled *Summary of Baseline Edema Assessment*. The Level 1 table layout will be used to present these results. The subjects will be summarized using counts and percentages for each qualitative question. The supportive data for this table will be presented in Listing 16.2.6 entitled *Baseline Edema Assessment.* This listing will be sorted by subject.

9.6. Baseline Wound Assessment

The data recorded on the Baseline Wound Assessment case report form will be summarized in Table 14.1.7 entitled *Summary of Baseline Wound Assessment*. The Level 1 table layout will be used to present these results. The subjects will be summarized using counts and percentages for each qualitative question. The supportive data for this table will be presented in Listing 16.2.7 entitled *Baseline Wound Assessment.* 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.

10.1. Treatment Administration and Accountability

A summary of Provant treatment regimen will be presented in Table 14.2.1 entitled *Summary of the Provant Treatment Regimen (ITT / Safety Population)*. The frequency of treatment and length of the individual treatment sessions will be summarized using counts and percentages. Listing 16.2.8 entitled *Study Device – Application and Accountability* will contain all of the recorded treatment information; this listing will be sorted by subject number.

10.2. Interim Visit Outcome Assessments

10.2.1. Description of the Data for Analysis

Data collected from the Outcome Assessments, Pain Intensity Assessment (Average), and Edema Assessment will be summarized. Results will be summarized in the following tables. Continuous variables will be summarized using descriptive statistics; categorical variables will be summarized using counts and percentages. Results will be presented using the Level 2 displays.

Table 14.4.1.1 Summary of the Interim Outcome Assessments (ITT / Safety Population)
Table 14.4.1.2 Summary of the Interim Pain Intensity Assessment (ITT / Safety Population)
Table 14.4.1.3 Summary of the Interim Edema Assessments (ITT / Safety Population)

The supportive data for these tables will be presented in Listing 16.2.9 entitled *Outcome Assessment*; Listing 16.2.10 entitled *Pain Intensity Assessment*; Listing 16.2.11 entitled *Final Edema Assessment*; These listings will be sorted by subject and relative day the measurements were recorded.

10.3. End of Study Assessments

10.3.1. Description of the Data for Analysis

The last intra-subject data collected from the Outcome Assessments, Pain Intensity Assessment (Average), and Edema Assessment will be summarized. Results will be summarized in the following tables. Continuous variables will be summarized using descriptive statistics; categorical variables will be summarized using counts and percentages. Results will be presented using the Level 2 displays.

Table 14.4.2.1 Summary of the Final Outcome Assessments (ITT / Safety Population)
Table 14.4.2.2 Summary of the Final Pain Intensity Assessment (ITT / Safety Population)
Table 14.4.2.3 Summary of the Final Edema Assessments (ITT / Safety Population)

The supportive data for these tables will be presented in Listing 16.2.9 entitled *Outcome Assessment*; Listing 16.2.10 entitled *Pain Intensity Assessment*; Listing 16.2.11 entitled *Final Edema Assessment*; These listings will be sorted by subject and relative day the measurements were recorded.

11. SAFETY

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

11.1. Adverse Events

11.1.1. 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.

11.1.2. Summaries of Adverse Events

All summaries of AEs will be based on treatment-emergent AEs and presented using the Level 3 table designs. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 18.1. 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 will also be provided. Serious adverse events and AEs leading to discontinuation from the study will be presented by system organ class and preferred term.

11.1.2.1. Summary of Adverse Events by System Organ Class and Preferred Term

Table 14.3.1.1 entitled *Summary of Adverse Events by System Organ Class and Preferred Term* contains the primary presentation of the AE data. This table is prepared without regard to causality or relationship to the study device. Subjects will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject within a period will be counted only once. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed by treatment . System organ classes, and preferred terms within system organ class, will be displayed alphabetically. The incidence of AEs will be summarized using counts and percentages.

11.1.2.2. Assessment of Severity

Table 14.3.1.2 entitled *Summary of Adverse Events by System Organ Class, Preferred Term, and Severity* provides 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 system organ class or preferred 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 body system and preferred term will be displayed by study device.

11.1.2.3. Assessment of Relationship to Study Medication

Table 14.3.1.3 entitled *Summary of Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study Device* provides the presentation of adverse events by relationship to the study device. The categories for assessment of the relationship to study device are defined in the protocol. Subjects with multiple occurrences of the same system organ class or preferred term within a period will be summarized using the event with the strongest relationship to the study device. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed by study device.

Listing 16.2.12 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.

11.1.2.4. 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 System Organ Class and Preferred Term (ITT / Safety Population). The structure of the table will follow Table 14.3.1.1.Listing 16.2.6.3 entitled *Adverse Events Leading to Discontinuation of Treatment* will display all treatment-emergent AEs resulting in an action taken of "Discontinued".

11.1.2.5. Summary of Serious Adverse Events

Results will be presented in Table 14.3.2 entitled *Summary of Serious Adverse Events by System Organ Class and Preferred Term* (ITT / Safety Population). The structure of the table will follow Table 14.3.1.1. Results will be presented in Table 14.3.2.1 entitled *Summary of Serious Adverse Events Related to the Study Device by System Organ Class and Preferred Term* (ITT / Safety Population). Listing 16.2.13 entitled *Serious Adverse Events* will present the AEs coded as *serious*. The format of Listing 16.2.13 will be similar to that of Listing 16.2.12 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.

11.2. Concomitant Medications

Listing 16.2.14 entitled *Concomitant Medications* will be presented by subject and include the medication name, start date, stop date, used for an AE, dose, units, frequency, and route of administration. This listing will be sorted by subject number and medication start date.

12. REFERENCES

1. SAS Institute Inc., SAS® Version 9.2 software, Cary, NC.

13. TABLE, LISTINGS, AND FIGURES

Refer to the appendix containing the index of tables and listings.