Official Title:
Statistical Analysis Plan (SAP): The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial

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Statistical Analysis Plan (SAP)

The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial

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TABLE OF CONTENTS:

1.0 Version Control

This Statistical Analysis Plan (SAP) is based on study protocol [redacted].

2.0 Objectives

The study objective is to gather post-market data regarding the safety and effectiveness of the peripheral nerve stimulation (PNS) therapy for the treatment of neuropathic pain following amputation.

3.0 Study Design

The current study is a prospective randomized, double-blinded, placebo-controlled, multicenter study to gather data regarding the treatment of neuropathic pain following amputation with the PNS therapy.

Individuals with a lower extremity amputation reporting neuropathic pain following amputation, including residual limb pain (RLP) and/or phantom limb pain (PLP) rated ≥ [redacted] on an 11-point numerical rating scale on the Brief Pain Inventory Short Form (BPI-SF Question #5), will be considered for enrollment into the study. After informed consent is obtained, potential subjects will be evaluated for general eligibility. The individuals who satisfy the preliminary criteria will be asked to complete a 7-day baseline diary to record their daily "average pain" intensity (Question #5 on the BPI-SF) for each region of post-amputation neuropathic pain (i.e., both RLP and PLP) for the amputated limb. Individuals must report in at least one region (RLP and/or PLP) an average pain intensity of ≥ [redacted] averaged across the 7-day diary to qualify for lead placement. A region of pain qualifies for analysis in primary and secondary endpoints if it: a) has an intensity ≥ [redacted] on average during the baseline period, and b) is in a limb that receives the PNS therapy.

Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). In all subjects, leads will be placed percutaneously [redacted] All subjects will be instructed to use the Stimulators [redacted] for the 8-week home trial. In Group #1, the system will deliver electrical stimulation, while in Group #2 the system will deliver sham (placebo) stimulation.

[redacted]

After lead removal, Group #1 subjects will be followed for up to 10 months (12 months from the start of treatment). Following the completion of a follow-up visit [redacted] Group #2 subjects will be given the option of crossing over to receive the PNS therapy. If subjects do not choose to receive stimulation, they may be terminated from the study. If subjects choose to receive stimulation, leads will again be placed percutaneously [redacted], and the system will deliver electrical [redacted] during an 8-week home trial. [redacted] After lead removal, the subjects will be followed for 12 months from the start of the crossover stimulation treatment.

[redacted]

[redacted]

3.1 Randomization

Qualifying individuals will be randomized to either Group #1 (Treatment) or Group #2 (Control) [redacted] Individuals will be blinded to their randomization assignment until the close of Visit 13. Each site will receive an approximately equal distribution of subject assignments to each group.

3.2 Sample Size Rationale

[redacted]

[redacted]

4.0 Endpoint Analyses

All primary and secondary endpoint data will be analyzed and reported. Analyses of the primary and secondary effectiveness endpoints will be conducted on the full analysis set and the per-protocol population set at each specified study interval.

4.1 Primary Endpoint

This study evaluates the effectiveness of percutaneous Peripheral Nerve Stimulation (PNS) for the treatment of post-amputation neuropathic pain. Neuropathic pain is prevalent after amputation, and can include pain both in the residual limb (68-76% of amputees) and phantom limb (72-85% of amputees)[1-4]. The presence of RLP is highly correlated with reports of phantom pain[1]; amputees are significantly more likely to experience RLP if they also experience PLP, and 66-70% of amputees report pain in more than one region[1-3]. Therefore, treatment that effectively reduces *both* RLP and PLP is of considerable importance because of the disability and reduced quality of life caused by neuropathic pain after amputation. Published and draft FDA Guidance discuss the use of within-subject multi-component endpoints to provide assurance that patients have benefit on multiple disease features, and when treatment effects on different components are generally concordant[5, 6]. Such endpoints are specifically recommended by FDA in some therapeutic areas [7, 8], and are used in evaluation of pain therapies when improvement in multiple pain symptoms or disease features are critical to success of the therapy[9]. [redacted]

Relief of neuropathic pain will be evaluated using the average pain intensity for each region of RLP and PLP that has an intensity ≥ [redacted] on average during the baseline period and receives treatment with the PNS device. All amputees will record two daily post-amputation pain scores (one daily score for RLP and one daily score for PLP) for the amputated limb in the 7-day diaries using BPI-SF Question #5. For each individual, the region(s) of post-amputation pain with a 7-day average ≥ [redacted] during baseline in a leg that receives blinded treatment will qualify to be used in the determination of clinically meaningful success for that subject throughout the study. Data will be collected [redacted] Each amputee must have ≥ 50% reduction in pain in all areas of qualifying neuropathic pain, whether RLP and/or PLP, to be considered a success in the primary efficacy endpoint analysis. [redacted] Group #1 will receive active stimulation and Group #2 will

receive sham stimulation during the 8-week home trial. [redacted] The primary endpoint compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve ≥ 50% reduction in all areas of qualifying RLP and PLP from baseline to Weeks 5-8 of the home trial.

4.2 Secondary Endpoints

Additional endpoints below will be assessed to document further the effectiveness of PNS therapy for the symptomatic relief and management of neuropathic pain after amputation.

4.2.1 Proportions of success, RLP and PLP Components during Weeks 5-8

The treatment effect on average pain intensity compares the proportion of subjects who successfully achieve ≥ 50% reduction from baseline in Group #1 during Weeks 5-8 of treatment relative to that in Group #2 during Weeks 5-8 of the sham period. This is done for RLP and PLP independently, to evaluate the effectiveness of treatment separately on each component of the primary efficacy endpoint. RLP will be evaluated only in patients with qualifying areas of residual limb pain at baseline, and PLP will be evaluated only in patients with qualifying areas of phantom limb pain at baseline. To be considered a success for RLP and PLP, subjects must have ≥ 50% reduction in all qualifying areas of that type of pain.

4.2.2 Long-term Durability of Primary Endpoint at 3, 6, 9, and 12 months after SOT

The analysis of the durability of the treatment effect on average pain intensity will be conducted at 3, 6, 9, and 12 months after the start of therapy by comparing the proportion of subjects who successfully achieve ≥ 50% reduction from baseline in Group #1 at each time point compared to 3 months after the start of therapy (the longest follow-up before crossover) in Group #2. The pain intensity scores will be determined for each subject by applying the same method used for the primary endpoint: taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score for the same region(s) of pain reported in the follow-up diary (i.e., 3, 6, 9, or 12 months after SOT). To be considered a success, subjects must have ≥ 50% reduction in all qualifying areas of RLP and PLP.

4.2.3 Average pain intensity during Weeks 1-4 of home trial

The proportion of subjects who successfully achieve ≥ 50% reduction from baseline in Group #1 during Weeks 1-4 of the 8-week home trial will be compared to that in Group #2 during Weeks 1-4 of the sham period. The pain intensity scores will be determined for each subject by applying the same method used for the primary endpoint: taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score for the same regions of pain reported over Weeks 1-4 of treatment (i.e., the average of all scores in the diaries during this period) for Group #1 and Group #2. To be considered a success, subjects must have ≥ 50% reduction in all qualifying areas of RLP and PLP.

4.2.4 Pain Interference at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT

The analysis of the treatment effect on pain interference compares the proportion of subjects who successfully achieve ≥ 50% reduction in average pain interference score in Group #1 at each time point relative to that in Group #2. Relief of pain interference will be evaluated using the average pain interference (BPI-SF Question #9) for each qualifying region of RLP and PLP (average pain ≥ 4 at baseline). The baseline average pain interference score will be compared to the average pain interference score for the same qualifying regions of RLP and/or PLP at each specified interval after start of therapy to determine the percent reduction in pain interference. To be considered a success, subjects must have ≥ 50% reduction in the average pain interference score in all qualifying regions of RLP and PLP pain. The proportion of success in Group #1 at 4 weeks, 8 weeks, and 3 months will be compared to Group #2 at 4 weeks, 8 weeks, and 3 months, respectively. [redacted]

4.2.5 Pain Disability at 4 weeks, 8 weeks, and 3, 6 and 12 months after SOT

The analysis of treatment effect on pain disability compares the proportion of subjects who successfully achieve ≥ 10-point reduction in PDI scores from baseline in Group #1 relative to that of Group #2. [redacted] Scores on the PDI can range from 0 to 70. A score of 0 indicates no disability while a score of 70 signifies that all of the activities in which the individual would normally be involved have been totally disrupted or prevented by pain. Changes in pain disability will be evaluated in subjects that have a PDI score of ≥ 10 at baseline. The baseline PDI score will be compared to the PDI score at the specified intervals after start of therapy. To be considered a success, subjects must have a ≥10-point reduction in PDI. [redacted]

4.2.6 Patient Global Impression of Change at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT

The analysis of treatment effect on the PGIC compares the rank scores (of 7 possible ranks, ranging from -3 to 0 to +3, where -3 is very much worse, 0 is no change, and +3 is very much improved) of Group #1 to Group #2. The mean rank score of Group #1 at 4 weeks, 8 weeks, and 3 months will be compared to Group #2 at 4 weeks, 8 weeks, and 3 months, respectively. [redacted]

4.2.7 Pain Medication Usage at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT

Pain medication usage between groups

The analysis of opioid pain medication usage compares medication usage between Group #1 and Group #2. Opioid medication consumption will be reviewed for Weeks 1-4 of therapy, Weeks 5-8 of therapy, and at 3, 6, and 12 months after the start of therapy. For this analysis, subjects

completed 7-day diaries in which they tracked their daily use of analgesic medications. For subjects using opioid analgesics at baseline, daily opioid consumption will be converted to a morphine equivalent dosage (MED), which is measured in units of morphine milligram equivalents (MME). The mean MED and standard deviation will be reported for subjects in Group #1 at all timepoints and reported for subjects in Group #2 through 3 months post-SOT (the last collected timepoint for Group #2 prior to crossover).

4.2.8 Pain Catastrophizing Scale (PCS) at 4 weeks and 8 weeks after SOT

PCS is a widely used, validated 13-question instrument to assess rumination (4 questions), magnification (3 questions), and helplessness (6 questions). The survey asks participants to think back on painful experiences in the past and reflect on how often they had specific thoughts or feelings. Each question is scored on a 0-4 scale with 0 = "not at all" and 4 = "all the time". Higher scores indicate a greater tendency towards catastrophizing pain, which has been correlated with worse pain and response to pain therapies.

The analysis of treatment effect on PCS examines the statistical superiority of the mean percent improvement from baseline at specified intervals in Group #1 relative to that of Group #2. The baseline PCS score will be compared to the PCS score at the specified intervals after start of therapy. [redacted]

4.2.9 Exploratory Analyses

[redacted]

[redacted]

5.0 Analysis Populations

[redacted]

5.2 Full Analysis Set (Using the Intent to Treat Principle)

The Full Analysis Set (using the Intent to Treat Principle) will include all subjects who sign a consent form, are randomized, and continue to meet eligibility criteria prior to the time of lead placement. All patients will be analyzed according to the treatment group to which they were randomized.

5.3 Per Protocol Set

The per-protocol set of subjects defines a subset of the subjects in the Full Analysis Set who also meet the following criteria:

- Were implanted with at least one MicroLead
- Reported [redacted] coverage [redacted] in the target areas during the primary endpoint period (Weeks 5-8) (Group #1 only)
- Not missing more than [redacted] of average pain intensity (BPI-5) scores in the diaries during the primary endpoint period (*i.e.,* Weeks 5-8 of home trial) for each qualifying area of limb pain (i.e., RLP and/or PLP)
- Continued study eligibility throughout treatment period (Weeks 1-8) [redacted]

5.4 Safety Population

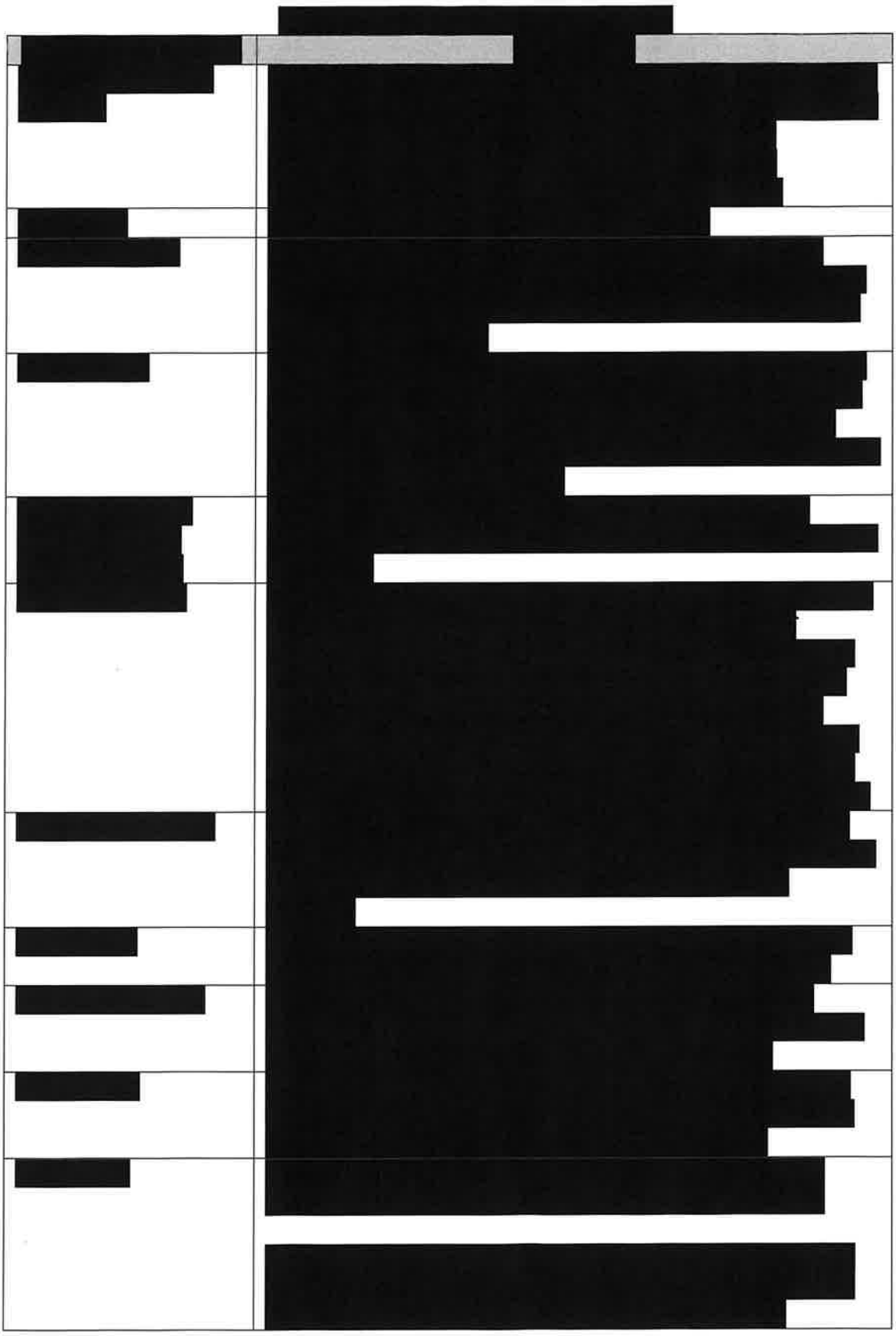
The Safety set is based on the Full Analysis Set with the following modifications:

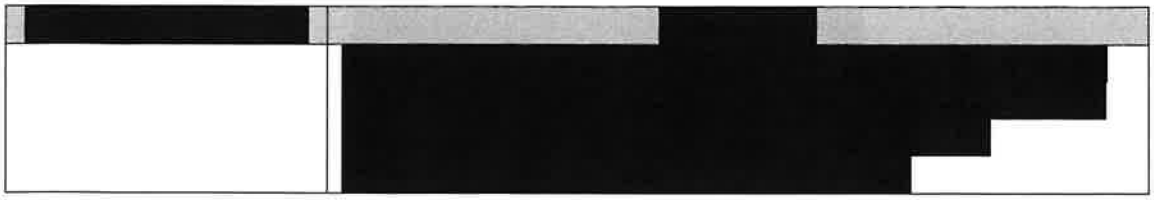
- Subjects will be assessed with an As Treated analysis, with therapeutic group determined by the treatment they actually received.
- Any subjects for whom treatment is not attempted (i.e. no attempted lead placement occurs) will be excluded.

6.0 Subject Disposition and Baseline Information

6.1 Subject Disposition

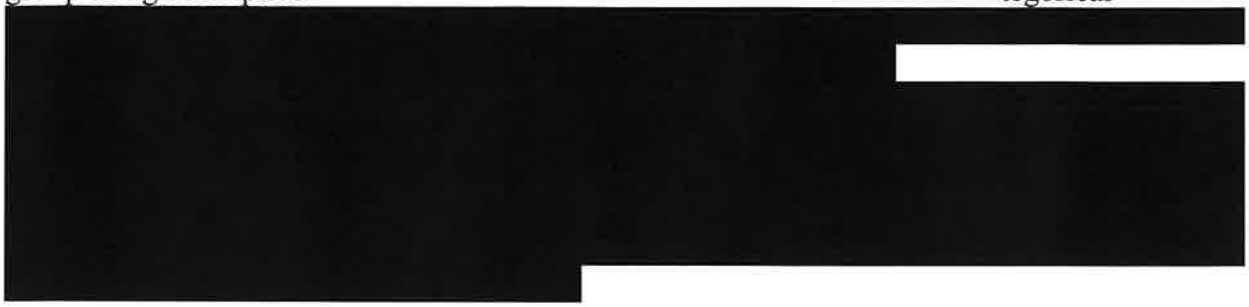
Study completion and withdrawal details, inclusion and exclusion criteria, randomization, and population assignment will be listed. [redacted]





6.2 Baseline and Demographic Characteristics

Demographic and baseline disease characteristic data will be listed and summarized for each group using descriptive statistics for continuous variables and tabulated for categorical variables.



7.0 Efficacy Analyses

All efficacy data will be analyzed in the Full Analysis Set and Per Protocol population.

7.1 Primary Efficacy Analyses

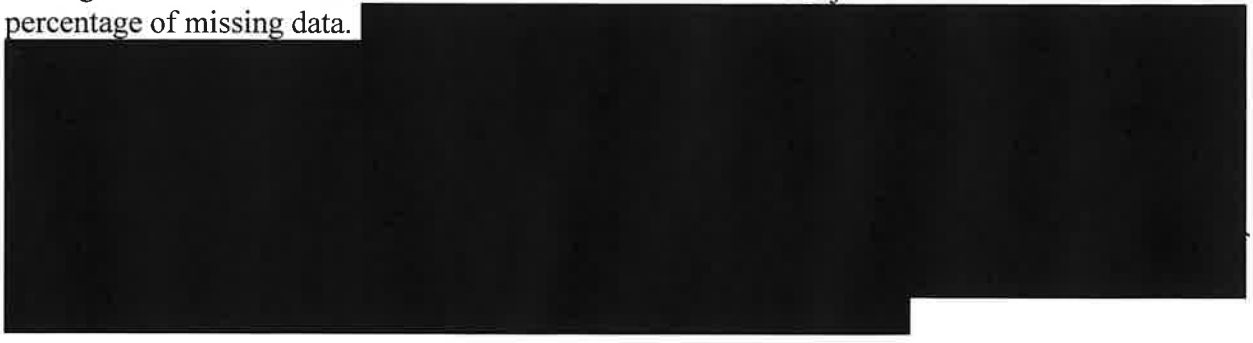
The effectiveness of percutaneous Peripheral Nerve Stimulation (PNS) for the treatment of post-amputation neuropathic pain will be assessed in the present study. The primary endpoint of the study compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve ≥ 50% reduction in neuropathic pain from baseline to Weeks 5-8 of the home trial. For this within-subject, multi-component endpoint[5, 6], each amputee must have ≥ 50% reduction in all qualifying areas of RLP and PLP to be considered a success in the primary efficacy endpoint analysis (see Section 4.1 Primary Endpoint).

7.2 Secondary Efficacy Analyses

Secondary outcomes will be analyzed as described in Section 4 and will be summarized to further assess the efficacy of PNS for the treatment of pain following amputation.

7.3 Handling Missing Data

Significant efforts will be made to maintain maximum subject retention and minimize the percentage of missing data.



[redacted]

[redacted]

8.0 Safety Analysis

All safety data will be analyzed using the Safety Analysis Set. Adverse device effects (ADEs) will be documented, reported, and categorized [redacted]

8.1 Adverse Device Effects

Adverse device effects (ADEs) will be reported and an overall summary of the number and percentage of subjects with at least one ADE, serious ADE, unanticipated ADE, or ADE leading

to death will be presented by treatment group. [redacted]

[redacted]

[redacted]