Statistical Analysis Plan

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Dorsal spInal cord STImulatioN vs mediCal management for the Treatment of low back pain
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Sponsor

Abbott Neuromodulation
6901 Preston Rd
Plano, TX 75024
United States

Statistical Analysis Plan

CIP 10343
DISTINCT

Dorsal spInal cord STImulatioN vs mediCal management for the Treatment of low back pain

Statistical Analysis Plan (SAP)

Version B

April 13, 2022

[redacted]

Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigation Plan (CIP) 10343, the DISTINCT study (CRD_988). This plan is based on CIP Version C, Apr 2022.

1.2 Clinical Investigation Objectives

The objective of this study is to evaluate the efficacy of BurstDR™ dorsal column stimulation, compared with comprehensive medical management, in improving pain and back pain-related physical function in subjects suffering with chronic, refractory axial low back pain, who have not had lumbar spine surgery and for whom surgery is not an option.

1.3 Clinical Investigation Design

This is a prospective, multi-center, randomized, controlled clinical trial with an optional crossover component. It is designed to evaluate the efficacy of BurstDR™ Spinal cord stimulation (SCS) in the treatment of chronic axial low back pain with a neuropathic component, compared with comprehensive medical management (CMM).

Subjects will be followed in-clinic for required study visits at 1,3, 6, 9, 12, 18 and 24 months and via phone call or optional clinic visit at 15- and 21-months. Due to the individualized nature of study therapies, patient reported outcomes will be continually assessed and additional patient outreach conducted in order to determine if therapy adjustment(s) are warranted to optimize pain control. The primary endpoint will be assessed at the 6-month follow-up visit. Upon completion of the 6-month follow-up visit, subjects who are dissatisfied with therapy and receiving inadequate improvement with their treatment assignment will be allowed to cross-over to the other treatment arm, if desired per Cross Over Instructions (CL1014686).

Up to 270 subjects will be randomized in the study which is split into two phases. Phase I will include the first minimal 200 randomized subjects. Phase II is the continued access phase and will include up to 70 randomized subjects.

Subject enrollment is expected to be completed within 18 months; subjects will be followed for 2 years. The total duration of the study is expected to be approximately 4 years, including enrollment, data collection from all subjects, and study close out.

1.4 Endpoints

1.4.1 Primary Effectiveness Endpoints

The primary effectiveness endpoint is the difference in responders between groups at 6 months. A subject is considered a responder for the primary endpoint if the following criterion is met:

- Improvement in pain, defined as a ≥ 50% decrease on Numerical Rating Scale (NRS)

1.4.2 Secondary Endpoints

- Secondary Endpoint #1: the composite responder rate, based on NRS or ODI improvements, at 6 months between groups. A subject is considered a composite responder if the following criteria are met:
    - Improvement in function, defined as a 13%-point decrease on ODI or score ≤ 20%,

    OR

    - Improvement in pain, defined as a ≥ 50% decrease on Numerical Rating Scale (NRS)
- Secondary Endpoint #2: the relative change on NRS from baseline to 6 months between groups
- Secondary Endpoint #3: the ODI change from baseline to 6 months between groups
- Secondary Endpoint #4: the PCS responder rate at 6 months between groups
- Secondary Endpoint #5: the Patient Global Impression of Change (PGIC) at 6 months between groups
- Secondary Endpoint #6: the relative change from baseline to 6 months for Pain Interference (PI) from PROMIS-29 between groups
- Secondary Endpoint #7: the relative change from baseline to 6 months for Physical Function (PF) from PROMIS-29 between groups

1.5 Randomization

After enrollment has been completed, subjects will be randomized (3:2 ratio) to either the SCS arm or the CMM arm at each site.

- Comprehensive Medical Management (CMM arm)

  During the follow-up period, subjects in the CMM arm will receive supervised medical care, including medication optimization and supervised non-interventional therapy. Medication optimization should include use of non-steroidal anti-inflammatories and muscle relaxants, as appropriate. Supervised non-interventional therapy may include, but is not limited to, physical therapy, chiropractic care, back school, cognitive behavioral therapy, and acupuncture. Interventional therapy such as injections and radiofrequency ablation, is also allowed.

- Spinal Cord Stimulation (SCS arm)

  A successful trial, defined as ≥ 50% decrease in back pain recorded on Numerical Rating Scale, is required for a subject to receive a permanent implant.

1.6 Blinding

For this study, the subject, site personnel, and some sponsor personnel will be aware of treatment assignment. Sponsor statisticians, including the DISTINCT Study Statistician, will not have access to any data that combines outcomes with treatment assignment prior to performing the primary endpoint analysis of the randomized cohort.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

The analysis populations include:

1. Intention-to-Treat (ITT) Population: includes all randomized subjects. Subjects will be analyzed according to the treatment group they are randomized to. The ITT population will be used as the primary analysis population for the primary endpoint.

2. Modified Intention-to-Treat (mITT) Population: includes all randomized subjects except for those who are randomized to the SCS group who fail the trial period, do not receive a permanent system implant. Subjects will be analyzed according to the treatment group they are randomized to.

3. Per-Treatment Evaluable (PTE) Population: includes all subjects in the mITT population who either receive permanent implant or receive CMM. Subjects will be analyzed according to the actual treatment received. The PTE population will be used as the primary analysis population for the study except the primary endpoint analysis.

2.2 Statistical Methods

2.2.1 Analysis of Continuous Data

For continuous variables (e.g., age, etc.), results will be summarized as number of observations, means, and standard deviations, and where applicable, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Difference between two groups, when specified, will be summarized with difference of the two means, and the 95% confidence interval of the differences. The p-values will be calculated based on either two-sample t-test or Wilcoxon rank sum test as appropriate.

Cumulative distribution function (CDF) may be used in displaying a continuous plot of the percent change from baseline on the horizontal axis and the cumulative percent of patients experiencing up to that change on the vertical axis. Kolmogrov-Smirnov test may be used to test whether two empirical distributions are different using proc npar1way in SAS® [1].

2.2.2 Analysis of Categorical Data

For categorial variables (e.g. gender, etc.), results will be summarized with subject counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson[2] confidence intervals. The p-values will be based on either Pearson's Chi-square test or Fisher's exact test by checking the expected frequency for each cell in the maximum contingency table against Cochran's rule[3] (i.e. if the expected frequencies for all cells are ≥ 5, then Pearson's Chi-square test will be used, otherwise Fisher's exact test will be used).

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables (e.g., time to all cause of death) in the following three scenarios:

- Subject with event of interest, the time to event will be calculated from the date of randomization /permanent implant to the date of event occurred.
- Subjects without events will be censored at the date of withdrawal, or

- Subjects without events with the date of the completion of their follow-ups, or at their last known event-free time point.

Survival curves will be constructed using Kaplan-Meier[4] estimates. Summary tables for events of interest will include event (failure) rates, Greenwood standard error, and confidence interval for the event rates.

2.2.4 Regression

2.2.4.1 Logistic regression model

Unconditional logistic regression may be used by adjusting baseline characteristic for binary variables.

2.2.4.2 Mixed effects model

For repeated measured variables, such as responder rate, patient report outcomes (PROs) at each visit, mixed effects models may be used to conduct exploratory analyses to evaluate the difference between SCS and CMM. Data can be analyzed using proc mixed for continuous variables or proc glimmix for binary variables from SAS®. Models will be compared and selected using likelihood ratio test, AIC or BIC.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The primary effectiveness endpoint is the difference in response rates between groups at 6 months. A subject is considered a responder for the primary endpoint if the following criterion is met:

Improvement in pain, defined as a ≥ 50% decrease on NRS.

2.3.1.1 The Hypothesis Test:

$$H_0: P_{SCS} = P_{CMM}$$

$$H_a: P_{SCS} \neq P_{CMM}$$

P_{SCS} and P_{CMM} denote the response rate at 6 months for SCS and CMM groups, respectively.

The ITT population defined in Section 2.1 will be used as the primary analysis. Trial failures (defined as having < 50% decrease in pain on the NRS from baseline to the end of the trialing, and who withdrew from the study per CIP), will be counted as non-responders in this analysis. All other subjects must complete their 6-month visit and have available primary endpoint data to be included in the primary analysis.

The response rates between the two groups will be compared using a two-sided Z-test with unpooled variance at the significance level of 0.05.

2.3.1.2 Sensitivity analysis for primary endpoint

An ITT analysis, where multiple imputation (MI) will be used to impute missing outcomes for all randomized subjects with missing data, will be used as a sensitivity analysis. Information on the MI analysis is included in Section 2.9.

The primary endpoint will also be analyzed based on available data for the mITT and PTE populations, using a two-sided Z-Test with unpooled variance at the significance level of 0.05.

2.3.2 Secondary Endpoints

2.3.2.1 Secondary Endpoint #1: the composite responder rate at 6 months, between groups.

A subject is considered a composite responder if the following criteria are met:

- Improvement in function, defined as a 13%-point decrease on ODI or score ≤ 20%,

OR

- Improvement in pain, defined as a ≥ 50% decrease on Numerical Rating Scale (NRS)

The hypothesis test:

$$H_0: P_{Composite\_SCS} = P_{Composite\_CMM}$$

$$H_a: P_{Composite\_SCS} \neq P_{Composite\_CMM}$$

$P_{Composite\_SCS}$ and $P_{Composite\_CMM}$ denote the composite responder rate for SCS and CMM groups, respectively.

2.3.2.2 Secondary Endpoint #2: the relative NRS change from baseline to 6 months between groups

The relative NRS change is defined as:

$$\Delta NRS = \frac{(NRS_{Baseline} - NRS_{6\ months})}{NRS_{Baseline}} \times 100\%$$

The hypothesis test:

$$H_0: \Delta NRS_{SCS} = \Delta NRS_{CMM}$$

$$H_a: \Delta NRS_{SCS} \neq \Delta NRS_{CMM}$$

ΔNRS_{SCS} and ΔNRS_{CMM} denote the relative NRS change for SCS and CMM groups, respectively.

2.3.2.3 Secondary Endpoint #3: the ODI change from baseline to 6 months

The ODI score is calculated as:

$$ODI = \frac{Total\ ODI\ sore}{(5 \times (number\ of\ non\ missing\ questions))} \times 100\%$$

Change of ODI is calculate as: $\Delta ODI = ODI_{Baseline} - ODI_{6\ months}$

The hypothesis test:

$$H_0: \Delta ODI_{SCS} = \Delta ODI_{CMM}$$

$$H_a: \Delta ODI_{SCS} \neq \Delta ODI_{CMM}$$

ΔODI SCS and ΔODI_{CMM} denote the change from baseline to 6 months for SCS and CMM groups, respectively.

2.3.2.4 Secondary Endpoint #4: PCS responder rate

PCS responder is defined as: subjects that are either clinically catastrophizing on PCS at baseline (PCS score ≥ 30) and report a score of < 30 at 6 months follow up or report a 40% decrease in score at 6 months follow-up compared to baseline regardless their baseline scores.

The hypothesis test:

$$H_0: P_{PCS\_SCS} = P_{PCS\_CMM}$$

$$H_a: P_{PCS\_SCS} \neq P_{PCS\_CMM}$$

P_{PCS_SCS} and P_{PCS_CMM} denote the PCS responder rate for SCS and CMM groups, respectively.

2.3.2.5 Secondary Endpoint #5: PGIC responder rate

PGIC responder is defined as: PGIC is 'Better' or 'Great Deal Better' at 6 months.

The hypothesis test:

$$H_0: P_{PGIC\_SCS} = P_{PGIC\_CMM}$$

$$H_a: P_{PGIC\_SCS} \neq P_{PGIC\_CMM}$$

P_{PGIC_SCS} and P_{PGIC_CMM} denote the PGIC responder rate for SCS and CMM groups, respectively.

2.3.2.6 Secondary Endpoint #6: the relative change of PI from baseline to 6 months between groups

The relative PI change is defined as:

$$\Delta PI = \frac{(PI_{Baseline} - PI_{6\ months})}{PI_{Baseline}} \times 100\%$$

The hypothesis test:

$$H_0: \Delta PI_{SCS} = \Delta PI_{CMM}$$

$$H_a: \Delta PI_{SCS} \neq \Delta PI_{CMM}$$

ΔPI_{SCS} and ΔPI_{CMM} denote the relative PI change for SCS and CMM groups, respectively.

2.3.2.7 Secondary Endpoint #7: the relative change of PF from baseline to 6 months between groups

The relative PF change is defined as:

$$\Delta PF = \frac{(PF_{6\ months} - PF_{Baseline})}{PF_{Baseline}} \times 100\%$$

The hypothesis test:

$$H_0: \Delta PF_{SCS} = \Delta PF_{CMM}$$

$$H_a: \Delta PF_{SCS} \neq \Delta PF_{CMM}$$

ΔPF_{SCS} and ΔPF_{CMM} denote the relative PF change for SCS and CMM groups, respectively.

2.4 Sample Size/Power Calculations

The study was designed to enroll approximately 200 subjects in Phase I and up to 70 subjects in Phase II. The following assumptions are used in the power calculation for the primary endpoint:

- Assumed response rate of 45% for the SCS group and 20% for the CMM group
- 3:2 (SCS:CMM) randomization ratio
- 25% attrition rate to primary endpoint (6 months) follow-up in both groups
- Two-sided alpha of 0.05
- Z-test with unequal variance

Based on the assumptions above, there is at least 90% power to evaluate the primary endpoint with the Phase I cohort.

The minimum detectable differences for secondary endpoints using phase I PTE cohort (assume approximately 80 SCS and 60 CMM) with 80% power are shown in Table 1 below.

Table 1: Minimum Detectable Differences (MID) for Secondary Endpoints

Secondary Endpoints	MID (standard deviation for each group)
#1: Composite Responder	23%
#2: Relative NRS Change in %	16.9(35)
#3: ODI Change	7.2 (15)
#4: PCS Responder	21%
#5: PGIC (%)	23%
#6: Relative Pain Interference Change in %	7.2 (15)
#7: Relative Physical Function Change in %	12.0 (25)

The sample size re-estimation will be based on the interim analysis (IA) population (Adaptive Design Plan CL1014964). The unblinded independent statistician will perform the sample size re-estimation for 4 endpoints (1 primary and secondary endpoints #1, #2, and #3) and generate a recommendation if more subjects are needed to meet the statistical significance of each endpoint.

The power calculation was performed using PASS 15 (NCSS LLC).[5]

2.5 Interim Analysis

Interim analysis for sample size re-estimation will be considered to determine the sample size and the timing of primary analysis. There is one planned interim analysis which will be conducted when 70% of the Phase I randomized subjects reach/or complete the 6-month visit. If the sample size is increased, the CHW weighted statistic[6] will be used in the final analysis of the primary and secondary endpoints 1, 2, and 3. Details are be shown in Adaptive Design Plan CL1014964. .

2.6 Timing of Analysis

Primary endpoint and secondary endpoints analyses will be performed after subjects in the ITT analysis population reach their 6-month follow-up visits for endpoints analysis.

Final analysis will be performed after all randomized subjects completed 24 months follow-up visit or withdrew before their 24 months follow-up visit.

2.7 Study/Trial Success

The study will be considered as successful if the primary effectiveness endpoint is met, i.e., SCS is superior to CMM with regards to the responder rate.

2.8 Subgroups for Analysis

Primary endpoint will be analyzed by age (e.g., by median of the age or 65 cutoff depending on data distribution), diagnosis, and other subgroups which may help to understand outcomes for specific patient populations.

2.9 Handling of Missing Data

As discussed in Section 2.3.1.2, for a sensitivity analysis of the primary endpoint, subjects with missing primary endpoint outcomes will have their outcomes imputed with multiple imputation (MI). PROC MI in SAS will be used to multiply impute missing outcomes. Multivariate imputations by fully conditional specification (FCS) methods with 20 burn-in interactions before each imputation, and the number of imputations equal to the percentage of missing data, and a seed of 8684915 will be used for analysis. If FCS methods fail to converge, other methods will be explored for the MI model.

The model may include, but not be limited to, the following predictors:

- Randomization group
- Age
- Sex at birth
- Lower back NRS at baseline and 3 months
- Duration of pain

If the model does not converge with this list of predictors, predictors will be removed from the model as needed to ensure convergence.

Once multiply imputed datasets have been generated, each imputation will be analyzed with standard statistical analyses before being combined for inferential analyses using PROC MIANALYZE. Example code which may be used is included in Appendix B.

2.10 Poolability Issue

The poolability analysis of the primary endpoint will be conducted by the sites at 6 months. To evaluate the site effect on the primary effectiveness endpoint, interaction effect between treatment and sites on the primary effectiveness endpoint will be tested against an alpha level of 0.15 using logistic regression model. Only sites with a sufficient number of subjects will be included in this analysis. Sites must have at least 10 or more subjects to be included in the poolability analysis. If the poolability model does not converge, the number of subjects needed to be included in the analysis will be raised until the model converges.

If there is evidence of inconsistency of the responder rate across the sites, or if there is interaction observed between treatment and sites, subject's demographics, medical history and baseline characteristics may be examined.

2.11 Multiplicity Issues

To control for type I error inflation, the test of secondary endpoints will be performed in a hierarchical order at two-sided 5% significance level:

1. Secondary endpoint #1
2. Secondary endpoint #2
3. Secondary endpoint #3
4. Secondary endpoint #4
5. Secondary endpoint #5
6. Secondary endpoint #6
7. Secondary endpoint #7

The secondary endpoints will be tested only if the superiority in the SCS group is demonstrated in the primary endpoint. If hypothesis testing for superiority of secondary endpoint #1 fails, no hypothesis testing for the rest of secondary endpoints, etc.

2.12 Sensitivity Analysis

Sensitivity analysis will be conducted for the primary endpoint, as specified in Section 2.3.1.2.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

Baseline and demographic variables will be summarized based on the ITT and PTE analysis populations.

3.2 Adverse Events

All subjects who completed their enrollments will be included in the analyses. Serious adverse events (SAEs) and AEs, will be summarized using number of events, the percentage of subjects with events, and event rates by subject year for all subjects and by the relatedness (including COVID related) of events.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized for all enrolled subjects.

3.4 Protocol Deviation

Protocol deviations will be summarized by category for subjects in whom a protocol deviation was reported. Number of protocol deviations and number of subjects with deviation will be summarized by deviation categories.

3.5 Descriptive Endpoints or Additional Data

3.5.1 Descriptive Endpoints

The descriptive endpoints will be analyzed in a PTE fashion. Subjects will be analyzed at each visit by the treatments they received. For example, for NRS, there will be a summary at each visit by the treatments received.

Descriptive endpoints include:

- Proportion of patients who elect to cross-over after the primary endpoint
- Change from baseline at each time point on the following:
    - ODI
    - NRS
    - PROMIS-29 questionnaire
    - Pain Catastrophizing Scale (PCS)
    - Pain-condition related medication usage
    - Exercise frequency
- Healthcare resource utilization
- Device programming and usage
- Patient satisfaction with therapy
- Patient Global Impression of Change (PGIC)
- Serious device-related adverse events

Responder analysis:

- Proportion of subjects with ≥ 30% decrease on NRS
- Proportion of subjects with ≥ 50% decrease on NRS
- Proportion of subjects with ≥ 13%-point improvement, at least one category improvement or score ≤ 20% on ODI
- Proportion of subjects within 1 SD of population norm or reach MCID on PROMIS-29 domains
    1. For the within 1 SD of population norm component:
        - Lower scores are better for negatively worded domains, like anxiety
            - Responder: needs a T-score of ≤ 60
        - Higher scores are better for positively worded domains, like physical function
            - Responder: needs a T-score of ≥ 40
    2. For the MCID component
        - MCIDs will be based on literature
- Proportion of subjects that are either clinically catastrophizing on PCS at baseline (PCS score ≥ 30) and report a score of < 30 at follow up or report a 40% decrease in score at follow-up compared to baseline.

3.5.2 Additional Analyses

An additional analysis will be performed for the subjects who crossed over from CMM to SCS after 6 months primary endpoint assessment. The analyses will be done by paired comparison (SCS crossover - CMM baseline value) at each visit. The p-value will be displayed for descriptive purpose.

In addition, the following analysis will be conducted on the PTE population for the primary endpoint:

- For the subjects with opioid medication increase (based on CDC dose markers, ≥90 MME daily if taking for at least 5 days within two weeks prior to 6 months visit), they will be considered as non-responders regardless their received treatment.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
CEC	Clinical Events Committee
CHW	Cui Hung Wang
CIP	Clinical Investigation Plan
CLBP	Chronic Low Back Pain
CMM	Comprehensive Medical Management
CRF	Case Report Form
CT	Computed Tomography
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention to Treat
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Multiple Imputation
mITT	Modified Intention to Treat
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
ODI	Oswestry Disability index
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change

PRO	Patient Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PTE	Per-Treatment Evaluable
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
UADE	Unanticipated Adverse Device Effect
US	United States

6.0 REFERENCES

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7.0 APPENDICES

APPENDIX A: EXAMPLE SAS CODE FOR MULTIPLE IMPUTATION

[redacted]

APPENDIX B: STATISTICAL ANALYSIS PLAN REVISIONS

This section documented changes in version number, revision details and rationale of SAP revisions. Administrative changes such as document date changes, reference numbering, editorial and grammatical changes are not captured.

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