Comparison of DTM™ SCS Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Spine Surgery

Statistical Analysis Plan, Version 3.0, 05 May 2022

NCT06442410

SGX International

Comparison of DTM™ SCS Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Spine Surgery

DTM-INT-2020PM2, Revision B

Statistical Analysis Plan

Version 3.0, 05MAY2022

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	18AUG2020	[redacted]	Initial Release
2.0	25MAR2022	[redacted]	Adding more details to handling of missing values sections (5.7.1.2 and 5.7.2.1.) to provide better clarity
3.0	05MAY2022	[redacted]	Add multiple imputation analysis for handling of missing data

Document Approval

Author	
Authored By	[redacted]
Signature	
Date	
Role	

Approval	
Approved By	[redacted]
Signature	
Date	
Role	

Approval	
Approved By	[redacted]
Signature	
Date	
Role	

Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol, Comparison of Differential Target Multiplexed Spinal Cord Stimulation (DTM™ SCS) Therapy Combined with Conventional Medical Management (CMM) to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Surgery. This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol DTM-INT-2020PM2, Revision B, 01APR2020. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Study Objectives

The primary objective of this study is to evaluate the effectiveness of DTM™ SCS in reducing back pain as compared to CMM for the treatment of intractable chronic low back pain. Other objectives of this study are to document the safety, clinical effectiveness and health economic analytics of DTM™ SCS in subjects with intractable chronic low back pain.

3 Study Design

This is a post-market, open-label, prospective, randomized, controlled, multi-center study comparing DTM™ SCS programming approach, delivered through the CE marked Intellis™ neurostimulator, to Conventional Medical Management (CMM). Data at follow-up visits will be compared between the two treatment groups, and compared to baseline assessments collected at the beginning of the study. There is an optional two-way crossover to the other treatment group available for all subjects who remain in the study at the 6-months visit.

3.1 Randomization

Subjects meeting study entrance criteria will be randomized in a 1:1 ratio to one of two study treatment groups:

- Test treatment group with DTM™ SCS programming approach with CMM
- Control treatment group with CMM alone

Randomization will be stratified by gender and whether the subject has leg pain or no leg pain at Baseline and by study site. Randomization will be done at each study site by randomly permuted blocks. Randomization assignments will be computer-generated and allocated via the Electronic Data Capturing (EDC) system.

3.2 Blinding

Due to the nature of the treatment groups, comparing an implantable medical device with conventional medical management that may involve multiple different treatments, it is not feasible to blind the subjects, implanting physicians or the clinical site personnel to the group assignments. The assessment of treatments are done by the subjects and not by the site personnel, so the lack of blinding of site personnel should not affect results as pain is the major assessment and subjects tend to describe pain truthfully since it affects their everyday life dramatically and not be influenced by knowledge of which treatment arm they are assigned to. In order to minimize potential assessment bias, the subjects will receive the standard instructions for completing the questionnaires.

4 Sample Size Determination

The clinical investigational plan requires a screening process for all subjects that provide written informed consent. These subjects will undergo screening to assess eligibility. Subjects may be excluded for various reasons during screening. Accordingly, in order to include an estimated 150 subjects to the point of randomization, up to 300 subjects may need to be consented and enrolled to account for exclusions prior to randomization.

The sample size estimate to determine primary endpoint is based on the primary objective of demonstrating superiority of the test group to the control group. Established methods were followed in determining the superiority criteria and the related sample size estimate

- Test basis: Pearson Chi-square binomial test for superiority
- Estimated responder rate of 60% in the test group and 30% in the control group
- Significance level, alpha, of 0.05 two-sided
- Randomization: 1:1

With these assumptions, a sample size of 50 subjects in each group will result in greater than 85% power for the study.

Based on the primary endpoint requirement, a minimum of 50 subjects per treatment group are required (100 total). To account for a combined estimated attrition of 33% for subjects that do not complete the Trial Phase, and subjects that exit study before the 6-month primary endpoint visit, approximately 150 subjects would need to be randomized.

To account for 50% attrition prior to randomization (including subject ineligibility after signing the informed consent and subject dropout), it is estimated that a total of up to 300 subjects would need to be enrolled in the study.

5 Statistical Analyses

5.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

5.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

5.1.2 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

5.1.3 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

5.2 Analysis Sets

The following analysis sets are defined for analysis:

- Modified Intent to Treat (mITT): All randomized subjects to the test arms who successfully complete the Trial Phase and all successfully randomized subjects to the control arm.
- Intent-to-Treat (ITT): All successfully randomized subjects who met all the enrollment criteria.
- Per-Protocol (PP): All test subjects who received a permanent device implant and all control subjects who contributed their data to the primary and secondary endpoint without any major protocol deviations (that would render their data unevaluable).

The primary analysis of the primary and secondary endpoints will be performed on the mITT population. Supportive analyses will be performed for the Intent-to-Treat and Per-Protocol population.

For secondary endpoint analyses incorporating crossover data (i.e. data gathered in the post 6-month periods), sensitivity analyses will be performed to examine the impact of crossover.

If a supportive analysis set is the same as the mITT set, the results will be the same and will not be regenerated for that supportive analysis set.

5.3 Handling of Missing Data

Missing data will be minimized by rigorous follow-up and investigator and site training. Additionally, for subjects in the DTM™ SCS arm who do not have a successful Trial Phase, results from the Trial Phase will be utilized for the primary endpoint as described in Section **Error! Reference source not found.**. Methods for handling missing data for primary and secondary endpoints are also described in 5.3 and 5.7.2.1. Additionally, sensitivity analyses for missing data will be performed. Unless otherwise specified, all other analyses will be based on the evaluable data with no imputation.

5.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. We will also summarize the number and percentage of subjects completing the Trial phase (with and without success), the number of subjects receiving a permanent implant, and the number of subjects with an explant. In addition, the number of subjects who complete the study or exit early will be summarized by reason. The number and percentage of subjects crossing over will be presented by visit.

5.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically-relevant baseline demographic, medical history, and clinical characteristic variables.

5.6 Repeated Measures Analyses Methods

For repeated measures models based on assessing measurements over time, estimation will be based on maximum likelihood (for binary data, based on a Laplace approximation). Such methods produce validate estimates when there is missing data that is “missing at random”. A compound-symmetric covariance structure will be used to account for within-subject correlation due to repeated observations on subjects. Time will be treated as a categorical variable. Least-square means estimates will be produced to assess differences between groups at each time point and averaged over the first 6 months.

5.7 Analysis of Study Endpoints

5.7.1 Primary Efficacy Endpoint

Pain rating on the 10 cm Visual Analog Scale (VAS) is considered the primary outcome measure. Analysis will be based on the percentage of individual responders, defined as a decrease in back pain VAS by at least 50% at 6 months after Permanent Device Activation (Test group) or 6 months post-randomization (Control group) as compared with Baseline.

5.7.1.1 Primary Analysis

The *primary efficacy endpoint* will be evaluated with a Pearson Chi-square binomial test for superiority at the two-sided 0.05 alpha level.

H_0: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 6 months in the Test group is the same as in the Control group.

$P_{Test} = P_{Control}$

H_1: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 6 months in the Test group is superior to that in the Control group.

$P_{Test} \neq P_{Control}$

Primary analysis will be based on the mITT analysis set.

In addition to the results from the hypothesis test, the numerator and denominator and percentage responders will be presented.

5.7.1.2 Handling of Missing Data

For subjects in the DTM™ SCS arm who do experience an unsuccessful Trial Phase, also referred to as a **Trial Failure**, results (i.e., VAS back scores) from the Trial Phase will be utilized for the primary endpoint. Specifically, the Trial Phase results of subjects who failed the Trial Phase will be attributed for each time point throughout the study, as if they remained in the study.

Subjects who did not complete the Trial Phase due to withdrawal (e.g., an adverse event experienced during the Trial Phase, physician withdrawal due to non-compliance, withdrawal of consent, etc.), will not be included in the mITT analysis data set.

In the event of missing primary endpoint data among the mITT subjects either randomized to control or DTM™ SCS subjects who did complete the Trial Phase, the primary analysis for the primary endpoint will be conducted using multiple imputation (MI) methodology rather than the methods specified in Section 5.7.1.1. The specified Pearson Chi-square test will be presented for the observed data as a supporting analysis.

For the MI analysis each missing datum is replaced by multiple values in multiple datasets. The imputed datasets are then analyzed and combined for inference. Since the primary efficacy, and secondary efficacy endpoints, are based on the same underlying data of change in VAS, and vary only in the parameterization (continuous VAS vs. dichotomized responder) or value used for the null hypothesis, the same imputed data sets will be used for the analysis of each endpoint. Imputation will be performed separately by treatment group.

For each imputation model, covariates will include:

• Baseline variables: age (years), gender, number of year(s) since diagnosed with chronic back pain, unilateral versus bilateral pain, back pain VAS

• Follow-up variables: end of trial phase back pain VAS, follow-up back pain VAS (after device activation) from 1 month through 24 months. The imputation models employed will correspond to the hypothesis being tested, for the primary and secondary endpoints through 6 months, the models will use data through 6 months. For secondary endpoints post 6 months, the model will be extended to the relevant time point.

Missing data will be imputed using the PROC MI procedure in SAS. PROC MI imputes missing covariates in the order variables are listed on the VAR statement. The variables will be listed on the VAR statement in the order listed above. Missing covariates will be imputed using fully conditional specification (FCS) methods. The regression method will be use to impute the missing endpoint values. If necessary to facilitate imputation, an augmented likelihood approach will be used. Explorations to omit predictors may be conducted if the primary effectiveness multiple imputation models will not converge.

For each multiple imputation model, 100 imputed datasets will be generated. The Pearson Chi-square statistic will be computed in each imputed dataset. The Chi-square statistics will be transformed using the Wilson-Hilferty transformation to provide an approximately normal test statistic and standard error. Additionally, the proportions of responders will be estimated for both arms in each imputation. The normalized test statistics and estimated proportions with the associated standard errors will then be combined for inference using standard methods such as those available in SAS PROC MIANALYZE or other valid statistical software.

An additional supporting analysis of the primary endpoint will use likelihood based repeated measures models to produce estimates of the primary endpoint by treatment group and the p-value for a difference between treatment groups in the presence of the missing data.

5.7.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

- If the primary efficacy endpoint in the test group is found to be superior to that in the control group, then a secondary endpoint will evaluate whether the proportion of subjects who achieve a 50% improvement in their back pain VAS score at 1, 3, 9, 12, 18 or 24 months in the test group is superior to that in the control group. A superiority test based on the difference in proportions will be performed based on the following null hypothesis, with a two-sided p-value of 0.05 or less considered evidence of statistical significance. A separate hypothesis test will be conducted for each time point.

H_0: The proportion of subjects (P) who achieve a 50% improvement in their back pain VAS score at 1, 3, 9, 12, 18, or 24 months in the Test group is less than or equal to that in the Control group.

$P_{Test} = P_{Control}$

H_1: The proportion of subjects (P) who achieve a 50% improvement in their back pain VAS score at 1, 3, 9, 12, 18, or 24 months in the Test group is greater than that in the Control group.

$P_{Test} \neq P_{Control}$

- Change in mean VAS will be evaluated with two-sample t-test of non-inferiority in means with a 0.65 cm non-inferiority margin at 6 months.

H_0: The change (C) in subject's VAS pain intensity score relative to baseline at the Primary Efficacy Assessment in the Test group is worse than that of subjects in the Control group by more than 0.65 cm.

$C_{Test} \geq C_{Control} + 0.65$ cm

H_1: The change (C) in subject's VAS pain intensity score relative to baseline at the Primary Efficacy Assessment in the Test group is no more than 0.65 cm worse than the mean change from baseline in the control group.

$C_{Test} < C_{Control} + 0.65$ cm

The non-inferiority margin of 0.65 cm was selected based on a previous study of a similar therapy against traditional SCS[i]. In that study, the experimental therapy showed a 4.9 point improvement while traditional SCS showed a 3.6 point improvement for a difference of 1.3 points. Taking 50% of this treatment effect yields the margin of 0.65 cm. If the null hypothesis is successfully rejected for the non-inferiority test, a test for superiority of treatment to control will be performed based on a two-sided 0.05 alpha level.

The following secondary endpoints do not have an associated hypothesis, and no significance level will be assigned to statistical tests that may be performed.

- Comparison of Back Pain Treatment Success (responder rate), measured as subjects with at least a 50% reduction in Back Pain VAS, between test and control
- Comparison of mean change from Baseline in Back Pain VAS, between test and control.

Repeated measures models will be used to produce estimates for these two secondary endpoints, with graphical presentation of the responder rates and mean changes from baseline.

Analysis of results through 6 months will be based on the mITT population. For time points after 6 months where crossover is allowed, crossover subjects will be counted as failures (i.e. non-responders) for endpoints defined in terms of responders, carrying forward the baseline (pre-treatment). Sensitivity

analysis of both secondary endpoints will also be performed to where crossover subjects are censored at the point of crossover.

5.7.2.1 Handling of Missing Data

Since the two secondary endpoints are based on the same underlying VAS data as that for the primary efficacy endpoint, a similar treatment of handling missing data will be applied for the trial phase outcomes. In particular, for subjects who have a successful Trial Phase and planned to receive a permanent implant, VAS data used for the secondary endpoints will correspond to the results observed at the corresponding collection times (i.e. 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months). For subjects who do not have a successful Trial Phase (based on subject's pain score), the VAS data for the secondary endpoints will utilize the results from the end of the Trial Phase.

Subjects who were not able to complete the Trial Phase (e.g., an adverse event experienced during the Trial Phase, physician withdrawal due to non-compliance, withdrawal of consent, etc.) will be removed from the mITT analysis data set as no back VAS pain score is available at the End of Trial visit.

In the event of missing secondary endpoint data the primary analysis of the secondary endpoints will be conducted using multiple imputation instead of the methods specified above. The multiple imputed datasets from the primary endpoint analysis will also be used for the analysis of the secondary endpoints as described in Section 5.7.1.2. The same methods will be used for the responder endpoint evaluation at 1, 3, 9, and 12 months. The evaluation of mean change in VAS at 6 months will estimate the mean change and difference in means between groups along with the associated standard errors which will then be combined across imputations. The imputation model will be extended as needed for the evaluation of the secondary endpoint at 9, 12, 18, and 24 months.

As an additional supporting analysis, likelihood based repeated measures models will be used to produce estimates for the secondary endpoints in the presence of missing data.

5.8 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary efficacy endpoint will be presented separately for each site using descriptive statistics. Poolability of the primary endpoint across investigational sites will be evaluated using a logistic regression model with fixed effects for treatment, site, and treatment by site interaction. Sites enrolling less than 5 subjects will be combined to form one-quasi site. If the quasi-site exceeds the maximum enrollment allowed per investigational site, centers will be combined based on geographical proximity to form multiple quasi-sites until at least 5 subjects are included in each quasi-

site. If the p-value for the interaction effect is 0.05, additional exploratory analyses will be performed to understand any variations in outcomes by site.

Subgroup analyses will be presented based on the following parameters: age (<65 versus ≥ 65 years of age), gender, and disease severity (< median versus ≥ median baseline back pain).

5.9 Safety Analyses

Safety will be assessed by characterizing adverse events at all study visits with descriptive statistics.

All Adverse Events assessed/determined to be study-related study will document seriousness, severity, treatment/intervention provided, relationship to the device/procedure, and resolution.

Adverse events (AE) will be reported for the mITT set. A sensitivity analysis of AEs based on the ITT set will also be performed. AEs will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Serious adverse events will also be tabulated. The rate of all AEs and SAEs reported in the study will be reported.

All AEs and SAEs will also be summarized by relatedness as described above. Adverse events leading to death or study discontinuation will be provided in listing format.

5.10 Interim Analyses

In order to monitor data on patient safety and to help ensure accuracy of data collection, administrative analyses may be performed. The results of the analyses will not be widely distributed, and access will be limited to those persons on a “need to know” basis. Administrative analyses will not be used to modify the trial or stop early for potential benefit. As there is no chance of early stopping, the type I error rate is not affected. Limiting changes to the protocol also prevents operational bias due to knowledge of interim results.

5.11 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation

of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

[redacted]