

Statistical Analysis Plan

Efficacy of BurstDR Spinal Cord Stimulation versus Sham in Established Responders: A Randomized, Double-Blind, Two-Period Crossover Trial

Companion SAP for the randomized, double-blind, two-period crossover study

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Prepared before database lock and before unblinding

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Endpoint-to-analysis overview

Endpoint	Derivation	Primary analysis
Pain intensity (primary)	Median of all available twice-daily NRS ratings across the 7-day randomized treatment period	Wilcoxon signed-rank; Hodges–Lehmann median paired difference; 95% CI
Treatment satisfaction	Single 0–10 score at end of each treatment period	Wilcoxon signed-rank; Hodges–Lehmann median paired difference; 95% CI
Sleep PGIC	Median of all available daily ratings within period	Wilcoxon signed-rank
Mood PGIC	Median of all available daily ratings within period	Wilcoxon signed-rank
Daily activity PGIC	Median of all available daily ratings within period	Wilcoxon signed-rank
Social activity PGIC	Median of all available daily ratings within period	Wilcoxon signed-rank
Blinding/perceptibility	Standardized pre-period perceptibility test before period 1 and end-of-period felt-stimulation response after each arm	Descriptive summaries only
Safety outcomes	Observed events during study participation	Descriptive summaries only

1. Purpose and Scope

This Statistical Analysis Plan (SAP) prespecifies the analysis methods for the randomized, double-blind, two-period crossover study evaluating BurstDR spinal cord stimulation versus sham in established responders. It is intended to be finalized before database lock and before treatment labels are revealed to the blinded analysis team.

The SAP should be read together with the study protocol. Where the SAP provides greater operational detail than the protocol, the SAP will govern the conduct of statistical analyses. Any deviations from this SAP will be documented, justified, dated, and archived prior to unblinding whenever feasible.

2. Trial Overview

The study is a single-centre, randomized, double-blind, two-period crossover trial. Participants will first complete 1 day of baseline diary data collection under the finalized active study settings. They will then be allocated 1:1 to one of two sequences: active BurstDR followed by sham, or sham followed by active BurstDR. Each randomized treatment period lasts 7 days. A 4-day washout with stimulation switched off will occur after the baseline day and before period 1, and a second 4-day washout will separate periods 1 and 2.

The primary endpoint is period-level pain intensity derived from twice-daily NRS recordings collected during each 7-day randomized treatment period. Baseline-day diary data are descriptive only and are not part of the primary endpoint. The principal comparison is within-participant and paired.

The target sample size is 28 participants with evaluable data from both randomized treatment periods for the primary paired efficacy analysis. Up to 35 participants will be recruited to allow for approximately 20% attrition or nonevaluable treatment periods. The sample size is based on a clinically relevant within-participant treatment difference of 2.0 NRS points, a conservative standard deviation of 3.0 NRS points for the paired treatment differences, and a two-sided alpha of 0.05. Under a normal model for the paired differences, Monte Carlo simulation of the planned two-sided Wilcoxon signed-rank test indicates approximately 91% power with 28 evaluable participants.

3. Objectives, Estimands, and Endpoints

Primary estimand

The primary estimand is the within-participant effect of active BurstDR stimulation, compared with sham, on period-level pain intensity during the planned 7-day randomized treatment periods in participants with evaluable data from both periods. The 1-day baseline observation is not part of the estimand and will be summarized descriptively.

Primary endpoint

For each participant and treatment period, all available NRS ratings (0–10) recorded across predefined pain areas and across the 7 treatment days will be pooled. The period-level median of these ratings will be the primary endpoint value.

Secondary endpoints

1. End-of-period treatment satisfaction (0–10).
2. Period-level median PGIC score for sleep quality.
3. Period-level median PGIC score for mood.
4. Period-level median PGIC score for daily activity.
5. Period-level median PGIC score for social activity.
6. End-of-period blinding/perceptibility assessment.
7. Adverse events and serious adverse events.

Direction of treatment effect

For pain outcomes, a positive paired difference will indicate lower pain during active BurstDR than during sham (defined as Sham minus Active). For outcomes where a higher score is better, a positive paired difference will indicate higher scores during active BurstDR than during sham (defined as Active minus Sham).

4. Analysis Populations

Randomized set

All participants randomized to a treatment sequence.

Modified intention-to-treat (mITT) set

All randomized participants with at least one evaluable treatment period.

Paired efficacy set

All mITT participants with evaluable endpoint data from both treatment periods. This will be the primary analysis population for paired efficacy analyses.

Per-protocol set

Subset of the paired efficacy set without major protocol deviations judged likely to affect treatment exposure, endpoint validity, or blinding integrity. Per-protocol analyses will be supportive.

Safety set

All randomized participants exposed to at least one study-assigned treatment condition, including sham.

5. Randomization and Blinding

Randomization assigns participants to the active–sham or sham–active sequence. Analyses will be conducted using blinded treatment labels until all data cleaning, derivation, and primary/secondary analyses have been completed on coded data. Unblinding will occur only after finalization of the principal analysis outputs or earlier if required for an approved emergency safety procedure.

Sequence allocation will be summarized descriptively. No inferential comparison of baseline characteristics by sequence is planned.

6. General Statistical Principles

All statistical tests will be two-sided with alpha 0.05 unless otherwise stated. Confidence intervals will be 95%. Because the study has a single primary endpoint and secondary endpoints are supportive/exploratory, no multiplicity adjustment will be applied.

Continuous and ordinal outcomes will primarily be summarized using medians, interquartile ranges, means, standard deviations, minima, maxima, and counts as appropriate. Categorical variables will be summarized using counts and percentages. The primary paired analyses are nonparametric and aligned with the median-based endpoint derivation.

No formal interim efficacy analysis is planned. Safety data may be reviewed periodically without inferential alpha spending because no early efficacy stopping is planned.

7. Derivation of Analysis Variables

Predefined pain areas

At baseline, each participant's predefined pain areas will be recorded in the case report form. Only those pain areas prespecified before randomization will contribute to the primary endpoint derivation. Baseline-day diary variables will be derived separately for descriptive summaries and will not be pooled with randomized treatment-period data.

Diary timing

Pain intensity is recorded twice daily, morning and evening. Daily PGIC domain ratings are recorded once per day according to the diary schedule. A baseline day under active study settings is captured before washout 1, and randomized treatment-period diaries are captured during each 7-day arm. Time stamps will be retained in the raw dataset but the primary endpoint will use only the period-level pooled median from the randomized treatment periods.

Blinding integrity variables will include (i) the standardized pre-period perceptibility test performed before period 1 under the final active settings and (ii) the end-of-period response after each arm indicating whether stimulation or paresthesia was felt at any point during that arm. These variables will be summarized descriptively by treatment condition and randomized sequence.

Evaluable treatment period

A treatment period will be considered evaluable for the primary endpoint if at least 6 post-period-start NRS ratings are available across at least 3 distinct treatment days. If a treatment period is stopped early under a protocol-defined stopping rule, all available ratings collected prior to discontinuation will be retained and the period will still be considered evaluable provided at least 2 NRS ratings were recorded.

Period-level pain score

For each participant and treatment period, the period-level pain score will be the median of all available NRS ratings across all predefined pain areas and all treatment days within that period.

Period-level PGIC scores

For each PGIC domain and treatment period, the period-level score will be the median of all available daily ratings during that period.

Paired difference variables

For pain outcomes, paired difference = Sham minus Active. For treatment satisfaction and PGIC outcomes, paired difference = Active minus Sham.

8. Descriptive Summaries

Participant flow will be summarized in a CONSORT-style diagram and supporting table showing screened, consented, randomized, treated, completing each period, and included in each analysis population.

Baseline characteristics will be summarized descriptively overall and by randomized sequence. Variables expected to be summarized include age, sex, pain diagnosis, pain duration where available, implanted device type, stimulation duration, medication status, and baseline pain descriptors. No hypothesis testing of baseline differences is planned.

A separate descriptive summary will present baseline-day diary values collected under active study settings before washout 1. These summaries are supportive only and will not be used for the primary paired efficacy comparison.

9. Primary Efficacy Analysis

The primary analysis will use the paired efficacy set. For each participant, the two period-level median pain scores (active and sham) will be derived and compared within participant.

The null hypothesis is that the distribution of the paired difference in pain scores is centered at zero. The primary inferential test will be the Wilcoxon signed-rank test applied to the paired period-level pain scores.

The primary estimate of treatment effect will be the Hodges–Lehmann estimate of the median paired difference with 95% confidence interval. For reporting, the paired difference will be expressed as Sham minus Active so that positive values favour active BurstDR stimulation. The matched-pairs effect size $r = Z/\sqrt{n}$ will also be reported, where n is the number of non-zero paired differences entering the signed-rank test.

A descriptive table will present, by treatment condition, the number of participants, median, interquartile range, mean, standard deviation, minimum, and maximum of the period-level pain scores.

10. Secondary Analyses

Secondary efficacy outcomes will be analysed in the paired efficacy set using the same paired, median-based framework as the primary endpoint.

Treatment satisfaction

End-of-period satisfaction scores (0–10) will be compared between active and sham using the Wilcoxon signed-rank test. Hodges–Lehmann median paired difference and 95% confidence interval will be reported. Positive values will favour active BurstDR.

PGIC domains

For sleep, mood, daily activity, and social activity, period-level median PGIC scores will be derived and compared using Wilcoxon signed-rank tests with Hodges–Lehmann estimates and 95% confidence intervals. Positive values will favour active BurstDR.

Blinding/perceptibility

Pre-period perceptibility findings and end-of-period blinding/perceptibility responses will be summarized descriptively by treatment condition and sequence. No formal hypothesis test is planned unless prespecified in a later blinded amendment.

All secondary analyses will be interpreted as supportive or exploratory.

11. Sensitivity and Exploratory Analyses

To assess robustness to within-period time effects, the primary paired analysis will be repeated using only days 1–3 and only days 3–5 of each treatment period, using the same median-based approach.

As an exploratory sensitivity analysis, a linear mixed-effects model will be fitted to the period-level median pain score with fixed effects for treatment, period, and sequence, and participant as a random intercept. The treatment coefficient from this model will be reported with 95% confidence interval and p value as a model-based supportive estimate.

Supportive per-protocol analysis

The primary paired analysis will be repeated in the per-protocol set.

Exploratory descriptive analyses

1. Descriptive trajectory plots of daily median pain scores by treatment period.
2. Descriptive summaries of rescue medication use by treatment condition.
3. Where sample size allows, descriptive subgroup summaries by broad pain phenotype or implant indication. No subgroup hypothesis testing is planned.

12. Missing Data, Early Discontinuation, and Protocol Deviations

No imputation of missing outcome data is planned. Missing diary entries within an otherwise evaluable treatment period will simply be ignored, and the period-level median will be calculated from all available observations.

If one treatment period is not evaluable, the participant will remain in the randomized, mITT, and safety sets as applicable but will not contribute to paired efficacy analyses requiring both periods. Early treatment discontinuation will not trigger imputation; all observations collected before discontinuation will be retained.

Protocol deviations will be listed and classified before unblinding. Major deviations potentially relevant to the per-protocol set may include incorrect sequence implementation, substantial off-protocol reprogramming, prohibited medication changes likely to affect pain outcomes, major blinding breaches, or serious diary non-compliance.

13. Safety Analyses

Safety analyses will use the safety set. Adverse events, serious adverse events, device-related events, withdrawals due to adverse events, and early treatment discontinuations will be summarized descriptively.

Where feasible, safety events will also be tabulated by treatment condition during which the event occurred (active treatment, sham treatment, or washout). Given the short crossover periods and small sample size, no formal comparative hypothesis testing of adverse-event rates is planned.

14. Planned Tables, Figures, and Listings

1. Participant disposition and analysis populations.
2. Baseline characteristics overall and by sequence, including a descriptive summary of the 1-day baseline diary.
3. Primary endpoint summary by treatment condition and paired treatment effect estimate.
4. Secondary endpoint summaries and paired treatment effect estimates.
5. Sensitivity analysis table including days 1–3, days 3–5, per-protocol analysis, and exploratory mixed-effects model.
6. Blinding/perceptibility summary table and adverse event summary tables.
7. CONSORT-style participant flow figure.
8. Descriptive figure of daily pain trajectories across both treatment periods.

15. Statistical Software and Reproducibility

Primary analyses will be performed using IBM SPSS Statistics version 29.0.2.0 or later. If needed for validation or model fitting, supportive analyses may also be reproduced in R (version 4.3 or later). The final analysis dataset, derivation logic, and output programs will be archived in a version-controlled study folder.

All analyses will be run on blinded, coded data. A dated record of the exact analysis scripts and outputs used for the final report will be retained.

16. References (methodological notes only)

Standard nonparametric and mixed-model methods will be used. No external methodological departures from standard biostatistical practice are anticipated.