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Randomized Study of the pdSTIM™ System (phrenic nerve to diaphragm STIMulation) in Failure to Wean Mechanically Ventilated Patients

(ReInvigorate Study)

Document: Statistical Analysis Plan (SAP)

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Stimdia

Randomized Study of the pdSTIM™ System

(phrenic nerve to diaphragm STIMulation)

in Failure to Wean

Mechanically Ventilated Patients

(ReInvigorate Study)

Protocol Number: CIP0002

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Statistical Analysis Plan

[redacted]

Version History

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[redacted]	[redacted]	[redacted]	Revisions to align with updated protocol: • N = 32 randomized Feasibility Cohort [redacted]

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1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected for the Feasibility Cohort under the CLINICAL INVESTIGATION PLAN (CIP), Randomized Study of the pdSTIM™ System (phrenic nerve to diaphragm STIMulation) in Failure to Wean Mechanically Ventilated Patients (ReInvigorate Study), Protocol Number: CIP0002. 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 pdSTIM [redacted] patients enrolled under CIP0002 effectively served as a feasibility cohort. [redacted] The small sample size precludes the ability to draw statistically or clinically meaningful conclusions.

Due to the exploratory nature of the Feasibility Cohort and smaller sample size than originally planned, statistically relevant conclusions will not be made from this small sample size [redacted] The sample size for this cohort is limited and was not determined based on statistical power considerations. As such, the data obtained will not be sufficient to support robust statistical inference or hypothesis testing.

Performing formal statistical analyses (e.g., hypothesis testing, hazard ratios, or cumulative incidence estimates) with such a small sample size would risk generating potentially misleading conclusions due to the high degree of uncertainty and wide variability in the estimates. [redacted]

Safety analyses are restricted to adverse events (AEs) and serious adverse events (SAEs) with a reasonable possibility of being related to the device, study procedures, or study assessments. [redacted]

[redacted]

This Statistical Analysis Plan (SAP) applies only to the Feasibility Cohort enrolled under protocol CIP0002. [redacted] This SAP is the governing document for all analyses and data displays associated with the Feasibility Cohort in the ReInvigorate Study. In the event of any discrepancies between this SAP and the protocol, CIP0002, the specifications in this SAP will take precedence for statistical analyses and reporting. The protocol CIP0002 remains the governing document for study conduct and overall study design, while the SAP provides the authoritative framework for statistical methodology, data handling, and presentation of results. Any deviations from this SAP will be prospectively documented where possible [redacted]

[redacted]

2 Study Objectives

The objective of this study was to evaluate the safety and efficacy of use of the pdSTIM System to increase diaphragm strength and reduce weaning time of subjects on mechanical ventilation when compared to standard of care.

3 Abbreviations

Abbreviation/Term	*Definition*
ITT	Intent-to-treat
MV	Mechanical ventilation
RSBI	Rapid Shallow Breathing Index
SAP	Statistical Analysis Plan

3.1 Study Endpoints

The primary endpoints will be assessed after all randomized subjects have either completed the 30-Day follow up period or been censored.

Efficacy analyses will be limited to subject-level listings without formal statistical comparisons. [redacted]

Safety analyses will focus on events with a reasonable possibility of being related to the device, study procedures, or study assessments, [redacted]

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to successful weaning from mechanical ventilation. [redacted]

Given the feasibility objective of this cohort and limited sample size, no statistical comparisons between treatment groups or summary descriptive statistics will be performed. [redacted]

3.1.2 Primary Safety Endpoint

The primary safety endpoint is an assessment of Serious Adverse Events (SAEs) possibly or definitely related to the device, study procedures, and/or study assessments. [redacted]

3.1.3 Secondary Endpoints

The following exploratory/supportive safety data will be provided:

- Non-serious AEs occurring in >5% of subjects possibly or definitely related to the device, study procedures, and/or study assessments through the earliest of successful weaning, Day 30, date of transfer to a non-study site facility, date of discharge from the study site, date of withdrawal of consent, date of lost to follow-up, or date of death (listed).
- All-cause mortality through the earliest of successful weaning, Day 30, transfer to a non-study site facility, discharge from the study site, withdrawal of consent, lost to follow-up, or death (summarized).

3.1.4 Additional Objectives

No other secondary or exploratory efficacy or safety endpoints will be evaluated in this feasibility cohort, including the originally planned additional objectives.

4 Study Design

The ReInvigorate Study was originally designed as a prospective, multicenter, randomized, controlled clinical study under CIP0002 to evaluate the safety and efficacy of the pdSTIM System to facilitate weaning from mechanical ventilation through phrenic nerve stimulation. The ReInvigorate Study now includes a Feasibility Cohort under CIP0002 [redacted] By restructuring the study to isolate this early phase from the pivotal cohort, we protect data integrity, ensuring meaningful evaluation of the final-use configuration; align with regulatory expectations for investigational device evaluation [redacted]

Potential participants who are on mechanical ventilation for at least four days and have failed at least one weaning attempt were considered for the Feasibility Cohort. Those enrolled were randomized in a 1:1 manner between a Treatment group that is standard of care with the pdSTIM System and a Control group that is standard of care.

4.1 Randomization

Subjects (n = 32) were randomized to either the Control or Treatment Group in a 1:1 ratio to prevent selection bias and generate a similar number of subjects to each group.

[redacted] Randomization was based on permuted block randomization by site, via an electronic database.

[redacted]

4.2 Blinding

This is an open-label study with no blinding.

5 Sample Size Determination

[redacted] 350 randomized subjects were originally planned. However, only a total n = 32 randomized subjects were enrolled in the Feasibility Cohort. This document outlines the Statistical Analysis Plan for the Feasibility Cohort only. See Statistical Analysis Plan: pdSTIM Pivotal Cohort for the statistical analysis plan for the Pivotal Cohort.

The sample size for this Feasibility Cohort is limited and was not determined based on statistical power considerations. As such, the data obtained will not be sufficient to support robust statistical inference or hypothesis testing.

6 Statistical Analyses

6.1 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.

6.1.1 Descriptive Statistics

Any summarized Continuous data reported will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Any summarized categorical variables reported will be summarized with frequency counts and percentages. No formal statistical comparisons will be performed.

[redacted]

6.1.3 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.

6.1.4 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value while standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

6.2 Analysis Populations

The following analysis populations are defined for analysis:

Intent-to-treat (ITT) analysis set: The ITT is defined as all randomized subjects. Analysis will be based on the randomized treatment assignment regardless of the actual treatment received.

[redacted]

Safety analysis set: The safety analysis set is defined as all randomized treatment subjects for whom treatment was attempted and all randomized control subjects who were not treated with the investigational device.

[redacted]

Unless otherwise specified, the primary analysis set for efficacy endpoints and outcomes is the ITT analysis set. Safety analyses will be based on the safety analysis set. [redacted]

6.3 General Handling of Missing Data

All attempts will be made to limit the amount of missing data. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed. Subjects lost to follow-up for the primary endpoint will be censored at their last known status date. Unless otherwise specified, analyses for other endpoints will be based on the available results without imputation for missing data.

6.4 Subject Disposition

Subject accountability will be summarized to document subject disposition throughout the feasibility cohort. [redacted]

Summaries will include the number of subjects screened, randomized, and excluded, as well as the numbers included in the intent-to-treat (ITT) [redacted]

6.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for the following variables: sex, race, ethnicity, age, time since initial episode of mechanical ventilation started at Baseline. [redacted]

6.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the Time to Wean within 30 days. Successful weaning is defined as breathing without mechanical ventilator assistance for 48 hours after extubation/removal from mechanical ventilation.

6.7.1.1 Primary Analysis

Successful weaning is counted as an event, with the time to the event measured from the day of randomization to the day of successful weaning. Accordingly, being "event-free" means a subject has not been successfully weaned and thus is a less favorable outcome than a subject who is successfully weaned.

No formal hypothesis testing will be conducted. [redacted]

6.7.1.2 Handling of Missing Data

Available follow-up information will be used for the primary efficacy endpoint, with subjects censored at the earliest of Day 30, transfer to a non–study site facility, discharge from the study site, withdrawal of consent, lost to follow-up, or death. Subjects who complete the Day 30 Visit in hospital at a study site without achieving successful weaning will be censored at Day 30. No statistical imputation of missing data will be performed.

6.7.2 Primary Safety Endpoint

The primary safety endpoint is an assessment of Serious Adverse Events (SAEs) possibly or definitely related to the device, study procedures, and/or study assessments.

6.7.2.1 Primary Analysis

No formal hypothesis testing will be conducted. [redacted]

[redacted]

6.7.2.2 Handling of Missing Data

No statistical imputation of missing data will be performed. If safety data are incomplete, not source verified, or otherwise unverifiable, those data will be excluded from the listings.

6.8 Safety Analyses

The following exploratory/supportive safety data will be provided:

- Non-serious AEs occurring in >5% of subjects possibly or definitely related to the device, study procedures, and/or study assessments through the earliest of successful weaning, Day 30, date of transfer to a non-study site facility, date of discharge from the study site, date of withdrawal of consent, date of lost to follow-up, or date of death (listed).
- All-cause mortality through the earliest of successful weaning, Day 30, transfer to a non-study site facility, discharge from the study site, withdrawal of consent, lost to follow-up, or death (summarized).

No formal hypothesis testing will be conducted, and no statistical imputation of missing data will be performed. If data are incomplete, not source verified or otherwise unverifiable (e.g., data reported during telephone visits), those data will be excluded from the listings

[redacted]

[redacted]

7 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amendment to this 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]