Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	16 Oct 2023	G. Arthur Carter, Steve Erickson, and Valeria Ursu	Initial release

Neuronetics

A Prospective, Randomized, Single Blind, Crossover Study to Evaluate Treatment Effects Associated With the Neurostar Softstart™ Treatment Feature

Neuronetics Protocol Number: 44-03054-000, Rev 1

Statistical Analysis Plan

Version 1.0, 16 October 2023

NAMSA Project Number: US033666

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 and should be read in conjunction with the study protocol and case report forms (CRFs). Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Abbreviations

Abbreviation/Term	*Definition*
CRF	Case Report Form(s)
MDD	Major depressive disorder
MT	Motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAP	Statistical Analysis Plan
SRS	Study Requirement Specification

3 Study Objectives

3.1 Primary Objective

The Primary objective is to evaluate the comfort associated with TMS treatment when applied with the standard Dash treatment protocol vs. the Dash protocol with the SoftStart feature enabled.

3.2 Secondary Objectives

The Secondary objectives are to evaluate the ability to reach the prescribed treatment intensity, the time it takes to reach the prescribed treatment intensity, maximum treatment intensity reached, patient treatment preference and other treatment effects between the two treatment protocols.

3.3 Study Endpoints

Primary endpoint: The difference in the change in VAS scores for Comfort after rTMS (repetitive transcranial magnetic stimulation) between treatments administered with the Dash protocol (treatment Y) and treatments administered with the Dash protocol with SoftStart feature enabled (treatment X). Comfort will be evaluated as a change for all observations between groups, observations from Baseline to end of escalation phase, observations between groups during the crossover phase and observations

within a patient between treatments in the cross-over phase. Comfort will also be analyzed over time and by number of treatments between groups.

After the final study treatment, the treatment protocol planned for remaining TMS sessions, and reason for choosing it, will be documented as a secondary study endpoint and the subject will be exited from the study.

If adverse events occur, those data will be summarized using standard descriptive statistics (frequency distributions, percentages, listings).

4 Study Design

This is a prospective, randomized, single center, single blind study conducted in an adult population being treated for MDD (major depressive disorder).

For each patient, the study will consist of up to approximately 14 days, one hour for screening and 30 minutes during each daily treatment session. The goal of the study is to monitor and compare patient comfort (treatment area sensitivity) using two different treatment protocols at the start of TMS therapy where the stimulation intensity is typically escalated over 1-10 treatments until the patient is comfortable with the prescribed treatment dose (% MT; typically, 120%).

Each subject, of approximately 40, will be treated with rTMS for MDD as diagnosed and prescribed by their treating physician. Following consent and successful study qualification, study subjects will be randomized to the standard Dash protocol or the modified Dash protocol with the SoftStart feature enabled.

Prior to rTMS stimulation, the Motor Threshold (MT) will be established for each subject individually. Total treatment time per day is 18 minutes 45 seconds for either of the two treatments. Every treatment day patients will receive 75 fifteen second cycles. Each cycle is a 40 pulse train of 4 seconds with 11 seconds off (Dash), or a 50 pulse train of 5 seconds with 10 seconds off (Soft Start Dash). The extra 10 pulses per Soft Start Dash train are an eight pulse ramp-up sequence and a two pulse ramp-down sequence.

At the start of the 6th Treatment session or the session after the subject reaches the prescribed dose, the subject will be switched to the alternative treatment protocol and continue to alternate treatment each day for the next 4 treatments.

Each day of these 4 treatment sessions, at end of the first time interval (3:45 min, total of a set of 15 fifteen second cycles) and the end of the session, the subject will complete the comfort/pain questionnaire and be asked whether they preferred the current treatment, or the treatment received at the previous session (Today's Treatment, Last Treatment, No Difference).

During treatments, the subject will be asked to complete several questionnaires, including comfort/pain, treatment preference, and depression questionnaires.

4.1 Randomization

Subjects will be randomized prior to study start, to the initial treatment received prior to first crossover. Randomization will be performed using random permuted blocks of sizes 2 and 4, stratified by gender, with a 1:1 allocation ratio (Dash protocol / Dash protocol with SoftStart). A single site handling 40 total subjects is planned. Extra subjects and sites will be randomized, in the event unforeseen changes become necessary. Randomized treatment will be assigned by paper envelopes only, no database will be utilized.

4.2 Blinding

Only the patients will be blinded to the treatment(s) received.

4.3 Study Assessments

VAS Scale (comfort and pain), at 3:45 and 18:45 of each treatment session

Preference Questionnaire, at 18:45 of each treatment session

PHQ-9 Depression Scale, at 18:45 of each treatment session

5 Sample Size Determination

A sample size of 40 total subjects, twenty to begin treatment with each of the two study arms, was selected as sufficient to perform a preliminary assessment of the differences between the two repetitive transcranial magnetic stimulation (rTMS) therapies for MDD. The sample size is not based on formal power requirements for a statistical hypothesis test but is based on a desire to obtain a reasonable initial data set for exploratory and planning purposes.

6 Statistical Analyses

6.1 General Considerations

Statistical analyses will be performed by the Biostatistics Section of the Sponsor or its designee. Any additional or supplemental data analyses performed independently by the Investigator should be submitted to the Sponsor for review and approval.

Except where otherwise specified, the following general principles apply to the planned statistical analyses. It is intended that all statistical analysis will be conducted using the EasyMedStat package within the sponsor database. If necessary, some summary analyses may be generated by a sponsor designee utilizing SAS version 9.4 or later, or other widely-accepted statistical or graphical software as required.

6.1.1 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.

6.1.2 Study Day

Study day 1 is the date of the first day of the Dose Ramp Phase. Day in study will be calculated relative to that day as follows:

Study Day = Procedure/Assessment Date – Date of first day of the Dose Ramp Phase + 1

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = Start Date – End Date

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 whether it is out of window.

6.1.4 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".

6.1.5 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. For continuous parameters, means, medians, and standard deviations will be reported to 1 additional decimal place 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:

1. **Intent-to-treat (ITT)***: The ITT population is defined as all subjects randomized.*
2. **Modified Intent-to-Treat (mITT)***: The mITT population is defined as all subjects in the ITT population where treatment was initiated.*
3. **Per protocol (PP)***: The PP population is defined as all subjects in with no significant protocol deviation, or adverse event that could compromise the validity of their assessments.*
4. **Safety (SAF)***: The SAF population is defined as all subjects that were exposed to any study device or treatment.*

The primary analysis set for efficacy endpoints and results will be the mITT set, with any other analysis sets defined as optional and supportive. The primary analysis set for safety endpoints and results will be the SAF set, with any other analysis sets defined as optional and supportive.

6.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed.

In the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 15th of the month will be used for analysis. In the rare case that the date is fully unknown, the date will be imputed as the Date of first day of the Dose Ramp Phase. Imputation of partial dates is subject to the condition that it must occur on or after the informed consent date. In the case where the imputed date is prior to the informed consent date,

the date of informed consent will be used. As death cannot occur before any documented subject contact, for date of death the imputed date of death must occur on or after last known contact in study.

6.4 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. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

6.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables, as well as other baseline characteristics.

6.6 Analysis of Study Endpoints

6.6.1 Primary Safety Endpoint

Comparison of the incidence, severity, and frequency of Adverse Events (AE) & Adjustments in Treatment Location between the experimental and the control group will be made descriptively.

6.6.2 Primary Efficacy Endpoints

The Primary study outcome assessments will be determined based on differences in the mean VAS ratings on a 0-10cm VAS scale for comfort (the scale ranges from 0-100, and 0 = no pain or discomfort, and 100 = extreme discomfort or worst pain imaginable). Statistical methods employed to detect differences between the experimental and the control groups, for the below outcomes, may include a t-test, Chi-Square test, and Fisher's Exact test. Test for normality and equality of variances may be used for continuous parameters. If data are found to fail one or both, then nonparametric methods may be employed, eg, Wilcoxon Rank Sum test. For assessments including crossovers, a relevant method accounting for period effect, repeated measures, and randomized order may be utilized.

Analyses outlined below will be done for the average of patient scores.

One of the following analysises will be employed as the primary analysis of the primary efficacy endpoint:

The difference in the change in Visual Analog Scale scores for Comfort after rTMS stimulation between treatments administered with the Dash protocol and with New feature enabled. Comfort will be evaluated as a change for all observations between groups, observations from Baseline to end of escalation phase, observations between groups during the crossover phase and observations within a patient between treatments in the cross-over phase.

At minute 3:45, and at the end of the treatment session, the subject will be asked to complete a Visual Analog Scale (VAS), for Comfort/Pain.

a. All over group (throughout the whole trial, Ramp phase & Crossover phase) – all VAS scores for X -> Y or Y -> X (similar to 1.d.ii above. Start with the average of the 3:45, 18:45 scores on each Day for each subject, then average each of the daily X averages and average each of the daily Y averages for each patient, comparing the average of the 40 X averages to the average of the 40 Y averages, a one-sided hypothesis test evaluating if the "with Comfort Start" group, X, has lower average scores)

b. Between group comparison: Prior to cross over (reaching 120%MT): combination of the scores at 3:45 min and at the end of treatment, 18:45 min; (start with the average of the these two scores for each subject that reached 120% (average of all scores prior to & including 120%), then compare the average of the X averages (at most 20) to the average of the Y averages (at most 20), a one-sided hypothesis test evaluating if the "with Comfort Start" group, X, has lower average scores)

a. Average of all the patient scores for all Crossover Phase treatments (start with the average of the 3:45 and 18:45 scores on each Crossover Day for each subject, then average each of the daily X averages and average each of the daily Y averages for each patient, comparing the average of the 40 X averages to the average of the 40 Y averages, a one-sided hypothesis test evaluating if the "with Comfort Start" group, X, has lower average scores)

6.6.2.1 Primary Analysis

The majority of the primary efficacy endpoints will be assessed with the following hypothesis:

H_0: Comfort Start Dash is equal to or inferior to Dash

H_a: Comfort Start Dash is superior to Dash

Note that some of the hypothesis testing will be two-sided, but the majority of inferential statistical testing will be looking at a one-sided alternative hypothesis that the treatment protocol with Comfort Start employed is superior to the Dash protocol without Comfort Start employed.

The endpoints will be evaluated using the mITT population.

The primary endpoints will be assessed via descriptive (unless otherwise specified) and superiority statistics.

6.6.3 Secondary Endpoints

The secondary endpoints may be assessed via superiority or non-inferiority testing, with any non-inferiority margins to be defined, or may be assessed with descriptive summaries only.

The Secondary study outcomes will be determined as follows:

The ability to reach the prescribed treatment intensity, the time it takes to reach the prescribed intensity, maximum treatment intensity reached, subject treatment preference and discontinuations due to treatment discomfort between the two treatment protocols.

Once TMS therapy begins, adjustments to lower the stimulation intensity can begin immediately, as needed, for subject tolerance. The treater will assess if the subject can tolerate escalating the treatment MT by 10% at different time points. At each interval and the end of treatment, the treater will record the current %MT achieved. The goal will be to reach and sustain the target MT established by the treating physician of 120%MT. Once the target MT has been achieved and sustained for a certain period recording and increases of %MT may be discontinued but re-started at central intervals if %MT is subsequently reduced.

6.7 Safety Analyses

Adverse events (AE) will be reported for the SAF population. 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 device deficiencies will be reported in listing format.

6.8 Subgroup Analyses

Subgroup analysis may also be performed based on gender, initial comfort scores, group assignments or other variables. Specifically, an examination may be done to determine if differences between treatment arms are consistent across males and females, to investigate whether females are more sensitive to pain overall, descriptively only, or additionally via one-sided hypothesis tests.

6.9 Interim Analyses

No interim analyses are planned.

7 Changes from Planned Analyses

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.

8 Subject Listings

A listing of patient demographics will be generated.

9 References

Bijur PE, Latimer CT, Gallagher EJ. Validation of a Verbally Administered Numerical Rating Scale of Acute Pain for Use in the Emergency Department. Acad Emergency Med 2003; doi:10.1111/j.1553-2712.2003.tb01355.x

10 Appendices

Appendix A. < Schedule of Events >

			Dose Ramp Phase					Crossover Phase			
Study Visits	Screening and Baseline		1[AB]	2[F]	3[F]	4[F]	5[F]	1[C,D]	2[C,D]	3[C,D]	4[C,D]
Patient Visit SOC	1	1	2	3	4	5	6	7	8	9	10
Informed Consent	X		X								
Medical History & Medications	X										
Inclusion and Exclusion Criteria	X										
Randomization			X								
Motor Threshold Determination[E]			X								
Study Exit											X
TMS Treatment Session - SOC			X	X	X	X	X	X	X	X	X
Efficacy Assessments											
VAS (comfort and pain)[G]			X	X	X	X	X	X	X	X	X
Subject Preference [H]				X	X	X	X	X	X	X	X
PHQ-9 [H]			X								X
Safety Assessments											
Adverse Events			X	X	X	X	X	X	X	X	X
Medication changes			X	X	X	X	X	X	X	X	X

[A] The stimulation dose for the DLPFC is determined by the physician

[B] The stimulation protocol is randomized to treatment X or Treatment Y

[C] The stimulation protocol is alternated between treatment X or Treatment Y

[D] The stimulation protocol preference of treatment X or Treatment Y is determined by the subject

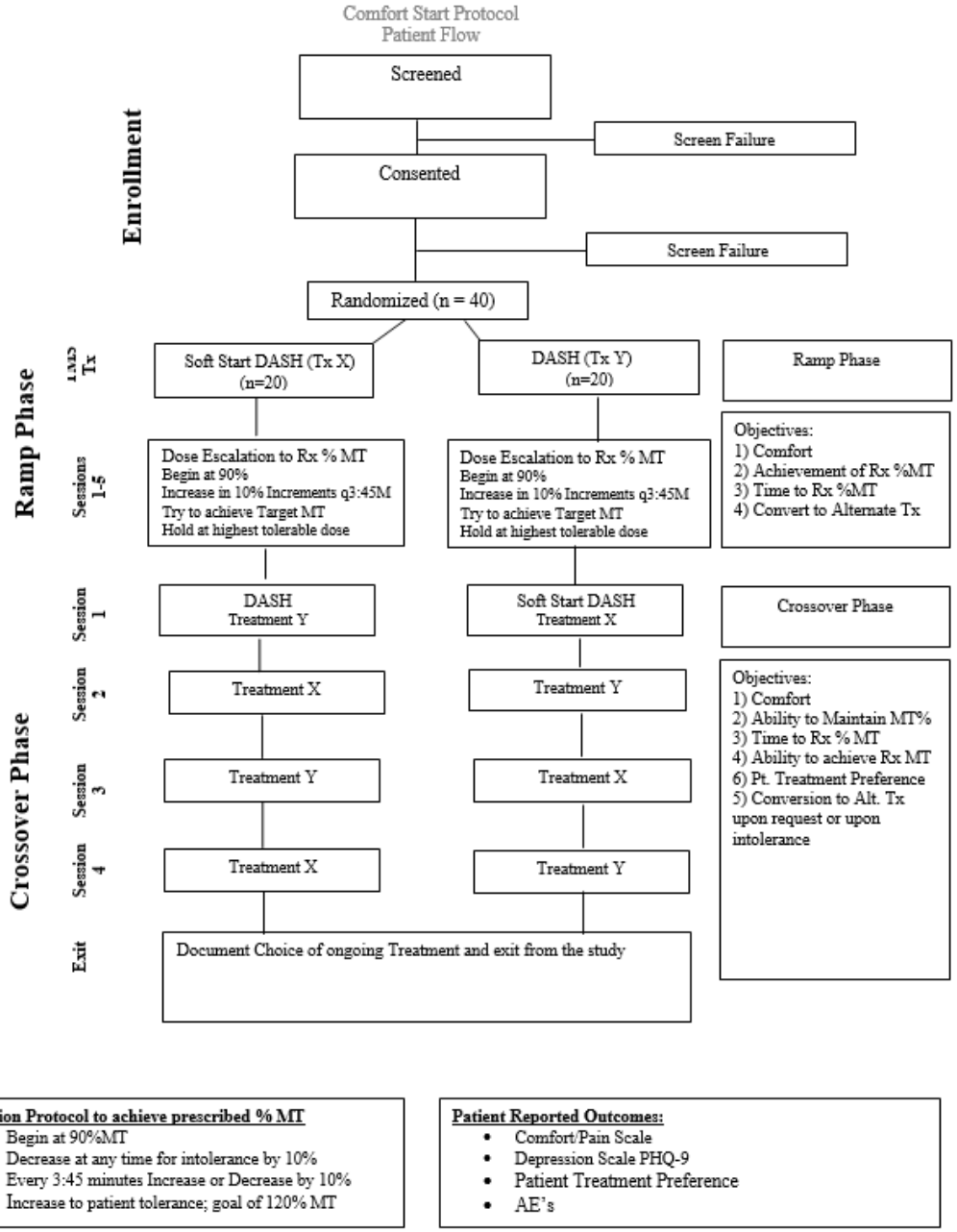
[E] Motor Threshold Determination will be completed as SOC and not dictated by the study procedures

[F] Study procedures for treatment visits 2-5 are only completed if the patient does not achieve target %MT and sustain that intensity for 3:45 min; Once achieved, subject will begin Crossover phase at the next visit

[G] Assessments completed before treatment, at minute 3:45 of treatment and end of treatment

[H] Assessments completed at the end of treatment visits

Appendix B. < Diagram of Study Design/Flow >



Treatment MT Escalation and Tracking Worksheet

Appendix C. < Treatment Escalation WorkSheet >

Subject ID#	Ramp Phase	Do NOT inform patient of treatment X or Y
	Start at 90%MT	Determine tolerance at each interval and increase %MT by 10% if Tolerable

Date	Treatment MT %	% MT Changes For Both Treatment X and Treatment Y									
		Initial Tx		3:45-7:30		7:30-11:15		11:15-15:00		15:00 - 18:45	
Treatment Day		Start	End	Start	End	Start	End	Start	End	Start	End
	60										
	70										
	80										
	90										
	100										
	110										
	120										

Do NOT Inform Pt. when they are changing % MT dose	First Treatment: Comfort Scale at minute 3:45 and End of Treatment; For all subsequent treatments include preference questions

Subject ID#	CrossOver Phase	Do NOT inform patient of treatment X or Y
	Start at Last Tolerable Dos	If not at 120%MT, continue to determine tolerance and increase %MT if Tolerable

Date	Treatment MT %	% MT Changes For Both Treatment X and Treatment Y									
		Initial Tx		3:45-7:30		7:30-11:15		11:15-15:00		15:00 - 18:45	
Treatment Day		Start	End	Start	End	Start	End	Start	End	Start	End
	60										
	70										
	80										
	90										
	100										
	110										
	120										

Do NOT Inform Pt. when they are changing % MT dose	Comfort Scale and preference questions at minute 3:45 and End of Treatment

Appendix D. < Visual Analog Scale (VAS) Scale >

Attachment F– Comfort Visual Analog Scale (VAS)

A Visual Analog Scale (VAS) will be used to for comfort assessment after each rTMS stimulation.

"Mark just **ONE** spot on the line below that best shows the level of discomfort/pain you may have felt during the treatment, where '0' means you didn't feel any discomfort/pain at all and '100' means you felt extreme discomfort/worst pain you can imagine. Please mark only **ONE** spot on the line with an **X** that looks about right for your pain level during treatment. **Do not think of or write in a number**."

No discomfort or pain

Extreme discomfort or worst pain imaginable

Appendix E. < Patient Preference Question >