Statistical Analysis Plan for Neuronetics Protocol 44-02219-000: A Randomized, Sham-Controlled Trial Evaluating the Safety and Effectiveness of NeuroStar Transcranial Magnetic Stimulation (TMS) Therapy in Depressed Adolescents

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Section 1. Study Design and Objectives

For a more complete description of the study protocol, please refer to the current version of the protocol, entitled, 44-02219-000, "A Randomized, Sham-Controlled Trial Evaluating the Safety and Effectiveness of NeuroStar Transcranial Magnetic Stimulation (TMS) Therapy in Depressed Adolescents, version C.

A. Trial Design Summary:

Study 44-02219-000 is a multi-center, randomized, sham-controlled clinical trial evaluating the safety and effectiveness of treatment with the NeuroStar TMS Therapy system in adolescent patients ages 12 through 21 who have failed to received treatment benefit from prior administration of antidepressant medications. The study is organized into 3 separate phases. During Phase I, patients meeting inclusion and exclusion criteria are randomly assigned in a 1:1 ratio to receive either daily treatment with the NeuroStar TMS Therapy device in the XPLOR research configuration or sham NeuroStar treatment for up to 6 weeks (30 treatments). Patients who do not meet criteria for clinically significant treatment benefit are offered the opportunity to enter Phase II, where open-label active NeuroStar TMS Therapy is provided to all patients for up to 6 weeks (30 treatments). Patients who receive clinically significant treatment benefit at the conclusion of either Phase I or Phase II are offered the opportunity to proceed into Phase III, where NeuroStar TMS Therapy is tapered, and patients are continually monitored for up to 6 months to determine the durability of effect of benefit from the acute treatment phases of the study. All patients are treated with NeuroStar TMS Therapy as a monotherapy, no antidepressant medications are permitted during the course of all three study Phases. During Phase III, patients are permitted to receive a reintroduction of an acute course of NeuroStar TMS Therapy if they meet protocol-defined criteria for symptom re-emergence.

B. Primary Study Objective:

- To evaluate the antidepressant effects of daily, active TMS (when compared with sham treatment) in adolescents meeting criteria for Major Depressive Disorder, single or recurrent episode (Phase I).

C. Secondary Study Objectives:

- To evaluate the acute and long-term safety of TMS treatment in adolescent MDD subjects.
- To evaluate the durability of benefit of TMS treatment over the course of 6 months in subjects who received clinical benefit from acute treatment course(s) (Phase III).
- To evaluate the benefit of daily, active, open-label TMS in Phase I subjects who did not receive protocol-defined clinical benefit; as new acute treatment (sham to active) or as extended treatment course (blinded active to open label active) (Phase II)

Section 2. Statistical Justifications

A. Sample Size Justification:

There are no large, randomized controlled trials of the use of transcranial magnetic stimulation (TMS) in the treatment of adolescent major depressive disorder that can be used to estimate effect size. Therefore, several different sources of evidence were used to estimate the expected effect size of treatment as proposed in this

protocol. First, evidence was reviewed from the study by Wall and colleagues, who reported preliminary data from a small patient population of adolescents treated with the NeuroStar TMS Therapy System in an open label study design (Wall, 2011). This study is especially relevant because it is the only available evidence using the specific TMS device (i.e., the NeuroStar TMS Therapy System) that will be utilized in the NeuroStar TMS Adolescent MDD RCT, and it used the identical stimulation parameters and duration of treatment proposed in this study protocol. In that report, eight adolescent patients participated who had previously failed to benefit from treatment with 2 or more antidepressant medications and were currently in stable treatment with a single ineffective (selective serotonin reuptake inhibitor, SSRI) antidepressant medication. Seven of 8 patients, ages 14-18 years, completed all 30 treatments in this study. The primary outcome measure was the Children's Depression Rating Scale-Revised (CDRS-R) which showed significant improvement from baseline (mean [SD]) (69.6 [6.6]) at treatment 10 (50.9 [12]), $P<0.02$, treatment 20 (40.1 [14]), $P<0.01$, treatment 30 (32.6 [7.3]), $P<0.0001$, and at 6-month follow up (32.7 [3.8]), $P<0.0001$.

Using this data, the mean change in CDRS-R total score was estimated to be approximately 33, with a standard deviation of 7.3. It is presumed that a treatment difference of 8.0 points on the CDRS-R scale between randomized treatment conditions may be anticipated in a sham-controlled study, and that a conservative estimate for a pooled standard deviation is 10.0 points, which results in an estimated standardized effect size of 0.80. This is considered to be the upper bound of an expected magnitude of treatment benefit in an adolescent depression study population. Under these assumptions, it is presumed that a sample size of approximately N=35 patients per treatment group, with an alpha level = 0.05 would provide approximately 90% power to detect a treatment difference between active and sham TMS groups.

Another important source of evidence to consider in estimating an effect size for this study can be derived from randomized controlled trial evidence from the study of antidepressant medications that are FDA approved as treatments for adolescent patients with major depressive disorder. The relevant medications to consider include the medications fluoxetine (Emslie, et al., 1997; 2002) and escitalopram (Emslie, et al., 2007). Replicated studies of the antidepressant fluoxetine have shown active versus sham treatment differences using the CDRS-R that range from approximately 7 to 9 points, with associated pooled standard deviations of approximately 9 to 12 points. Estimated standardized effect sizes in these studies are reported as moderately large, approximately 0.50 (Emslie, et al., 1997; 2002). Results of similarly designed studies of escitalopram suggest a lower estimated standardized effect size of approximately 0.30 (Emslie, et al., 2009).

In addition to these data, the results of a large, federally-supported multisite study of the use of antidepressant medication for the treatment of adolescent major depression are also relevant to consider. This study was not specifically directed at the question of antidepressant medication monotherapy alone, rather the design was intended to examine the effectiveness of the combination of antidepressant medication with cognitive-behavior therapy (CBT). Nevertheless, examination of the medication alone treatment condition in this study provides important supportive information in an estimation of the anticipated standardized effect size in adolescents. The Treatment of Adolescent Depression Study (TADS) (March, et al., 2004) examined the benefit of the use of fluoxetine alone, CBT alone, or the combination of the two versus a placebo condition. In that report, the use of fluoxetine alone versus placebo was observed to demonstrate a standardized effect size of 0.68, similar in magnitude to the results of the Emslie and colleagues studies described above (Emslie, et al, 1997; 2002). It should be noted, however, that these studies with antidepressant medication utilized a treatment-naïve study population, excluding patients with treatment resistant depression.

Based on the aggregate evidence described here, it is anticipated that this study, if effective in demonstrating the superiority of NeuroStar TMS Therapy® compared to sham TMS in adolescent patients with treatment resistant major depressive disorder, may be expected to demonstrate a standardized effect size of approximately 0.50 to 0.60. As a stand-alone analysis, it is therefore expected that a sample size of 50 patients per treatment arm, at an alpha level of 0.05, should provide greater than 85% power to detect a statistically significant difference between the treatment groups. However, as noted further below, efficacy also may be established by analysis of the adolescent study data using a frequentist approach which borrows data from two prior adult RCTs in major depression using the NeuroStar TMS Therapy System.

B. Discussion of Statistical Methods:

This study in adolescent patients is a randomized, parallel-group comparison of treatment with TMS as compared to a sham control. It will be conducted at approximately 16 sites in the United States and Canada, with independent randomization protocols within each site, using a permuted block design to improve balance within site. The primary outcome is the last post-treatment symptom score (LV) measured using the primary efficacy outcome measure (efficacy variable and point of declaration are blinded to the Investigator) for each subject. LV will come from the 6-week visit, unless the data is missing, in which case the last observation will be carried forward (LOCF). The analysis will be performed on the strict intention-to-treat sample of all evaluable subjects, meaning those subjects with a baseline and at least one post-baseline observation available for analysis.

Poorly recruiting sites, defined as those with fewer than 2 randomization blocks, will be pooled into one or more pseudo-sites for purposes of analysis. To ensure that nearly all sites will be of adequate size we will adopt a strict closure policy for sites that do not show early signs of enrollment success. With 16 sites, the average number of subjects per site is approximately 18, so there may be a few sites with fewer than 2 randomization blocks. A site that has not randomized at least 2 subjects in the first quarter of their enrollment may be closed. Then if as many as 2 sites are closed, and one poorly performing site eludes closure, there will be no more than one pseudo-site comprising a total of no more than 2 subjects from the closed site and approximately 11 from the poorly performing site, or no more than 13 subjects in all (i.e. <5% of the total sample).

As noted elsewhere in this protocol, the sites were blinded to the point of primary efficacy declaration in order to improve the study's signal detection ability. Point of declaration for the primary outcome measure is included in this document, which was not shared with any of the study sites.

The null hypothesis will be tested in an analysis of covariance of the LV (value from 6-week visit unless it is missing, then LOCF used), using baseline score, and ATR medication resistance level as fixed effect covariates, adjusting for site differences using a random effect. As discussed elsewhere, the ATR medication resistance levels will group subjects categorically by number of medications which have shown an adequate degree of resistance for that subject. These resistance levels will be grouped into two categories in statistical model, 0-1 in the current episode or 2-4 in the current episode, unless the final distribution of ATR scores in the study population suggests another allocation would be more statistically appropriate. All tests are two-sided, at the 5% level. The primary outcome should be available and meaningful for nearly all subjects, so the main analysis will be by strict intention-to-treat as defined above. An analysis of observed cases only will be performed as a secondary outcome measure. A site by treatment interaction analysis will be done as a secondary analysis to see if there is significant heterogeneity in the effect of TMS across sites. In particular, we will examine site-specific treatment effects (with confidence intervals) to test for evidence of true reversal of effect.

Secondary outcomes include other continuous measures, and within-subject dichotomous variables as outlined in the efficacy variables described elsewhere in this protocol. The treatment effect null hypothesis will be tested by logistic regression on treatment group assignment with adjustment for site and ATR medication resistance level. In addition, the longitudinal symptom scores will be analyzed with a general linear model adjusting for baseline scores and ATR medication resistance level, using a saturated means model for time since baseline, with treatment effect parameterized by a linear effect in time. The correlation of scores within individuals over time will be handled by allowing a within-subjects residual covariance matrix selected by exploration of the sample semi-variogram, as described by Diggle, Liang and Zeger. If this exploration reveals that a mixed model approach will fit the covariance structure better, random effects will be included in the model. As in the main analysis, site by treatment interactions will be tested.

In addition to testing the hypothesis noted above in the study alone, a meta-analysis will be used to establish evidence of efficacy. Specifically, in addition to the evidence to be obtained in this study protocol, there are

already two large, randomized, multisite sham-controlled studies of the use of the NeuroStar TMS Therapy® System in adult patients (ages 18-70 years of age) with major depressive disorder. These data are statistically important to consider in the interpretation of the data to be collected in the adolescent study population using the NeuroStar® TMS device. Therefore, a frequentist analysis will be used to demonstrate the effectiveness of the NeuroStar TMS Therapy System across ages 12-70 by borrowing data from the two adult studies to be used in a meta-analysis with the adolescent study data. This approach effectively allows meaningful computational use of the preponderance of adult study evidence with the adolescent study data to permit a "sample-sparing" adolescent study design. This approach is clinically justified by the substantial evidence of safety and effectiveness already shown in the adult patient population, the biological and clinical continuity of the disease state from adolescence to adulthood, the shared mechanism of action of transcranial magnetic stimulation across age groups, and because of the significant unmet need in treatment options available for adolescent patients with major depressive disorder.

C. Meta Analysis:

The meta-analysis will include data from all three studies. The model for this analysis will include the following terms: treatment (active vs. sham), baseline score (continuous), medication resistance level as determined using the Antidepressant Treatment Record (ATR), (ATR=1 'Lo' vs. ATR=2-4 'Hi'), and Study (adolescent study (IDE G120121), and the two adult studies combined (O'Reardon, et al, 2007 and George, et al, 2010) as fixed effects, and, interaction terms for "study-by-treatment" and "ATR medication resistance level-by-treatment". A random effect of "site nested within study" will also be included to assess any potential side effects.

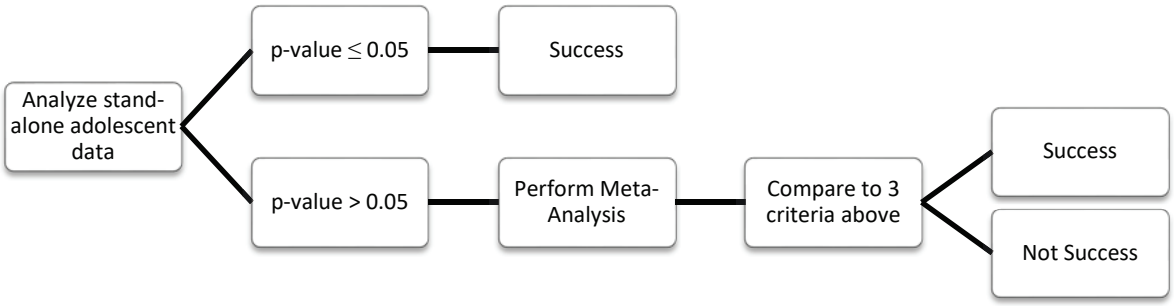
D. Flow of Analysis:

First, the adolescent study data will be analyzed standing alone. If the results of the analysis of the adolescent study shows a statistically significant treatment group difference in favor of the active treatment at a pre-specified alpha level = 0.05, then this study alone will be sufficient to establish efficacy in the adolescent population. If the stand alone analysis does not have statistically significant results, the meta-analysis will be performed.

Based on this meta-analysis, there are 3 essential criteria to declare success and conclude that the evidence rejects the null hypothesis of no difference between active TMS and sham TMS in adolescent patients with treatment resistant major depressive disorder. These criteria are:

1) The main effect of treatment on the primary efficacy variable of mean change from baseline on the HAMD24 in the adolescent/adult studies meta-analysis will be statistically significant, and fall below the specified alpha level of 0.05,
2) There will be no statistically significant evidence of interaction between Study and Treatment on the primary efficacy outcome variable at the pre-specified alpha level $\geq$ 0.10,
3) The study-specific treatment effect observed for the primary efficacy outcome variable in the adolescent study as a stand-alone analysis will reside between the ranges of 1.7 points to 5.5 points on the HAMD24, and to meet the maximum Type I error rate of 15%.

The criteria above are clinically justified based on the results using the HAMD24 outcome measure in the prior adult studies which ranges from 1.7 to 2.5 (O'Reardon, et al, 2007; George, et al, 2010). The maximum Type I error rate of 15% for the adolescent data alone is justified given the large dataset available in adults (N=491) and that adult and adolescent populations should respond similarly to TMS Therapy. Simulations using data from the adult studies and N=100 adolescents, shows that with a type I error rate of 5%, the observed HAMD24 mean difference between active and sham treatment would need to be 2.67, which would require a result greater than what it would need to achieve had it been considered alone. For this reason, the 15% type I error rate for the adolescent data is justified.



Section 3. General Analysis Definitions

A. Study Phases:

The following are phase descriptions are included from the study protocol synopsis for the adolescent protocol. The phases/separate protocols are included in the protocols for the two adult programs.

1. Phase I (Randomized, Blinded):

For subjects randomized to the active treatment, stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. Repositioning of coil, per NeuroStar User Manual, and prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable. During the first week of treatment only, in the event that the subject cannot tolerate the treatment at these dose parameters, dose intensity may be titrated downward to 110% of the motor threshold, with all other dose parameters remaining the same. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A maximum total of 36 treatments will be completed within 9 weeks of Phase I (including the 6 treatments administered during the 3-week taper phase). If the subject meets criteria (blinded to Site personnel) to enter Phase II, they will not complete the 3-week taper phase, resulting in a maximum total of 30 treatments.

2. Phase II (Non-Randomized, Open-label):

Subjects who do not achieve protocol-defined clinical benefit to treatment in Phase I will be offered the opportunity to undergo acute TMS treatment using the known-active therapy coil in Phase II. A maximum total of 36 treatments will be completed within 9 weeks of Phase II (including the 6 treatments administered during the 3-week taper phase).

Therefore, subjects who are randomized to active treatment during Phase I and subsequently enroll into Phase II will receive up to a total of 66 active treatments using stated study parameters within the 15-week combined timeframe (including one taper phase).

Subjects who are randomized to sham treatment during Phase I and subsequently enroll in Phase II will receive up to a total of 36 active treatments using stated study parameters within the 15-week combined timeframe (including one taper phase).

3. Phase III (Long Term Follow up):

Subjects who achieve protocol-defined clinical benefit from treatment in Phase I or Phase II will be followed for 6 months after treatment.

If a subject experiences re-emergence of depressive symptoms, an acute TMS retreatment course will be initiated. The TMS retreatment course will continue up to 6 weeks until symptom score is at or below Phase III entry score. Each successful retreatment is followed by a 3-week taper. Subjects could receive retreatment on more than one occasion; therefore, any subject could receive up to 72 treatments in Phase III over 6 months, in addition to Phase I and II exposure.

B. Schedule of Events:

[from adolescent study protocol Appendices A, B, and C]

Phase I:

Phase	1-Week Prestudy		6-Week Acute Treatment						3-Week Post-Treatment Taper[m]		
Week	Wk –2 to -1[a] (Screening)	Wk 0[a] (Baseline)	Wk 1[b]	Wk 2[b]	Wk 3[b]	Wk 4[b]	Wk 5[b]	Wk 6[b,c]/ET	Wk 1	Wk 2	Wk 3
Day(s)	-7[a]	0[a]	1-5	8-12	15-19	22-26	29-35	36-42	43-49	50-56	57-63
Informed Consent/Assent/HIPAA	X										
Psychiatric/Medical History/TASS	X										
Antidepressant Treatment Record (ATR)	X										
M.I.N.I. / M.I.N.I. KID	X										
Pre/Post-TEEQ-P[d]		X						X			
Pre/Post-TEEQ-A		X						X			
Efficacy Assessments[e]											
$HAMD_{24}$/MADRS[f]	X	X				X[d]		X[c,e]			X[e]
CDRS-R	X	X				X[d]		X[c,e]			X[e]
CGI-S	X	X				X[d]		X[c,e]			X[e]
QIDS-A17-SR	X	X				X[d]		X[c,e]			X[e]
Neuropsychological Assessments[e]											
NIH Toolbox Cognition Battery		X						X[c,e]			
Safety Assessments											
Physical examination	X										
Vital Signs		X						X[c]			
YMRS[e]		X									
C-SSRS[e]	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[c,e]	X[e]	X[e]	X[e]
Laboratory determinations[g]	X										
Urine drug screen	X										
Pregnancy test[h]	X										
Structural MRI[i]	X							X			
Audiometry assessment		X						X[c]			
Adverse Events[j]	X ----------X										
Prior/Concomitant Treatment[k]	X ----------X										
Motor Threshold Determination[l]	X[l]										
TMS Treatment Session[b] (daily x 5 weekdays/week)			X---X[b]	X---X[b]	X---X[b]	X---X[b]	X---X[b]	X---X[b]			
Post-Treatment Taper TMS Session(s)[m] (3X/Wk1, 2X/Wk 2, 1X/Wk 3)									X	X	X

a. A minimum of 7 days may elapse between the screening and baseline visits; a maximum of 5 days may elapse between the baseline visit and the first treatment day of Week 1. All baseline assessments must be completed and laboratory results received before 1st TMS treatment.
b. The first visit during each week of treatment should occur on a Monday, with daily treatment sessions occurring on Monday through Friday of each week.
c. Subjects who prematurely discontinue should complete all Week 6 procedures within 2 days after their last TMS treatment session.
d. If subject <18 yrs of age or the legal age requirement of the state
e. Efficacy, neuropsychological and safety assessments to be performed after last TMS treatment session on last day of the treatment week when assessments are required. Y-MRS to be completed if symptom indicating mania occurs. If positive, a M.I.N.I./M.I.N.I. KID must be repeated to determine if subject meets full DSM-5 criteria for mania or hypomania. If positive, subject to be discontinued from the study and followed clinically.
f. Subject must have been off of any antidepressants for at least one week.
g. Laboratory determinations to include standard hematology, and blood chemistry.
h. If subject is female of childbearing potential, a urine pregnancy test will be performed in the office at screening.
i. Performed on a subset of subjects at participating sites,
j. Adverse events occurring prior to randomization will be recorded as part of each patient's medical history. Those AEs occurring following the first TMS treatment session through 30 days after last study visit will be collected.
k. Medication treatment for emergent insomnia and emergent anxiety is permitted (refer to protocol for usage allowance). Refer to Appendix D for the Concomitant Medication List.
l. In addition to the indicated day, Motor Threshold Determination (MT) may be repeated at any time during the course of the active TMS treatment sessions based on clinical assessment of the supervising physician. Justification for the additional MT must be documented and pre-approved by the Sponsor when possible.
m. Taper occurs only if exiting the study or transitioning directly to Phase III.

Phase II:

Phase	6-Week Open Label Acute Treatment						3-Week Post-Treatment Taper [i]		
Week	Wk 1[b]	Wk 2[b]	Wk 3[b]	Wk 4[b]	Wk 5[b]	Wk 6[b,c]/ET	Wk 1	Wk 2	Wk 3
Day(s)	1-5	8-12	15-19	22-26	29-35	36-42	43-49	50-56	57-63
Informed Consent/Assent	X[a]								
Efficacy Assessments[d]									
$HAMD_{24}$/MADRS				X[d]		X[c,d]			X
CDRS-R				X[d]		X[c,d]			X
CGI-S				X[d]		X[c,d]			X
QIDS-A17-SR				X[d]		X[c,d]			X
Neuropsychological Assessments[d]									
NIH Toolbox Cognition Battery						X[c,d]			
Safety Assessments									
Vital Signs						X[c]			
C-SSRS[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[c,d]	X[d]	X[d]	X[c,d]
YMRS[d]						X[c,d]			
Structural MRI[e]						X			
Audiometry assessment						X[c]			
Adverse Events[f]	X ----------X								
Concomitant Treatment[g]	X ----------X								
Motor Threshold Determination	X[h]								
TMS Treatment Session[a] (daily × 5 weekdays/week)	X---X[b]	X---X[b]	X---X[b]	X---X[b]	X---X[b]	X---X[b]			
Post-Treatment Taper TMS Session(s)[i] (3X/Wk1, 2X/Wk 2, 1X/Wk 3)							X	X	X

a. An Informed Consent/Assent for this study must be signed prior to initiating any study-related procedures.

b. The first visit during each week of treatment should occur on a Monday, with daily treatment sessions occurring on Monday through Friday of each week.

c. Subjects who prematurely discontinue should complete all Week 6 procedures within 2 days after their last TMS treatment session.

d. Efficacy, neuropsychological and safety assessments to be performed after last TMS treatment session on last day of the treatment week when assessments are required. YMRS to be completed if symptom indicating mania occurs. If positive, a M.I.N.I./M.I.N.I.-KID must be repeated to determine if subject meets full DSM-5 criteria for mania or hypomania. If positive, subject to be discontinued from the study and followed clinically.

e. Performed on a subset of subjects at participating sites

f. Adverse events occurring prior to randomization will be recorded as part of each subject's medical history. Those AEs occurring following the first TMS treatment session through 30 days after last study visit will be collected.

g. Medication treatment for emergent insomnia and emergent anxiety is permitted (refer to protocol for usage allowance). Refer to Appendix D for the Concomitant Medication List.

h. Motor Threshold Determination (MT) is to be performed prior to the administration of the first active TMS treatment session. In addition, MT may be repeated at any time during the course of the active TMS treatment sessions based on clinical assessment of the supervising physician. Justification for the additional MT must be documented and pre-approved by the Sponsor when possible.

i. Taper occurs at end of acute treatment and prior to entry into Phase III..

Phase III:

Phase	6-Month Long-term follow up					
Timepoint	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6/ET[b]
Day(s)	Taper-30	Day 60	Day 90	Day 120	Day 150	Day 180
Informed Consent/Assent	X[a]					
Efficacy Assessments[c,h]						
$HAMD_{24}$/MADRS			X			X
CDRS-R			X			X
CGI-S	X	X	X	X	X	X
QIDS-A17-SR	X	X	X	X	X	X
Neuropsychological Assessments						
NIH Toolbox Cognition Battery						X
Safety Assessments						
Vital Signs						X
YMRS[d]						
C-SSRS[e]						
Structural MRI[f]						X
Audiometry Assessment[g]						X
Adverse Events[h,i]	X ----------					----------X
Concomitant Treatment[h,j]	X ----------					----------X
Motor Threshold Determination[k]						
TMS Retreatment[c, ,e,l] (5x/week for 6 weeks) See protocol text for description of retreatment parameters						

a. An Informed Consent/Assent for this study must be signed prior to initiating any study-related procedures.

b. Subjects who prematurely discontinue should complete all Month 6 procedures within 2 days after their last TMS treatment session.

c. TMS retreatments should begin on a Monday, with daily treatment sessions occurring on Monday through Friday of each week. All efficacy and safety assessments must be completed prior to the start of retreatment. Efficacy assessments must be completed every other week during each TMS retreatment with the assessment beings conducted after the last treatment for the two-week block. TMS treatment to stop when the CGI-S value returns to the Phase III entry score or a full 6 weeks of TMS treatment has been completed. A 3-week taper should follow each retreatment session. TMS retreatment can occur multiple times if symptom re-emergence occurs.

d. Y-MRS to be completed if symptom indicating mania occurs. If positive, a M.I.N.I./M.I.N.I. KID must be repeated to determine if subject meets full DSM-5 criteria for mania or hypomania. If positive, subject to be discontinued from the study and followed clinically.

e. C-SSRS to be performed after last TMS retreatment session on last day of the retreatment week.

f. Performed on a subset of subjects at participating sites.

g. Audiometry assessments must be performed immediately prior to the start of the TMS retreatment and at the completion of the retreatment course.

h. Efficacy assessments to be performed the end of each month for monthly visits. Subjects will be called to assess safety and well-being between visits at approximately 2 weeks post previous months visit.

i. Those AEs occurring following informed consent signature through 30 days after the last study visit will be collected.

j. Medication treatment for emergent insomnia and emergent anxiety is permitted (refer to protocol for usage allowance).

k. A Motor Threshold Determination (MT) is to be performed prior to the administration of the first TMS treatment in each treatment course. In addition, motor threshold may be repeated at any time during the course of the active TMS treatment sessions based on clinical assessment of the supervising physician.

l. TMS retreatment is to occur if the CGI-S increases by 1 from the score at entry into Phase III and is confirmed one week later.

C. Study Populations:

Efficacy outcomes will be computed as described in the sections below for both the intent-to-treat and per-protocol study populations in order to demonstrate the generalizability and consistency of the study findings. Safety analyses will be conducted on all enrolled population.

1. All Enrolled Population:

The all-enrolled study population is defined as those individuals who signed an informed consent, and were subsequently randomized in the study (this population includes both the evaluable and the non-evaluable patient samples). The reasons for patient non-evaluability will be itemized in the final study report, however, no other summary statistics of demographics or clinical outcomes will be reported for the all-enrolled study population. This population will constitute the safety analysis dataset.

2. Intent-to treat/Evaluable:

The intent-to-treat study population (also known as the evaluable patient population) is defined as all subjects who signed an informed consent, were enrolled in the study and received at least one treatment (whether partial or complete), and for whom a complete post-baseline observation is available for analysis in Phase I.

3. Per-protocol:

The per-protocol study population (also known as the completer population) is defined as all subjects who signed an informed consent, were enrolled in the study, who met inclusion/exclusion criteria, completed all efficacy assessments at Week 4 or Week 6, and received at least 30 treatments within 6 weeks of treatment initiation of the Phase I acute treatment.

The per-protocol study population 2 is defined as all subjects who signed an informed consent, were enrolled in the study, who met inclusion/exclusion criteria, completed all efficacy assessments at week 4 or week 6, and met the protocol requirements treatment compliance. The protocol defines treatment compliance as a subject cannot miss ≥3 treatments in daily sequence or be missing more than 20% of the total number of treatment sessions occurring during the 6 weeks of acute treatment (does not include taper treatments) in either Phase I or Phase II

To satisfy the requirements and definitions of the original study SAP, analyses of the effectiveness outcomes will be performed using per-protocol study population 1, however, the results from per-protocol population 2 will be considered the primary per-protocol analyses for the study given per protocol treatment regimen.

D. Center Pooling Methods:

The distribution of patient sample sizes across study sites will be inspected at completion of enrollment. In order to permit a meaningful evaluation of between site variance in the statistical analyses of efficacy outcome, sites with small numbers of patients may be pooled to form a single pseudo-site for purposes of statistical analysis. If a site did not randomize at least one randomization block (6 subjects), they will be combined for 1 pseudo-site.

E. Handling of Missing Data:

Missing data will be handled using the Last Observation Carried Forward (LOCF).

- Individual Missing items will not be imputed. If one or more items are missing for a given assessment, the total score will be missing for that visit.

- The last non-missing post-baseline assessment will be carried forward if the next scheduled assessment is missing (e.g., if the week 6/ET assessment is missing, the week 4 assessment would be carried forward, if available)
- Baseline observations will not be carried forward (e.g., if a subject is missing the week 4 assessment but has a Week 6 assessment, the subject would not be included in the Week 4 analysis, but would be included in the Week 6 analysis.

A sensitivity analysis may be performed imputing data if deemed necessary.

F. Handling of Data Windows:

For visit-based assessments, a data point will be attributed to an analysis time point according to the nominal visit entered on the CRF. In phase I and II, visits are allowed to occur within 4 days of the expected visit date. In phase III, visits should occur within 7 days of the expected date. If many visits occur outside these windows, a sensitivity analysis will be conducted to assess if there is an impact of visits occurring outside of the window.

G. Definition and Distribution of Age Brackets:

All sites are expected to recruit an evenly distributed proportion of patients across three defined age brackets, age 12 to 14, age 15 to 17, and age 18 to 21. Patient accrual will be actively monitored across these age brackets as the study progresses, and sites will be restricted from further recruitment within an age bracket if there is an imbalance in the distribution from that expected.

Section 4. Population Demographic and Clinical Characteristics at Study Entry

As noted above, for all variables, data tables will be separately provided for the intent-to-treat and the per-protocol study populations. Unless otherwise stated, the primary and secondary outcomes of this study will be based upon analysis of the intent-to-treat study population observations, and the per-protocol study population will serve as a supporting analysis.

A. Demographic and Clinical Variables:

The following demographic variables will be described for both study populations (Table 1).

Table 1. Key Demographic Variables

Variable Name	Type	Items
Gender	Categorical	Male Female Percentage
Age	Categorical by year at entry	Age year, Percentage Grouped by 12-14, 15-17, 18-21
Ethnicity	Categorical	• Hispanic or Latino • Not Hispanic or Latino Percentage
Race	Categorical	• White • Black / African American • Asian • American Indian or Alaska Native • Native Hawaiian or other Pacific Islander • Other Percentage

B. Illness Descriptive Variables:

The following illness descriptive variables will be described for both study populations at entry at phase I and will be described for each group for subjects entering Phases II and III (Table 2).

Table 2. Illness Descriptive Variables

Variable Name	Type	Items
Primary Psychiatric Diagnosis	Categorical	Diagnosis Codes and Descriptions
Secondary Psychiatric Diagnoses	Categorical	Diagnosis Codes and Descriptions Note: For purposes of statistical analysis, secondary diagnoses should be dichotomized as None/Any Secondary Diagnosis
Prior Treatment History • Prior ECT Treatment • Prior Inpatient Hospitalization for Major Depression • Prior Psychotherapy	 Categorical Categorical Categorical	 Yes/No Yes/No Yes/No
Prior Mania/Hypomania by YMRS	Categorical	Symptoms at entry of phase I
Baseline Symptom Severity • HAMD24 Total Score • HAMD17 Total Score (subset from HAMD24) • MADRS Item Total Score • CDRS-R Total Score • CGI-Severity of Illness Total Score • QIDS-A17-SR	 Continuous Continuous Continuous Continuous Continuous Continuous	 Mean, SD, Median, Range Mean, SD, Median, Range Mean, SD, Median, Range Mean, SD, Median, Range Mean, SD, Median, Range Mean, SD, Median, Range

The following variables will be used to describe pre-treatment psychiatric medication treatment history (Table 3). For the Antidepressant Treatment Record (ATR) medications, a listing will be provided showing the medications by class

C. Psychiatric Medication History:

Table 3. Psychiatric Medication History

Variable Name	Type	Items
Antidepressant Treatment Record • ATR-verified adequate antidepressant treatments • ATR-verified inadequate antidepressant treatments	 Continuous Categorical Continuous Categorical	 Mean, SD, Median, Range Histogram of distribution of ATR categories Mean, SD, Median, Range Histogram of distribution # of antidepressant treatments not meeting ATR adequacy criteria
Other Psychiatric Medications	Categorical	Listing of medications used
Other Non-Psychiatric Medications	Categorical	Listing of medications used

Section 5. Summary of Patient Disposition

A. CONSORT Diagram

Patient disposition (i.e., number of patients achieving a particular critical study stage) should be displayed for all consented patients in CONSORT diagram manner. At each study stage, the reasons for discontinuation up to and including that study time point should be listed. Each Phase of the study should have its own separate CONSORT diagram documenting patient disposition through that study Phase.

B. Reasons for Discontinuation

All enrolled patients should have a disposition recorded on the termination record, and this should be summarized in tabular fashion listing the proportion of patients discontinued and the recorded reason for discontinuation at the specific study stage listed above. Reasons for termination from the study as captured on the termination record are listed in Table 6. The number of patients whose data are missing, but the patient is not dropped from study; at each specific study stage should be indicated.

Table 4. Reasons for Study Termination

Reason for Study Termination
Non-Evaluable • No TMS treatment received • No post-baseline assessments obtained
Study Complete • Phase 1 complete (number of weeks of treatment) • Enrolled in Phase II • Completed Phase II • Enrolled in Phase III • Completed Phase III
Study Not Complete (reason given) • Satisfactory response – efficacy • Adverse event (specified on AE form) • Failed to return • Unsatisfactory response – efficacy • Patient request • Other (specified on termination record)

Upon inspection of the proportion of reasons for discontinuation, a separate listing of the verbatim reasons categorized as 'Other' may be performed.

Section 6. Summary of Study Treatments and Concomitant Therapy

A. Motor Threshold Determinations and TMS Stimulation Parameters:

Motor threshold determination is determined prior to initiation of treatment in each study phase and at the beginning of each reintroduction treatment occurring in Phase III. Ad hoc motor threshold determinations may be repeated at any time if clinically indicated based on the opinion of the attending physician. Information for the baseline motor threshold determinations prior to each study phase or reintroduction treatment block, and any ad hoc motor threshold determinations will be summarized as part of the general summary of TMS treatment parameters as noted in Table 7.

Table 5. Motor Threshold and TMS Treatment Session Summary Information

Variable	Type	Items
Motor Threshold Determinations		
• Baseline Motor Threshold at each study phase (all patients)	Continuous	Mean, SD, Median, Range
• Proportion of patients with a post-baseline motor threshold at each study phase	Categorical	N, % of patients
• Number of post-baseline motor thresholds obtained	Categorical	Number of ad hoc MTs (per study phase)
	Continuous	Mean, SD, Median, Range (for each ad hoc MT)

Section 7. Efficacy Analyses

A. Efficacy Objectives:

The specific efficacy outcome variables, the time points of observation, and the data sets for analysis of these variables are summarized in Table 8. For each of the measures, the scoring conventions are shown in the Attachment at the end of this statistical plan. Statistical differences will be assessed between groups in phase I. Data analysis in phase II and III will be descriptive.

NOTE: The timing of assessment of the primary outcome measure is blinded to the investigator's and study team's view and is not specified in the protocol. This information is contained in the statistical plan summary document here, and should not be provided to any study personnel under any circumstances.

B. Primary and Secondary Outcomes:

Table 6. Summary of Primary and Secondary Efficacy Study Measures, Prioritized Order of Analysis, and General Definitions of Outcome Measures

Primary Efficacy Outcome Measure	**Definitions**
HAMD24: total score, intent to treat sample using last post-treatment score	HAMD24 total score change from baseline value through week 6
Secondary Efficacy Outcome Measures	**Definitions**
Continuous outcomes HAMD17, HAMD24 (per protocol), MADRS, CDRS-R, QIDS-A17-R, CGI-S: total score, intent to treat sample using last post-treatment score	For each indicated measure, total score change from baseline value through week 6
Responder categorical outcome HAMD (24 and 17 Item versions) MADRS CDRS-R QIDS-A17-SR CGI-S	For HAMD, MADRS, CDRS-R, and QIDS-A17-SR: proportion of patient population achieving an end of acute phase total score reduction of ≥50% compared to baseline score For CGI-S: End of acute treatment score of 1, 2 or 3.
Factor scores derived from the HAMD including (using the last post-treatment value) Anxiety/Somatization Core Factor Maier Gibbons Retardation Sleep	 Anxiety/Somatization (sum of items 10, 11, 12, 13, 15, 17) Core Factor (sum of items 1, 2, 3, 7, 8) Maier (sum of items 1, 2, 7, 8, 9, 10) Gibbons (sum of items 1, 2, 3, 7, 9, 10, 11, 14) Retardation (sum of items 1, 7, 8, 14) Sleep (sum of items 4, 5, 6)
Remitter categorical outcome HAMD (24 and 17 Item versions) MADRS CDRS-R CGI-S	 For HAMD24: End of acute treatment score < 11 For HAMD17: End of acute treatment score < 8 For MADRS: End of acute treatment score < 10 For CDRS-R: End of acute treatment total score < 28 For CGI-S: End of acute treatment score 1 or 2

C. Subset Analyses:

In order to determine the generalizability of the reported outcome measures, subset analyses will be performed for the specific population groups described in Table 9.

Table 7. Subset Populations and Criteria for Subsets

Subset Population	Criteria for Subset
• Gender • Secondary Anxiety Disorder Diagnosis • Prior Hospitalization for Major Depression • ATR Status • Baseline MT	• Male, Female • Present, Not Present • Yes, No • ATR = 1, ATR = 2 thru 4 • Median split of Baseline MT value • Quartile split of Baseline MT value

The criteria may be revised for any of these subsets and additional subsets declared based on the final inspection of the data distributions for pre-treatment study characteristics of the population at data lock.

Subsets will be examined using the following outcome measures only: HAMD24, MADRS, and CDRS-R.

D. Study by Study Assessment:

In order to assess the study populations in the meta-analysis, demographics for each study will be characterized as described in Table 10.

Table 8. Subset Populations and Criteria for Subsets

Variable Name	Type	Items
Study	Categorical	Study 1 Study 2 Study 3 Subset
Gender	Categorical	Male Female Percentage
Ethnicity	Categorical	• Hispanic or Latino • Not Hispanic or Latino Percentage
Race	Categorical	• White • Black / African American • Asian • American Indian or Alaska Native • Native Hawaiian or other Pacific Islander • Other Percentage

Section 8. Safety Analyses

A. Data Safety Monitoring Board:

A Data Safety Monitoring Board is convened for this study. The DSMB will be provided with periodic reports including data specified in Attachment 2.

B. Adverse Event Reporting:

The general methodology for adverse event collection is discussed in the study protocol. All verbatim reported adverse events are coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events are categorized by the investigative site staff by severity (3-tier) and by relatedness to the study device (5-tier).

Protocol-emergent adverse events will be reported separately for the Phase I, Phase II, the taper phase, and Phase III. For each study phase, tabular display of adverse events should be provided as follows:

1) Adverse events by system organ class and preferred term
2) Adverse events by system organ class, preferred term and severity
3) Adverse events by system organ class, preferred term and relationship to study device.

C. Summary of Serious Adverse Events:

All serious adverse events that occur during the course of the study will be indicated on the adverse event record. A listing should be provided with treatment group. This will include serious adverse events that are considered either related or unrelated to the study device.

Patient narrative summaries will be provided for each report.

D. Special Topics-Headache, Pain/Discomfort:

After summary of the overall adverse event reports is complete, inspection of these adverse event terms will be performed and selected term grouped for the two key domains of headache and pain/discomfort near the treatment location will be clustered. These group terms will be summarized in terms of their incidence across the time points of observation in Phase I to determine whether or not there is severity and time course of accommodation to these effects.

E. Columbia Suicide Severity Rating Scale:

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used in this study to measure the occurrence of suicidal events and behavior. Assessments are completed prior to baseline, each week during active treatment, and at end of phase.

1) Number of Patients with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior with Suicidal Intent (following the format of Table 1 described in the C-SSRS Rating Guide)

   Note: This table will report the proportions of patients between active and sham conditions who report positive response on the suicidal ideation items (1-5), the suicidal behavior items (6-10) by item.

2) Table: Shift Table to Demonstrate Changes in C-SSRS Categories from Baseline During Treatment (following the format of Table 3 of the C-SSRS Rating Guide)

   Note: This table will report the proportion of patients between active and sham conditions who report positive response on the suicidal ideation items (1-5), the suicidal behavior items (6-10)

F. Vital Signs:

Vitals were completed before baseline and at the end of each phase. Changes in Height, Weight and Vitals will be provided.

G. Cognitive Function Testing:

Cognitive testing will be conducted using the NIH Toolbox. All sites are provided with the NIH Toolbox recommended computer set-up, and are trained on the specific procedures for implementation of the measures to be use in this study. Specifically, eight tests contained within the NIH Toolbox Cognition domain are being obtained in subjects at up to 4 time points in the study (please see the Schedule of Events elsewhere in this document for the specified time points of NIH Toolbox administration).

Data output from the NIH Toolbox are summarized for each test in Table 4 above, and includes Computed Score or Raw Score, Age-Adjusted Scale Score, Fully-Adjusted Scale Score, and Age-Adjusted National Percentile. Data output is extracted from the NIH Toolbox website.

Cognitive Function values are measured at baseline prior to treatment, at the end of each phase, and include the measures listed in Table 4. During the study, the test was moved from a desktop version to an IPAD tablet based version. There were slight changes in the test but both versions contained the same test battery elements.

Table 9. NIH Toolbox Cognitive Function Testing Outcomes

Variable Name	Type	Items
Episodic Memory		
Auditory Verbal Learning Test (Rey)	Continuous	Raw Score Mean, SD, Median, Range
Picture Sequence Memory Test	Continuous	Computed Score(Age-Adjusted Scale Score) Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD Median, Range
Working Memory		
List Sorting Working Memory Test	Continuous	Raw Score (Age-Adjusted Scale Score), Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD, Median, Range
Executive Function		
Dimensional Change Card Sort Test	Continuous	Computed Score(Age-Adjusted Scale Score) Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD Median, Range
Flanker Inhibitory Control and Attention Test	Continuous	Computed Score(Age-Adjusted Scale Score) Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD Median, Range
Processing Speed		
Pattern Comparison Processing Speed Test	Continuous	Raw Score (Age-Adjusted Scale Score), Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD, Median, Range
Language		
Oral Reading Recognition Test	Continuous	Computed Score(Age-Adjusted Scale Score) Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD Median, Range
Picture Vocabulary Test	Continuous	Computed Score(Age-Adjusted Scale Score) Fully-Adjusted Scale Score Age-Adjusted National Percentile Mean, SD Median, Range

H. Young Mania Rating Scale:

The Young Mania Rating Scale is assessed in all subjects prior to baseline. Upon any indication of activation, mania or hypomania, the scale is repeated during any phase. Descriptive data analysis will be completed for changes reported.

I. Magnetic Resonance Imaging Substudy:

The MRI substudy was conducted at a subset of sites and was collected before first treatment, and at the end of each phase. The purpose of this study is to evaluate the acute and long-term safety of daily, active TMS in adolescents meeting criteria for Major Depressive Disorder (MDD), single or recurrent episode, as determined by clinical assessment of brain structural integrity using magnetic resonance imaging (MRI) of the head. Clinical assessment will be performed by blinded neuroradiologist reading of patient scans and clinical assessment by standard reading of each scan as normal or abnormal. Analysis will be descriptive.

J. Auditory Threshold Testing:

Air conduction auditory threshold is obtained at baseline, and repeated up to 3 additional time points in the study depending upon the subject's participation in the various study phases (see Schedule of Events above). Air conduction threshold results are reported as means of right and left dB readings for each of the 8 specified test frequencies across the baseline and end of study phase time points, and the change in dB readings from baseline at the end of study phase time points, using a standard audiogram format and summarizing by study group.

For each of the 8 specified test frequencies both the observed outcome and the change from baseline to end of study phase will be summarized (using the standard audiogram format as noted above). The treatment groups will be compared with respect to the baseline outcome and the change from baseline to end of study phase. The null hypothesis of the equality of the treatment group means will be tested using a t-test. Within each treatment group the statistical significance of the mean change from baseline to end of study phase will be assessed using a paired t-test. For each treatment group the data will be summarized showing the sample size, mean, median, standard deviation, minimum, and maximum.

Section 9. Other Analyses

A. Concomitant Medications:

A listing of all permitted concomitant medications used will be provided, including a listing of the proportion of patients who received any concomitant medications listed on the Excluded Medications List.

Subjects were allowed to take non-psychotropic medications and limited medications for sleep and breakthrough anxiety medications. These medications were all to be clearly documented regarding dates of administration, not just dates of prescription. Psychotherapy was allowed if consistent in focus and frequency throughout study. Other non-behavioral or psychological therapies were allowed.

Table 10. Descriptive inclusion of medications and other therapies should be included by group in all phases.

Variable Name	Type	Items
Concomitant psychotropic medication		
Anxiolytic	Categorical	By medication
Sleep medication	Categorical	By medication
Antidepressant	Categorical	By class (SSRI, SNRI, Other)
Other non-AD	Categorical	By class (Hormone, Antimigraine, Anti-convulsant)
Concomitant non-psychotropic medication		
NSAID	Categorical	By class
Other	Categorical	By class
Concomitant Therapy		
Psychotherapy	Categorical	Yes/No
Other	Categorical	By therapy

B. Study Blinding:

The Treatment Expectations and Experience Questionnaire (TEEQ) was completed prior to baseline and after acute treatment course during phase I. Parents were only required to complete forms in subjects under 18 but could voluntarily provide input. This data will be analyzed to characterize the impression of patient and parent when completed. The questionnaire responses will be analyzed descriptively with frequencies and percentages. If p-values are provided, they will be for informational purposes only.

C. Suicidality Change Scores in HAMD:

Change from baseline will be assessed for all timepoints in phase I. This data will be exploratory only and not correlated for any decisions of suicidality.

Attachments

Attachment I. Scoring Algorithms and Conventions for Major Symptom Assessments:

Assessment Tool	Scoring Methods/Conventions
Hamilton Depression Rating Scale, 24 and 17 Item versions (HAMD24, HAMD17)	Total Score – 17 Item Version: Sum of items 1 through 17 24 Item Version: Sum of items 1 through 24 Response – Criterion for both versions: ≥ 50% reduction compared to baseline (Visit 2) total score Remission – Criterion for HAMD17: Total score < 8 Criterion for HAMD24: Total score < 11 Factor Scores – Anxiety/Somatization: Total of items 10, 11, 12, 13, 15, 17 Core Depression: Total of items 1, 2, 3, 7, 8 Maier: Total of items 1, 2, 7, 8, 9, 10 Gibbons: Total of items 1, 2, 3, 7, 9, 10, 11, 14 Retardation: Total of items 1, 7, 8, 14 Sleep: Total of items 4, 5, 6
Montgomery-Asberg Depression Rating Scale (MADRS)	Total Score – Sum of items 1 through 10 Response Criterion: ≥ 50% reduction compared to baseline Remission Criterion: Total score < 10
CDRS-R	Total Score – Child Rating Scale score: Sum of Items 1 through 17 Response Criterion: ≥ 50% reduction compared to baseline Remission Criterion: Total score < 28
Clinician Global Impressions – Severity (CGI-S)	Integer score on 7 point scale Item Score and Categorical Distribution reported Response Criterion: Score of 3 or less Remission Criterion: Score of 2 or less
QIDS-A17-SR	Total Score – Sum of the following: 1) Highest score of any sleep item (Items 1 thru 4) 2) Highest score of either the mood sad or mood irritable item (Items 5 or 6) 3) Highest score on any 1 appetite/weight item (Items 7 thru 10) 4) Items 11, 12, 13, 14, 15 each scored as reported 5) Highest score on either of the 2 psychomotor items (Items 16 or 17) Response Criterion: ≥ 50% reduction compared to baseline Remission Criterion: Total score < 6

Attachment 2. Data Safety Monitoring Board Reporting:

A Data Safety Monitoring Board is convened for this study. The DSMB will be provided with periodic reports which will include the following information:

Summary of Serious Adverse Events

The DSMB will receive report sof all serious adverse events that occur during the course of the study. This will include serious adverse events that are considered either related or unrelated to the study device. In the event of the occurrence of a serious adverse event that is considered related to the study device and unexpected based on the labeled safety profile of the device, the DSMB will be asked to recommend an action on the future conduct of the study.

Special Safety Topic: Evidence for Deterioration of Illness/Emergent Suicidality:

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used in this study to measure the occurrence of suicidal events and behavior. The DSMB will be provided with the following specific reports from the C-SSRS:

3) Table: Number of Patients with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior with Suicidal Intent (following the format of Table 1 described in the C-SSRS Rating Guide)

   Note: This table will report the proportions of patients between active and sham conditions who report positive response on the suicidal ideation items (1-5), the suicidal behavior items (6-10) by item.

4) Table: Shift Table to Demonstrate Changes in C-SSRS Categories from Baseline During Treatment (following the format of Table 3 of the C-SSRS Rating Guide)

   Note: This table will report the proportion of patients between active and sham conditions who report positive response on the suicidal ideation items (1-5), the suicidal behavior items (6-10)