NeoSync™

PROTOCOL NND-3002

A Prospective, Multicenter, Double-Blind, Sham-Controlled Adaptive Design Study to Confirm the Safety and Efficacy of NEST sTMS in Subjects with Major Depressive Disorder Who Have Not Responded to at Least One Antidepressant Medication in the Current Episode

07 JANUARY 2018

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STUDY SYNOPSIS

Study Objective	The primary objective of this study is to confirm the safety and effectiveness of synchronized TMS (sTMS) therapy in subjects with Major Depressive Disorder who have not responded adequately to at least one anti-depressant medication in the current episode.
Study Design	Prospective, randomized, double-blinded, sham-controlled, parallel group adaptive design study to confirm the safety and efficacy of sTMS in subjects with major depressive disorder who have not responded to at least one anti-depressant medication in the current episode. This is a multicenter study in which approximately 120 subjects will be enrolled in the trial to obtain 92 evaluable subjects who fully complete the primary study phase of the trial. Randomized subjects will be treated 5 days per week for 6 weeks. After signing informed consent, subjects who qualify for enrollment will discontinue use of their current antidepressant treatment (if applicable). Subjects must have discontinued the antidepressant medication a minimum of 1 week prior to their baseline measurements and initiation of treatment with the sTMS. Following wash-out of the antidepressant medication, an additional evaluation will be performed to determine whether the protocol eligibility criteria are still met before treatment. Qualified subjects will be randomized to either sTMS or sham treatment groups. Treatment will be initiated on Day 1 of the study. Subjects will visit the clinic for 5 daily treatment sessions per week for a total of 6 "treatment" weeks. A visit interval of 5-10 calendar days has been set for each "treatment" week. Treatment will be discontinued at the end of Treatment Week 6 (30 treatment sessions). Subjects will be clinically evaluated for safety and efficacy at the end of each of the six weekly treatment courses. At the end of Treatment Week 6, subjects will have completed the primary study phase treatments and will be offered either open label sTMS therapy (if criteria are met) or alternate treatment as clinically indicated.
Study Population	Approximately 120 male and female subjects, age 22 to 65 years, who are suffering from Major Depressive Disorder, will be enrolled into the study.
Study Center(s)	Multicenter, up to 16 clinical sites

Inclusion and Exclusion Criteria	*INCLUSION CRITERIA* Subjects must meet all of the following inclusion criteria to qualify for enrollment into the study: 1. All subjects will be 22 – 65 years of age. 2. Major Depressive Episode Diagnosis, Severity, and Duration: a. Subjects will meet the DSM-IV-TR primary diagnosis of initial or recurrent Major Depressive Disorder by DSM-IV-TR criteria rendered by structured interview using the Mini International Neuropsychiatric Interview (MINI). b. HAM-D_{17} total score $\geq$ 17 and Item 1 score greater than or equal to 2 at Screen and Baseline visits. c. HAM-D_{17} total score decrease of 5 or fewer points between Screen and Baseline visits. d. The definition of an episode is demarcated by a period of $\geq$2 months when the subject met full criteria for the DSM-IV-TR definition of Major Depressive Episode. Maximum duration of current episode cannot exceed 2 years. 3. Subjects have not responded adequately to at least one antidepressant medication in the current episode, with dose and duration defined as minimum confidence level 3 on the Antidepressant Treatment History Form (ATHF). 4. The baseline EEG is of sufficient duration and quality that it can be processed for quantitative analysis and determination of a valid IAF. 5. Subjects are willing and able to adhere to the intensive treatment schedule and all required study visits. *EXCLUSION CRITERIA* Subjects will be excluded from study participation if one of the following exclusion criteria applies: 6. Subjects are unable or unwilling to give informed consent. 7. Diagnosed with the following conditions (current unless otherwise stated): a. Any other current primary Axis I mood, anxiety, or psychotic disorder. b. Depression secondary to a general medical condition, or substance-induced. c. History of substance abuse or dependence within the past 6 months (except nicotine and caffeine). d. Any bipolar disorder or psychotic disorder (lifetime), including schizoaffective disorder, or major depression with psychotic features in this or previous episodes. e. Eating disorder (current or within the past year). f. Obsessive compulsive disorder (lifetime). g. Post-traumatic stress disorder (current or within the past year).

	h. ADHD (currently being treated). 8. Subjects meeting criteria for Axis II cluster A or B diagnosis based upon DSM-IV-TR criteria, which in the judgment of the Investigator may hinder the subjects in completing the procedures required by the study protocol. 9. Subjects with a clinically defined neurological disorder including, but not limited to: a. Any condition likely to be associated with increased intracranial pressure. b. Space occupying brain lesion. c. Any history of seizure EXCEPT those therapeutically induced by ECT (childhood febrile seizures are acceptable and these subjects may be included in the study). d. History of stroke. e. Transient ischemic attack within two years. f. Cerebral aneurysm. g. Dementia. h. Mini Mental Status Exam (MMSE-2) score ≤24. i. Parkinson's disease. j. Huntington's disease. k. Multiple sclerosis. l. Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or currently taking medication that lowers the seizure threshold. Medications that lower the seizure threshold are included in the Prohibited Concomitant Medication (Section 5.8). m. Any history of traumatic brain injury with loss of consciousness ≥30 minutes 10. Subjects who are currently hospitalized due to severity of depression symptoms. 11. Subjects with any of the following treatment histories: a. TMS within 6 months prior to the screening visit. b. Lifetime history of treatment with sTMS therapy. c. ECT treatment within 1 year prior to the screening visit. d. Failure to respond to TMS or ECT treatment (i.e., consistent with ATHF confidence level 3 or higher) in this or any previous episode. e. Lifetime history of treatment with Deep Brain Stimulation (DBS) or Vagus Nerve Stimulation (VNS). f. Participation in any investigational drug or device trial within six months of the randomization visit. g. Subjects who have been treated with fluoxetine within the past four weeks. h. If participating in psychotherapy, must have been in stable treatment for at least 2 months prior to entry into the study, with

	no anticipation of change in the frequency of therapeutic sessions, or the therapeutic focus over the duration of the trial. 12. Use of any medication(s) listed on the Prohibited Concomitant Medication (Section 5.8) within 1 week of randomization. 13. Subjects are adequately benefiting from current antidepressant medication(s). 14. Significant acute suicide risk, defined as follows: a. Greater than or equal to 1 suicide attempt in the past 12 months; or b. Has a clear-cut plan for suicide and states that he/she cannot guarantee that he/she will call his/her regular psychiatrist or the Investigator if the impulse to implement the plan becomes substantial during the study; or c. In the Investigator's opinion, is likely to attempt suicide within the next 6 months. 15. Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease. 16. Intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, stents, or electrodes) or any other metal object within or near the head, excluding the mouth, which cannot be safely removed. 17. Clinically significant abnormality or clinically significant unstable medical condition, as indicated by medical history, physical examination, ECG results, or clinical laboratory testing, that in the Investigator's judgment might pose a potential safety risk to the subject or limit interpretation of the trial results, e.g., any uncontrolled thyroid disorders, hepatic, cardiac, pulmonary and renal malfunctioning. 18. Women who are currently pregnant or not using a medically acceptable means of birth control and women who are breastfeeding. 19. Positive urine drug screen for illicit substances. (A positive urine drug screen at screening may be repeated once prior to randomization). 20. Any condition which in the judgment of the Investigator would prevent the subject from completion of the study.
Study Product, Dose, Regimen	The low emission NeoSync EEG Synchronized TMS Technology generates a sinusoidal magnetic field set at the peak Intrinsic Alpha Frequency (IAF) calculated from the subject's electroencephalogram (EEG). The treatment is administered for 30 minutes per day, 5 days per treatment week, for 6 treatment weeks. A treatment week is defined as a 5-10 calendar day interval. Each subject who completes the trial as intended will have a total of 30 treatments within 60 calendar days. Those subjects who qualify for the sTMS open label follow-up phase will receive an additional 6 weeks (30 treatments) of sTMS therapy. The treatment is administered for 30 minutes per day, 5 days per treatment week, for 6 treatment weeks. A treatment week is defined as a 5-10 calendar day interval. Each subject who completes the open label follow-up phase of the trial will have a total of 30 treatments within 30-60 calendar days.
Schedule of Visits	Screening Baseline (Day 0) Week 1 (Treatment Day 1-5) Treatment Visit(s)

	Week 1 (Treatment Day 5) Evaluation Visit Week 2 (Treatment Day 6-10) Treatment Visit(s) Week 2 (Treatment Day 10) Evaluation Visit Week 3 (Treatment Day 11-15) Treatment Visit(s) Week 3 (Treatment Day 15) Evaluation Visit Week 4 (Treatment Day 16-20) Treatment Visit(s) Week 4 (Treatment Day 20) Evaluation Visit Week 5 (Treatment Day 21-25) Treatment Visit(s) Week 5 (Treatment Day 25) Evaluation Visit Week 6 (Treatment Day 26-30) Treatment Visit(s) Week 6 (Treatment Day 30) Evaluation Visit Open Label Treatment and Evaluation Visits: Week 7 (Open Label Treatment Day 1-5) Treatment Visit(s) Week 7 (Open Label sTMS Treatment Day 5) Evaluation Visit Week 8 (Open Label Treatment Day 6-10) Treatment Visit(s) Week 8 (Open Label sTMS Treatment Day 10) Evaluation Visit Week 9 (Open Label Treatment Day 11-15) Treatment Visit(s) Week 9 (Open Label sTMS Treatment Day 15) Evaluation Visit Week 10 (Open Label Treatment Day 15-20) Treatment Visit(s) Week 10 (Open Label sTMS Treatment Day 20) Evaluation Visit Week 11 (Open Label Treatment Day 21-25) Treatment Visit(s) Week 11 (Open Label sTMS Treatment Day 25) Evaluation Visit Week 12 (Open Label Treatment Day 26-30) Treatment Visit(s) Week 12 (Open Label sTMS Treatment Day 30) Evaluation Visit
Outcomes	*Primary Efficacy Outcome* The primary endpoint is incidence of clinical response, defined by at least 50% reduction on the HAM-D_{17} total symptom scores from Baseline through 6 weeks of treatment. *Additional Efficacy Outcomes* • The change in mean total symptom scores on the HAM-D_{17} through 6 weeks of treatment • The change in mean total symptom scores on the MADRS through 6 weeks of treatment. *Safety Outcomes* Safety will be assessed by the following: • The incidence and severity of all adverse events (including, but not limited to, serious adverse events and device-related adverse events) • Changes in Columbia Suicide Severity Rating Scale (C-SSRS) • Adequacy of blinding will be assessed using a Blinding Questionnaire administered at the Week 1 and Week 6 clinical assessment visits.
Statistical Methodology	The primary efficacy analysis will be performed on both the ITT and evaluable Per Protocol subgroup, with results from the Per Protocol analysis used for confirmation of the previous NEST study results. The incidence of clinical response, defined as a reduction in HAM-$D_{17} \geq 50\%$ at 6 weeks will be the primary efficacy outcome measure. The sample size estimation for this confirmatory study is based on the treatment resistant population results from the original NEST study, which demonstrated a 34% response rate for sTMS versus 8% for Sham treatment for the Per Protocol population. Assuming

	true population response rates of 34% for sTMS and 8% for Sham, power analysis indicates that a sample size of 92 evaluable (Per Protocol) subjects (46 subjects per treatment group evaluable at week 6) yields 81% power to demonstrate superiority of sTMS over Sham, where the statistical test is Fisher's exact test at a two-sided 0.05 level of significance. A total of approximately 120 subjects will be enrolled and randomized to account for expected rates of premature withdrawal. Due to uncertainty regarding the expected sham response rate and treatment effect differential, this study will utilize an adaptive design that allows one blinded interim sample size re-estimation after a minimum of 70 subjects have been enrolled and completed treatment. The pre-specified maximum allowable sample size following re-estimation will be 240 enrolled (~184 evaluable).

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
Ag/AgCl	Silver/Silver Chloride
ATHF	Antidepressant Treatment History Form
BDNF	Brain-Derived Neurotrophic Factor
BP	Blood Pressure
C-SSRS	Columbia Suicide Severity Rating Scale
CRA	Clinical Research Associate
CRF	Case Report Form
DBS	Deep Brain Stimulation
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
EEG	Electroencephalogram
ERD	Event Related Desynchronization
ERS	Event Related Synchronization
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAM-D	Hamilton Rating Scale for Depression (can also be referenced as HRSD)
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
Hz	Hertz
IAF	Individualized Alpha Frequency
ICH	International Conference on Harmonization
IDS-SR	Inventory of Depressive Symptomatology (Self-Report)
IFU	Indications for Use
IRB	Institutional Review Board
ITT	Intent to Treat
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Affairs
MINI	Mini International Neuropsychiatric Interview
MMSE-2	Mini Mental Status Exam- Version 2
MMRM	Mixed Model of Repeated Measures
MOA	Mechanism of Action
NEST	NeoSync EEG Synchronized TMS
NIMH	National Institute of Mental Health
PHI	Protected Health Information
PP	Per Protocol
PPM	Patient Passport Model
rTMS	repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-IV-TR disorders
SD	Standard Deviation
SNRI	Serotonin/Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depress Study

sTMS	synchronized Transcranial Magnetic Stimulation
SubID	Subject Identification
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Event
USB	Universal Serial Bus
VAC	Volts Alternating Current
VNS	Vagus Nerve Stimulation
YLDs	Years Lived with a Disability

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1 INTRODUCTION AND RATIONALE

Major Depressive Disorder (MDD) is a mental disorder associated with significant functional impairment and disability. Affected individuals present with depressed mood, loss of interest or pleasure, feelings of guilt, low self-worth, disturbed sleep or appetite, low energy, and poor concentration. Depression can become chronic or recurrent, and at worst, can lead to suicide. It is the most prevalent DSM-IV-TR Axis I disorder, affecting more than 16% of US adults during their lifetime (Kessler, 2005). The 2013 National Survey on Drug Use and Health reports an estimated 15.7 million adults and 2.6 million adolescents in the U.S. suffer from MDD, which is estimated to be the second leading contributor to the global burden of disease, as measured by years lived with a disability (YLDs). In 2010, the economic burden of depressive disorders was an estimated $210.5 billion in the U.S., more than 45% of which was attributable to direct medical expenses (Greenberg, 2015).

Psychopharmacological therapy as today's mainstream treatment has revolutionized the clinical management for major depressive disorders and has been shown to improve the quality of life for many patients. Antidepressants currently in use include selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), fluvoxamine (Luvox), escitalopram (Lexapro), and serotonin/norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Effexor) and duloxetine (Cymbalta). Additionally, monoamine oxidase inhibitor (MAOIs) and tricyclic antidepressants have been used to treat severe depression, but are generally second line agents due to the adverse side effect profiles.

As discussed in a critical review by Belmaker (2008), while newer antidepressants are effective, they have not shown clear improvements in efficacy over previous treatments. Results released from the Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D), conducted by the National Institute of Mental Health (NIMH), **show that approximately 30% of depressed subjects respond to an SSRI** in their first trial, despite adequate dosing and duration of treatment. The SSRI antidepressants do have a more favorable side effect profile than older medications, but they still may be difficult for some patients to tolerate because of gastrointestinal distress, anxiety, insomnia, and sexual dysfunction. A rare adverse event associated with SSRI treatment is increased risk of suicidal ideation in children and young adults (Hans-Jurgen, 2008).

In addition to the psychopharmacologic treatments for depression, other device based therapies have been shown to have a potential therapeutic effect in MDD. ECT induces seizures electrically in anesthetized subjects. It is generally safe and effective; however the procedure can have the negative side effect of memory loss and confusion. The exact mechanism of ECT is unknown, although there are changes in a host of neurochemicals following ECT, including acetylcholine, norepinephrine, and serotonin (Essman, 1973

TMS uses magnetic pulses which cause activation of specific areas in the brain. Treatment with repetitive stimulation (rTMS) is intended to stimulate groups of cells in areas of the brain linked to MDD. The exact mechanism by which this therapy works is still unknown (Fitzpatrick, 2000). While the therapy is non-invasive, it is expensive and requires subjects to be treated daily at a treatment center because of the complexity of locating the point and optimum strength of stimulation as well as the potential for seizures. Efficacy is difficult to compare to that of antidepressant medications because of a paucity of head-to-head studies, but it may compare favorably to that of approved antidepressants, **with 25%**

responders in the treatment group, compared to 9.2% for sham (Thase, 2008). More recently, an NIMH funded study (OPT-TMS) showed a statistically significant **remission rate (as defined by HAM-D_{24} scores < 3 or 2 consecutive HAM-D_{24} scores < 10) of 14% compared to 5% for sham (George, 2010).**

Studies of the motor system suggest that a mechanism through which TMS exerts its effects may be related to the resetting of cortical oscillators. TMS pulses lead to an immediate synchronization of EEG activity in the alpha and beta bands, consistent with triggering of oscillators and facilitate a resetting of oscillatory mechanisms (Brignani et al., 2008; Paus et al., 2001; Fuggetta et al., 2005; 2008), reflected in increased power (Brignani et al., 2008; Fuggetta et al., 2005) and coherence (Fuggetta et al., 2008) in the alpha frequency band on QEEG. Resetting is marked by ERS in the areas that have been stimulated, preparing for an ERD to follow (Brignani et al., 2008; Jancke et al., 2006; Zarkowski et al., 2006; Sauseng et al., 2008). The effects of TMS pulses on motor and cognitive functions are complex, with some studies showing detrimental effects and others enhancement effects on task performance. This appears to depend upon several factors including whether the pulses are delivered before, during, or after the task (Brignani et al., 2008; Evers et al., 2001; Hamidi et al., 2009; Hamilton and Pascual-Leone, 1998; Klimesch et al., 2003; Pascual-Leone et al., 2000; Sparing et al., 2001; Wassermann et al., 1999). Klimesch and colleagues (2003) have proposed that one key factor determining whether TMS pulses are inhibitory or facilitory of task performance is the relationship of the frequency of TMS stimulation to the subjects' Intrinsic Alpha Frequency (IAF). This group demonstrated rTMS delivered at subjects' IAF plus 1 Hz (IAF + 1) rather than at a lower (IAF – 3) or higher (20 Hz) stimulation frequency enhanced performance on a mental rotation task. Similarly, Hamidi and colleagues (2009) observed that in subjects performing cognitive tasks in association with 10 Hz rTMS, there was a trend towards those subjects with higher IAF to have higher task performance accuracy. None of these studies have specifically examined the effects of TMS pulses delivered at the actual IAF.

The central role for modulation of alpha band activity in the MOA of TMS is consistent with the increased understanding of the importance of alpha frequency band activity in regulating brain functions. Alpha activity no longer is thought to represent a "passive resonance phenomenon" of the brain (Klimesch et al., 2007), but instead plays a central coordinating role in regulating brain activity. Higher mean IAF is associated with greater regional cerebral blood flow (Jann et al., 2010). In contrast, higher power and broadly synchronized alpha is associated with lower blood flow (Feige et al., 2005). Taken as a whole, these findings suggest that intrinsic alpha activity can lead to activation or inhibition of a brain region depending upon the intensity, frequency, and synchronization of the activity.

NeoSync, Inc. has developed an EEG synchronized TMS (sTMS) system for the treatment of MDD. The sTMS device uses low energy alternating magnetic fields at a subject's Intrinsic Alpha Frequency (IAF). This development is in line with others that have shown clinical efficacy in treating MDD using low energy rTMS (Martiny et al., 2010).

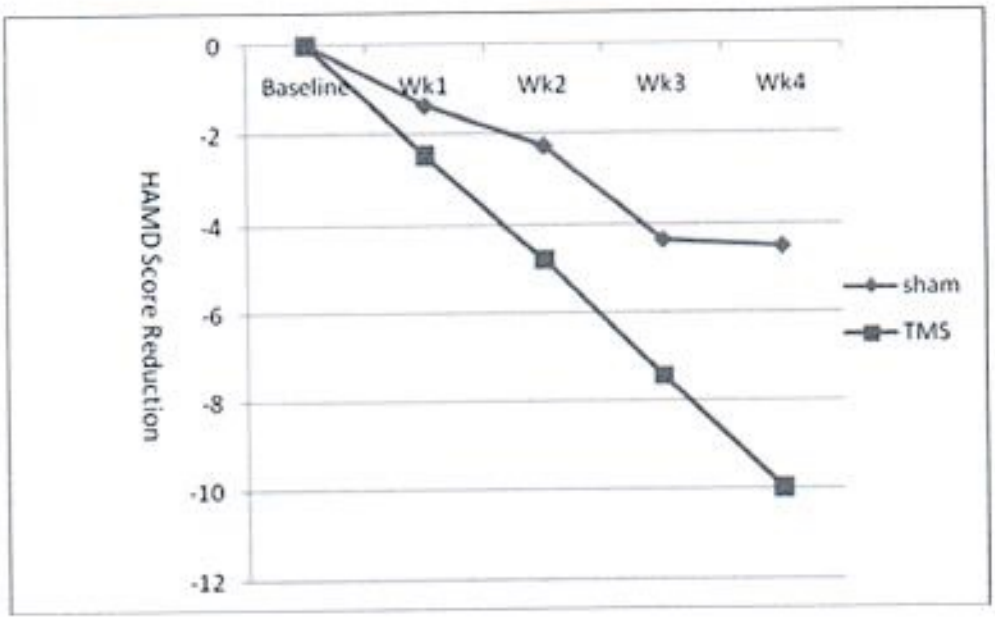
1.1 Clinical Data with sTMS

Initial Feasibility Study

A four-week, sham controlled, randomized, double-blind multi-center study was conducted by NeoSync, Inc. using the sTMS prototype to treat subjects with MDD (Jin and Phillips, 2014). The study consisted of 45 subjects, 14 in the US and 31 in China (21 males and 24 females; Avg. age = 43.7 ± 14.3 years). To enter the study, subjects were required to have been diagnosed with MDD and have a Hamilton Depression (HAM-D_{17}) score of 17 or greater. The mean baseline HAM-D_{17} score was 21.0 ± 3.3. The group was randomized with a sTMS: Sham ratio of 2:1.

Since there was no treatment by study site interaction ($F_{1, 43} = 0.22$, $P = 0.64$), the data from the US and Beijing sites was combined.

FIGURE 1
CHANGE IN DEPRESSIVE SYMPTOMS FOLLOWING SHAM AND ACTIVE NEOSYNC sTMS



After the fourth week of treatment, the sTMS group was significantly better (Fig. 1) than the Sham as an overall measure ($F_{1, 43} = 10.17$, $P = 0.003$), or on a time by treatment interaction ($F_{3, 129} = 6.7$, $P = 0.0003$) A responder was defined as a subject who had at least 50% improvement in symptoms. **Table 1 gives the responder data for the sTMS (55.2%) and Sham (12.5%).**

TABLE 1
RESPONDERS VS. NON-RESPONDERS FOR THE SHAM AND sTMS TREATMENTS.

	NON-RESPONDER	RESPONDER	TOTAL
SHAM	14 (87.5%)	**2 (12.5%)**	16
STMS	13 (44.8%)	**16 (55.2%)**	29
TOTAL	27	18	45

There were significantly more responders after sTMS treatment (16/29) compared to Sham (2/16) ($\chi^2 = 7.82$, $P = 0.005$).

US Multicenter NEST Study

Protocol NND-3001 was a randomized, double-blinded, sham-controlled, parallel group study designed to evaluate the safety and efficacy of the NeoSync sTMS device in subjects with Major Depressive Disorder (MDD). In this multicenter study, two hundred and two (n=202) patients with MDD participated across 17 investigational sites in the United States.

Subjects could be enrolled if they 1) had not received any anti-depressant therapy for the current episode, 2) received anti-depressant therapy but were intolerant or received an inadequate dose, or 3) failed to

achieve satisfactory improvement from one or more anti-depressant medication treatments in the current episode of depression.

NEST Pivotal Trial

The study analysis for the NEST trial focused on three pre-defined populations:

Intent to Treat (ITT) Analysis Set: Includes all subjects who signed an informed consent, met all Inclusion/Exclusion criteria, were subsequently randomized, and received at least 1 treatment [active synchronized TMS (sTMS) or sham] session in the double-blind phase (n=202). The criteria for defining the ITT analysis dataset were predefined prior to unblinding treatment group assignment and data analysis.

Completers (COMP) Analysis Set: Includes all subjects who signed an informed consent, met study criteria, were randomized to a treatment arm, received at least 80% (24/30) of scheduled treatments within 60 days and completed the required treatment and post-baseline assessments in the double-blind phase (n=135). The criteria for defining the Completers analysis dataset were predefined prior to unblinding treatment group assignment and data analysis.

Per Protocol (PP) Analysis Set: Includes all subjects who signed an informed consent, met study criteria, were randomized to a treatment arm, received at least 80% (24/30) of scheduled treatments *at the correct IAF* within 60 days and completed the required treatment and post-baseline assessments in the double-blind phase (n=120). The criteria for defining the PP analysis dataset were predefined prior to unblinding treatment group assignment and data analysis.

No significant differences between active and sham groups in either the mean change in HAM-D_{17} score (-6.67 $\pm$ 7.18 vs. -6.34 $\pm$ 6.34, p=0.96) or response rate (27.2% vs. 27.3%, p=0.85) were observed in the ITT sample. A more detailed analysis of the findings suggests that efficacy of sTMS in the ITT sample was obscured by an unexpectedly high sham response rate in treatment-naïve subjects (18/37, 48.6%). These subjects are known to have a somewhat higher placebo response rate than other subjects based on prior antidepressant medication studies, but the very high sham response rate seen in treatment naïve subjects had a major negative impact on the interpretation of this trial. If these treatment-naïve subjects were excluded, there was a statistical trend towards superior response rate for active treatment versus sham for subjects in the ITT sample both on the HAM-D_{17} (27% vs. 15%, p = 0.17) and MADRS (28.6% vs. 16.7%, p=0.13) response rates. Similar to the ITT sample analysis, no significant differences were observed between active and sham groups in either the mean change in HAM-D_{17} score (-7.64 $\pm$ 7.29 vs. -6.62 $\pm$ 5.70, p=0.38) or response rate (31.4% vs. 27.7%, p=0.66) in the overall COMP cohort. Again, analysis suggests that a high sham response rate in treatment naïve subjects (15/25, 60%) obscures overall efficacy results. In the non-treatment naïve population, response rates utilizing either the HAM-D_{17} (32.6% vs. 7.7%, p=0.01) or MADRS (32.6 vs. 7.7%, p=0.01) were statistically higher in the sTMS group, while mean change in HAM-D_{17} scores was near significance (-7.39 $\pm$ 7.33 vs. -4.59 $\pm$ 4.74, p=0.09). Statistical power in the COMP sample was further eroded by inclusion of subjects who were treated at the wrong IAF. These subjects had significantly less improvement on the HAM-D_{17} than those who were treated at the correct IAF (mean decrease -3.82 $\pm$ 7.36 vs. -9.00 $\pm$ 6.54, respectively, p=0.002). This finding is consistent with the proposed mechanism of action of sTMS. If all subjects had been treated at the correct IAF, the statistical power in the ITT and COMP sample would have been greater and would have been sufficient to show statistical separation in the treatment non-naïve sample (i.e., Treatment Resistant Depression).

A fundamental principle of sTMS's presumed mode of action is that magnetic stimulation must be synchronized to a subject's IAF, as measured using a single channel EEG. Consequently, the NEST system utilizes single channel EEG recording and signal processing capabilities which are used to establish the correct treatment parameters at baseline. At the conclusion of patient enrollment, but prior to unblinding of the treatment group assignments, all EEG recordings, derived IAF's, and assigned treatment IAF values were reviewed to confirm that subjects were treated at the correct IAF, regardless of treatment group assignment. As a result, 15 subjects (11 active sTMS, 4 sham) were removed from the PP analysis dataset.

The most appropriate analysis set for the purpose of assessing the potential effectiveness of the NEST device is the PP analysis set. The reason for this is that the "ITT" cohort includes subjects who either, dropped out of the study before receiving any treatment, had significant protocol violations or received too few treatments. The reason the "Completers" cohort is not appropriate is because although similar to the PP cohort, the completer analysis included subjects treated at the incorrect IAF. The pre-defined Per Protocol cohort analyzed those subjects that received both a minimum requisite number of treatments ($\geq$ 24) AND were treated at their correct IAF; that is the Per Protocol group evaluated subjects meeting the inclusion/exclusion criteria, received a minimum number of treatments that is standard for antidepressant drug trials (*i.e.,* 80% compliance with intended therapy regime), and received adequate therapy during those treatments (treated at the subject's intrinsic alpha frequency).

The PP analysis set included 120 subjects (59 active sTMS and 61 Sham) between the ages of 22 and 65, who met a primary diagnosis of initial or recurrent Major Depressive Disorder by DSM-IV-TR criteria rendered by structured interview using the Mini International Neuropsychiatric Interview (MINI). Duration of current depressive episode must have met a minimum duration of 8 weeks and could not exceed 2 years. At Baseline, a HAM-D_{17} total score $\geq$ 17 was required with an Item 1 score $\geq$ 2.

At the end of the 6-week double-blind treatment phase, all subjects who did not achieve remission were allowed to participate in a four-week open label treatment phase using the active NEST device and were assessed at the Week 10 time point (n = 89). Those subjects not eligible to participate in the open label phase were also assessed at the Week 10 time point (n= 31).

The primary efficacy endpoint for the study was mean HAM-D_{17} total score change from Baseline (Day 0) to Week 6 compared between the active treatment and sham-controlled groups. Salient results for the Per Protocol patient cohort were as follows:

- The active sTMS treatment was shown to be significantly more effective than sham treatment for the primary efficacy endpoint (change in HAM-D_{17} total score)
- The mean relative treatment effect (-9 Active vs. -6.56 Sham, p=0.03) is clinically significant and consistent with, or larger than, prior rTMS and antidepressant drug trials.
- Secondary Clinical Rating scales (HAM-D_{24}, HAM-D_{28}, IDS-SR, and MADRS) support efficacy in this population,
- There were no significant differences between Sham and Active sTMS treatment in incidence rates of:
    - Any AE
    - Intensity of AE's
    - Relationship to study treatment

- Clinically significant AE's
- Study drop-out rates

- The "open label" participants were observed to improve in their HAM-D_{17} total score over the four- week treatment ($p = 0.01$).

The actual performance of the sTMS device in clinical practice is more likely to be reflected by the results of the PP analysis in the non-treatment naive population. These are the subjects who are most likely to seek sTMS treatment based upon the recommendation of their physicians. **Subjects who had attempted or completed prior antidepressant treatment in the current episode (ATHF 1 - 6) demonstrated significantly greater benefit from sTMS treatment compared to sham (-8.58 vs. -4.25, p=0.005), while treatment-naïve subjects (ATHF 0) showed no significant difference between active and sham (-9.76 vs. -10.08; p=0.28). Subjects who had attempted or completed prior antidepressant treatment in the current episode also had a statistically significantly higher response rate (34.2% vs. 8.3%, p= 0.017)** and a numerically but not significantly higher remission rate (13.2% vs. 5.6%, p=0.26) with active treatment than with sham; treatment-naïve subjects showed the opposite pattern. The magnitude of the improvement seen in this population is similar to or greater than that seen with medication and already-approved rTMS devices.

One conclusion from this study was that poor quality EEG recordings (i.e. high variability, poor electrode preparation) could result in the assignment of an inappropriate treatment IAF, and that patients treated at a frequency greater than 1 HZ from their IAF did not respond as well as those treated at the correct value. Consequently, NeoSync modified the NEST software to include an automatic EEG quality qualification process to improve the assignment of the correct treatment frequency. **The present study is designed to confirm that treatment with the modified software produces clinical improvement comparable to that demonstrated in the previous study in the non-treatment naive PP sub population**. Therefore, only patients who failed to respond to at least one AD medication in the current episode (i.e. treatment resistant) will be studied in this trial.

2 STUDY OBJECTIVE

The primary objective of this study is to confirm the safety and effectiveness of synchronized TMS (sTMS) therapy in subjects with Major Depressive Disorder who have not responded adequately to at least one antidepressant medication in the current episode.

3 STUDY DESIGN

This clinical trial is a prospective, randomized, double-blinded, sham-controlled study to confirm the safety and efficacy of sTMS in subjects with Major Depressive Disorder who have not responded to at least one anti-depressant medication in the current episode. This is a multicenter study in which approximately 120 subjects will be enrolled and undergo sTMS therapy in the trial. Randomized subjects will receive 5 daily treatments per treatment week for 6 treatment weeks (total of 30 treatments). Following completion of their treatment period, subjects who have not remitted (remission defined as a HAM-D_{17} score of ≤ 7 (Zimmerman et al., 2004)) may be offered an additional 6 weeks of open label sTMS treatment, if the clinician feels this is appropriate for that subject.

Alternatively, if the clinician feels it is not appropriate for the subject to participate in the open label sTMS follow-up, the subject chooses not to participate in the open label follow-up or if the subject has remitted in the blinded phase, subject will be deemed to have completed participation in this study.

For subjects who participate in the open label sTMS follow-up, a weekly evaluation will be conducted at Week 7, 8, 9, 10, 11 and 12.

After signing informed consent, subjects who qualify for enrollment based upon assessments performed at Screening will discontinue use of their current antidepressant treatment (if applicable). Subjects must have discontinued the antidepressant medication a minimum of 1 week prior to initiation of treatment with the sTMS. An additional evaluation (Baseline) will be performed at least one week following screening to determine whether the protocol eligibility criteria are still met before randomization and the first treatment. Subjects who show an improvement of more than 5 points on the HAMD-17 between the screening and baseline assessments will be excluded from the study.

Qualified subjects will be randomized to either active sTMS or sham treatment groups in a 1:1 ratio on an individual basis. Randomization will be stratified by site in blocks of 10 determined by a computer generated randomization table defined prior to the start of the trial. Each site will be given a set of 10 randomized PPMs. Treatment will be initiated on Day 1 of the study. Subjects will come to the clinic for 5 daily treatment sessions for a total of 6 "treatment" weeks. A visit interval of 5-10 calendar days has been set for each "treatment" week to accommodate visit scheduling flexibility. Treatment will be discontinued at the end of Week 6 (30 treatment sessions). Subjects will be clinically evaluated for safety and efficacy at the end of each of the six weekly treatment courses.

4 SUBJECT POPULATION

Approximately 120 male and female subjects, aged 22 to 65 years who are suffering from Major Depressive Disorder will be enrolled in the trial. Randomized subjects will receive sTMS or sham treatment, with randomization in a 1:1 ratio with approximately 60 subjects enrolled per arm. Subjects who have provided informed consent, who are capable of comprehending the nature of the study, and who are likely to comply with the visit schedule are to be entered into the study provided they conform to the following criteria.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to qualify for enrollment into the study:

1. All subjects will be 22 – 65 years of age
2. Major Depressive Episode Diagnosis, Severity, and Duration:
    a. Subjects will meet the DSM-IV-TR primary diagnosis of initial or recurrent Major Depressive Disorder by DSM-IV-TR criteria rendered by structured interview using the Mini International Neuropsychiatric Interview (MINI).
    b. HAM-D_{17} total score $\geq$ 17 and Item 1 score greater than or equal to 2 at Screen and Baseline visits.
    c. HAM-D_{17} total score decrease of 5 or fewer points between Screen and Baseline visits.
    d. Duration of current episode $\geq$8 weeks. The definition of an episode is demarcated by a period of $\geq$2 months when the subject met full criteria for the DSM-IV-TR definition of Major Depressive Episode. Maximum duration of current episode cannot exceed 2 years.
3. Subjects have not responded adequately to at least one antidepressant medication in the current episode, with dose and duration defined as minimum confidence level 3 on the Antidepressant Treatment History Form (ATHF).
4. The baseline EEG is of sufficient duration and quality that it can be processed for quantitative analysis and determination of a valid IAF.
5. Subjects are willing and able to adhere to the intensive treatment schedule and all required study visits.

4.2 EXCLUSION CRITERIA

Subjects will be excluded from study participation if one of the following exclusion criteria applies:

1. Subjects are unable or unwilling to give informed consent.
2. Diagnosed with the following conditions (current unless otherwise stated):
    a. Any other current primary Axis I mood, anxiety, or psychotic disorder, including bipolar disorder.
    b. Depression secondary to a general medical condition, or substance-induced.
    c. History of substance abuse or dependence within the past 6 months (except nicotine and caffeine).
    d. Any bipolar disorder or psychotic disorder (lifetime), including schizoaffective disorder, or major depression with psychotic features in this or previous episodes.
    e. Eating disorder (current or within the past year).
    f. Obsessive compulsive disorder (lifetime).
    g. Post-traumatic stress disorder (current or within the past year).
    h. ADHD (currently being treated).
3. Subjects meeting criteria for Axis II cluster A or B diagnosis based upon DSM-IV TR criteria, which in the judgment of the Investigator may hinder the subjects in completing the procedures required by the study protocol.
4. Subjects with a clinically defined neurological disorder including, but not limited to:
    a. Any condition likely to be associated with increased intracranial pressure.
    b. Space occupying brain lesion.
    c. Any history of seizure EXCEPT those therapeutically induced by ECT (childhood febrile seizures are acceptable and these subjects may be included in the study).
    d. History of stroke.
    e. Transient ischemic attack within two years.
    f. Cerebral aneurysm.
    g. Dementia.
    h. Mini Mental Status Exam (MMSE-2) score of $\leq$24.
    i. Parkinson's disease.
    j. Huntington's disease.
    k. Multiple sclerosis.
    l. Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or currently taking medication that lowers the seizure threshold. Medications that lower the seizure threshold are included in the Prohibited Concomitant Medication (Section 5.8).
    m. Any history of traumatic brain injury with loss of consciousness $\geq$30 minutes
5. Subjects who are currently hospitalized due to severity of depression symptoms.
6. Subjects with any of the following treatment histories:
    a. TMS treatment within 6 months prior to the screening visit.
    b. Lifetime history of treatment with sTMS therapy.
    c. ECT treatment within 1 year prior to the screening visit.
    d. Failure to respond to TMS or ECT treatment (i.e., consistent with ATHF confidence level 3 or higher) in this or any previous episode.
    e. Lifetime history of treatment with Deep Brain Stimulation or Vagus Nerve Stimulation.
    f. Participation in any investigational drug or device trial within 6 months of the randomization visit.
    g. Subjects who have been treated with fluoxetine within the past four weeks.
    h. If participating in psychotherapy, must have been in stable treatment for at least 2 months prior to entry into the study, with no anticipation of change in the frequency of therapeutic sessions, or the therapeutic focus over the duration of the trial.

7. Use of any medication(s) listed on the Prohibited Concomitant Medication (Section 5.8) within 1 week of randomization.

8. Subjects are adequately benefiting from current antidepressant medication(s).

9. Significant acute suicide risk, defined as:

- Greater than or equal to 1 suicide attempts in the past 12 months; or
- Has a clear-cut plan for suicide and states that he/she cannot guarantee that he/she will call his/her regular psychiatrist or the Investigator if the impulse to implement the plan becomes substantial during the study; or
- In the Investigator's opinion, is likely to attempt suicide within the next 6 months.

10. Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease.

11. Intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, stents, or electrodes) or any other metal object within or near the head, excluding the mouth, which cannot be safely removed.

12. Clinically significant abnormality or clinically significant unstable medical condition, as indicated by medical history, physical examination, ECG results, or clinical laboratory testing, that in the Investigator's judgment might pose a potential safety risk to the subject or limit interpretation of the trial results, e.g., any uncontrolled thyroid disorders, hepatic, cardiac, pulmonary and renal malfunctioning.

13. Women who are currently pregnant or not using a medically acceptable means of birth control and women who are breastfeeding.

14. Positive urine drug screen for illicit substances. (A positive urine drug screen at screening may be repeated once prior to randomization).

15. Any condition which in the judgment of the Investigator would prevent the subject from completion of the study.

5 STUDY PROCEDURES

5.1 SUBJECT SCREENING AND ENROLLMENT

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent must be obtained from the Institutional Review Board (IRB) or Ethics Committee (EC).

Subjects interested in participating in this clinical trial will be assessed for eligibility. If a potential participant is found to be eligible for enrollment, the study consent form will be reviewed with the subject and the study methods and requirements will be explained. Written informed consent will then be obtained. A pre-screening log will be maintained for all subjects who are screened for enrollment but either do not qualify or decide not to participate in the study.

Once a subject has been consented, the screening process will begin. For each subject this will include verification of their ATHF for the current episode of depression. Verification consists of a detailed interview with the patient to obtain history of illness and treatments. When possible, and with the subjects permission, verification may be supplemented by a phone interview with the subject's attending physician/psychiatrist and a full review of the subject's medical records of present history, including pharmacy records.

A copy of the signed consent form will be provided to the study participant and the original signed consent form will be maintained in the subject's files.

The Screening and Baseline assessments will be split by at least 7 days. Screening visits maybe performed before an antidepressant medication washout period (if applicable), while Baseline visits must be post-washout, which will be done at least one week following screening but before randomization. The HAM-D_{17} assessment conducted at screening will be confirmed by independent review to determine eligibility (HAM-D_{17} greater than or equal to 17). The Baseline visit clinical assessment results will then be used as the baseline values for the study. Subjects must meet eligibility requirements at both Screening and Baseline visits and not show improvement of >5 points between these visits to remain eligible for randomization in the study.

5.2 Assignment of Subject Identification

Once a subject has consented to enrollment in the study, a sequential Subject Identification (SubID) Number will be assigned. This number will consist of the following format: NNDXXXX-XXX-XXX. The first
7 letters/digits represent the protocol number, the next three digits represent the pre-assigned site number, and the last three digits represent the numerical sequence of enrollment, such that the first study subject at any site will be "001," the second "002" etc. The first enrolled subject for this trial at Site 1, for example, will be assigned SubID number NND3002001001.

The SubID number is to be recorded on all study documents and will link the study treatment and the study documents to the subject's name and medical record. To maintain confidentiality, the subject's name should not be recorded on any study document other that the informed consent form.

5.3 Randomization and Blinding

This study is randomized, double-blind, and sham-controlled to minimize bias. Subjects will be randomized following the post-washout baseline assessment (Day 0) to one of the two treatment groups (sTMS vs. sham treatment), at a 1:1 ratio. Randomization will be stratified by site in blocks of 10 determined by a computer generated randomization table defined prior to the start of the trial. Each site will be given a set of 10 randomized PPMs. The assignment is determined by a computer generated randomization table defined prior to the start of the trial. Each Patient Passport Module (PPM) has a 128-bit number preprogrammed for use with a corresponding active or sham device. This number is independent of the Subject ID or device serial number, and is not shown on the PPM or displayed by the device. It is impossible to determine if the PPM is to be used with an active or sham device just by looking at the number. Instead, the software embedded in the device reads the number and uses a decoding algorithm to determine if the PPM is to be used with that particular device. If not, the device will inform the user that the PPM is not valid for that device. The decoding algorithm is kept with the manufacturer, and is not known by the clinical site or any clinical monitor.

These PPMs are labeled with a sequential number to maintain the blinding. At the time an individual subject is randomized, the site will select the next PPM in the instructed numerical order and assign it to that subject. Each site will keep a log of the PPM number assigned to each subject. (See Section 6 for additional information on the PPM). Investigators who perform the assessments, those administering treatment, and subjects who participate in the trial will be blinded to study treatment. A Treatment Blinding Questionnaire will be completed by those performing the assessments, those administering treatment, and subjects at the Week 1 and Week 6 Evaluation Visits for sponsor review to ensure the blind is maintained.

Both the active and sham sTMS devices have the same outer structure and motor functions, and will look, sound and operate in a similar fashion in order to maintain blinding of the treatment. However, the sham devices will not deliver the alternating magnetic fields that the active device produces. Besides a subtle mechanical vibration, neither active nor sham device will produce any physical sensation. The trial equipment will be labeled with serial numbers that indicate whether they are active or sham. The treatment site will be kept blind of the assignment code.

5.4 Open Label Follow-up Phase

Following completion of their treatment period, subjects who have not remitted (remission defined as a HAM-D_{17} score ≤ 7) may be offered 6 weeks of open label sTMS treatment, if the clinician feels this is appropriate for that subject.

Subjects that enter the open label sTMS follow-up phase will continue to use their existing PPM. These PPMs will function in the open label device regardless of whether they were associated with an active or sham device for Weeks 1 through 6.

The open label sTMS device will deliver the same therapy as the active device does during the treatment phase. However, the device will look and sound different than either the active or sham to help maintain the blind.

5.5 Unblinding Procedures

It is expected that the need to unblind the treatment group randomization will be rare. In those rare instances, it is expected that the Investigator contact the Sponsor for unblinding instructions. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner. In all cases, any breaking of the blind must be followed by a written narrative of the event within 5 days.

5.6 Access to the Randomization Code During the Study

The master randomization code will be maintained by the Sponsor's authorized representative who is not directly associated with the conduct of trial. This representative will provide individual patient information as requested; in those rare events there is a need to unblind.

5.7 Prior and Concomitant Medication

Prior medications are defined as all medications taken within 30 days (whether continuing or not) prior to post-washout screening/baseline (Day ≤ 0). All prior and concomitant medications must be listed in the subject's medical record and recorded on the CRF. Subjects should be questioned at each study visit concerning any new medications or changes in current medications.

For each medication taken, the following information will be collected:

- Medication trade name.
- Indication for which the medication was given.
- Dose, route, and frequency of administration.
- Date started.
- Date stopped.

Subjects will be instructed not to begin any new medication before consulting with the Investigator (unless required for emergency medical use). The subject will be instructed that this prohibition applies to over-the-counter and herbal products as well as prescription drugs.

All subjects will be tapered off their existing antidepressant medications during Screening (if applicable) and may receive only permitted concomitant medication as deemed necessary by the Investigator. All antidepressant medications must be discontinued for 1 week (7 days) prior to post-washout Baseline assessments (Day 0). Concomitant medications should be kept to a minimum during the study. The Investigators are recommended to use these medications in accordance with usual clinical practice and only medications essential for the subject's well-being should be used. If such medication is deemed essential, subjects should stay on their usual medication regimens at stable doses during the entire course of the study.

If necessary, benzodiazepines (≤0.5mg/2xweek lorazepam or equivalent dose of benzodiazepine) may be used for agitation/anxiety. For sleep, partial benzodiazepine agonists, including zolpidem 5 to 10 mg/day, zaleplon 5 to 10 mg/day, and eszopiclone 2-3 mg/day, may be used on an exceptional basis for insomnia/sleep disturbance within the prescribing doses for insomnia. Any equivalent short half-life non-benzodiazepine hypnotic may be substituted if zolpidem, zaleplon, or eszopiclone are not available (i.e. chloral hydrate). These drugs should not be used for 72 hours prior to the initial evaluation visits.

Questions regarding the use of concomitant medications should be addressed to the study Monitor.

5.8 PROHIBITED CONCOMITANT MEDICATION

Use of the following concomitant medications is prohibited within 72 hours of the baseline EEG (Day 0), but are otherwise allowable in the study:

- Anti-Migraine
- Benzodiazepines and Partial Benzodiazepine Agonists (see section 5.7 for clarification)
- Non-Benzodiazepine Hypnotics
- Non Sedating Antihistamines
- Cough Suppressants (Dextromethorphan, etc)

Uses of the following concomitant medications are excluded throughout the study and should be washed out at least 1 week prior to baseline (Day 0):

- Anticholinergics
- Anticonvulsants
- Antidepressants (note: fluoxetine shall be washed out 4 weeks prior to baseline)
- Antihistamines (with sedating effects)
- Anti-Parkinsonian medications
- Antipsychotics
- Barbiturates
- Codeine or Oxycodone containing compounds
- Corticosteroids (tablet forms only)
- Cold Pills (with sedating ingredients)
- Medications that are known to reduce seizure thresholds:
    a. Accurbron/Accubron
    b. Doxepin
    c. Ambenonium Chloride
    d. Amitriptyline
    e. Imipramine
    f. Amoxapine
    g. Trazodone
    h. Amphetamine sulfate
    i. Baclofen
    j. Chlorpromazine
    k. Clozaril
    l. Cocaine
    m. Lithium
    n. Protostat
- Mood stabilizers
- Muscle relaxants
- Other sleep aid medications with anticholinergic properties (prescription OR over-the-counter)
- Opioid analgesics

- Pseudoephedrine combination forms that contain excluded medication (pseudoephedrine (e.g, Sudafed) in pure form is acceptable during the study)
- Psychostimulants

The following Nutritional supplements are excluded throughout the study and should be washed out at least 1 week prior to baseline (Day 0):

- CQ-10
- Ginkgo Biloba
- Ginseng containing supplements
- Sam-E
- St John's Wort
- High doses of Omega-3 fatty acids and fish oil supplements (note: this is acceptable if subject is taking ≤1000mg QD or reported taking the supplements for at least one month prior to starting the study).

Caffeinated Beverages (e.g. Energy Drinks, Coffee, Cola Products): The subject should not deviate from their normal consumption patterns. EEG should not be collected within one hour of consumption of any caffeinated beverage.

Alcoholic Beverages: Subjects should refrain from overconsumption of alcoholic beverages on the night preceding and the day of their EEG visits.

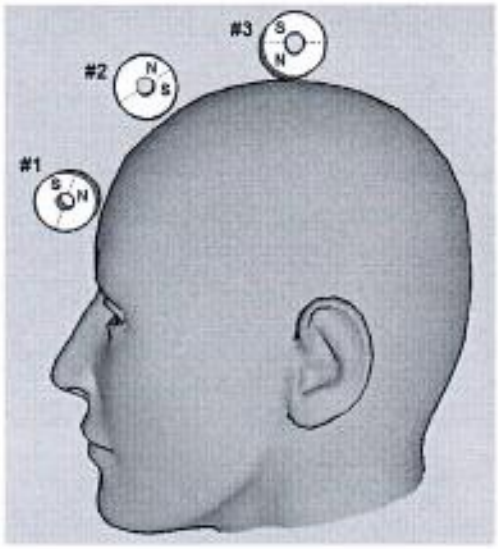
6 INVESTIGATIONAL DEVICE

6.1 DESCRIPTION

The NeoSync sTMS device provides therapy for MDD by generating an alternating magnetic field in close proximity to the head of the subject. It does this using diametrically magnetized cylindrical neodymium magnets, 1 inch diameter and length, with a surface field of approximately 6,400 Gauss (0.64 Tesla). These magnets rotate to generate a sinusoidal magnetic field set at precisely the average individualized alpha frequency (IAF) calculated from the subject's EEG.

The NeoSync sTMS device contains three magnets in the sagittal line above the subject's scalp, which rotate along a transverse axis, as shown in Figure 2.

FIGURE 2
DRAWING SHOWING THE LOCATION OF THE THREE ROTATING DIAMETRICALLY MAGNETIZED CYLINDRICAL MAGNETS ABOVE THE SUBJECT'S HEAD.



Magnet #1 is located just above the nasium, overlying the frontopolar region of the brain. Magnet #2 is located ventral to the first magnet over the frontocentral region, approximately overlying the superior frontal gyrus. Magnet #3 is located further ventral over the central head region, approximately overlying the secondary somatosensory cortex in the parietal lobe. sTMS stimulation therefore is delivered broadly over the prefrontal and frontal regions of the brain. The NeoSync sTMS device consists of a housing that encloses the 3 rotating magnets and keeps them in close proximity to the subject's scalp.

During therapy, the subject lies still, relaxed, with eyes closed. The subject should not sleep during therapy. Each therapy session lasts 30 minutes. In order to prevent a subject from undergoing therapy more than once per day, a 10-hour lockout of the device occurs after a therapy session has ended or is cancelled.

The IAF is stored on a Patient Passport Module (PPM), which is inserted into the USB port on the NeoSync sTMS device.). The PPM comes programmed with the unique PPM number and the number is labeled on the outside of the PPM as well.

To determine the IAF, the NeoSync sTMS system includes an EEG recording module. A single channel (sensing lead, reference lead, and a ground reference) EEG must be recorded (Baseline, post-washout, Day 0) before the PPM may be used with the device to administer therapy. At Screening (pre-washout, if applicable), all subjects will have an EEG recorded using a separate, generic PPM. This PPM is unable to deliver therapy or store a subject's IAF, but allows an EEG to be collected to verify they meet inclusion criteria.

To record EEG, 3 disposable patch Ag/AgCl snap-type electrodes are affixed to the subject's head, one in the center of the forehead (FpZ) approximately 1" (two fingers) above the nasal bridge between the eyebrows; one on the subject's forehead right of center (Fp1); and one (OZ) approximately 1" (two fingers) above the protuberance of the occipital bone (inion). EEG recording is done automatically at the push of the START button. This recording takes approximately 5-15 minutes while the subject lies still, relaxed, with eyes closed. The subject should not sleep during the EEG recording. A new automatic quality discrimination routine is used to determine whether the initial EEG recording is of sufficient quality to allow calculation of a valid IAF. If the first EEG recording is determined to be too variable, the user will be prompted to adjust the EEG electrodes and record another EEG sample until an EEG sample of sufficient quality to determine a valid IAF is obtained. If for any reason it is not possible to record an adequate EEG after 8 attempts, the subjects will be excluded from the protocol.

The NeoSync sTMS device uses a proprietary algorithm to determine the IAF and records the value to the PPM, then indicates to the user that EEG recording has completed. After this, the PPM is considered valid and may be used to adjust the sTMS treatment frequency to match the IAF whenever the subject undergoes therapy. The IAF obtained during this baseline recording is used throughout the study.

The EEG recording data is not stored directly to the PPM. Instead, the data is stored in memory internal to the NeoSync sTMS device which was used for the recording. The Clinical Monitor will periodically download the EEG data for all subject sessions.

The NeoSync sTMS device is powered by a medical-grade power supply that will plug into any 110-220VAC wall socket. More details on the device and proper use can be found in the NEST User Guide, which will be supplied with all devices.

6.2 Device Packaging

Each of the devices will come packaged in a kit consisting of the following items:

- NeoSync sTMS Device
- User's Instruction Manual
- Power Supply
- Power Cord

Note that the PPMs and EEG supplies are not contained in the device packaging. They will be provided separately.

6.3 Device Receiving, Storage, Dispensing, Usage and Return

Receipt of Device

The study equipment will be delivered via a local courier to the location designated by the study site for shipments. The device will be shipped with the Investigational Device Receipt Form. Once signed, the original Investigational Device Receipt Form should be returned to NeoSync, Inc., and a copy will be maintained in the Investigator's Files. It is important that the designated study personnel counts and verifies that the shipment contains all the items noted in the shipment inventory upon receipt. Any damaged or unusable study device in a given shipment will be documented in the study files. The Investigator must notify the Sponsor of any damaged or unusable study devices that were supplied to the Investigator's site.

Device Storage

The NeoSync sTMS device should be stored away from items sensitive to magnets (e.g. computer monitors, credit cards, watches, cell phones, etc.).

6.4 The USB Patient Passport Module and EEG Recording

After signing informed consent, meeting all other study criteria, and randomization, the site will use the NeoSync sTMS device to record the subject's EEG and determine his/her Individual Alpha Frequency (IAF) for treatment. The selected PPM will be assigned to the subject and will be used for every therapy session the subject undergoes, including the open label follow-up phase (if applicable).

To record the EEG, the clinician inserts the PPM into the appropriate NeoSync sTMS device USB port, attaches disposable Ag-AgCl electrodes to the subject's scalp, connects the leads, and presses the START button. EEG recording is automatic from this point. After EEG recording, the NeoSync sTMS uses a proprietary algorithm to determine the IAF, and will program the PPM with that value. Afterwards, the PPM is considered valid, and may be used during daily therapy sessions for the subject with the corresponding device.

It should be noted that the PPM will not work if connected to an incorrect device at any point after the PPM has been assigned to a subject for a specific randomization arm. If the PPM is plugged into the

incorrect device for determination of a subject's Baseline IAF or for any given therapy session, the device will provide audio and visual cues to indicate that a different sTMS device must be used.

After each therapy session, usage data is stored on the PPM, which includes treatment time and whether the therapy was cancelled or was successful, as well as any pauses in therapy that may have occurred. The PPM should be available to the Study Monitor during the study to check compliance. Following completion of the study, all PPM's must be returned to the Study Monitor.

The PPM is specific to the subject, and should ONLY be used for therapy sessions of that subject with the corresponding device. Files stored on the PPM should never be altered in any way by the clinician.

An additional, generic PPM will also be provided to the sites for use during screening visits. This PPM is used to allow an EEG to be recorded for the purpose of determining if the subject is eligible (Inclusion Criteria #4) to participate in the trial. This generic PPM does not activate treatment nor does it store the EEG or IAF. It simply allows the device to run in EEG acquisition mode. This generic PPM will work with all study devices.

Subjects who participate in the 6-week open label phase will continue to use their existing PPM. All PPMs, regardless of active or sham, will also operate the open label device.

6.5 Accountability and Return of Study Equipment

Documentation of receipts, dispensing, and return of all investigational devices and USB Patient Passport Modules must be maintained by the Investigator or his/her designee. It is the Investigator's responsibility to ensure that all investigational devices are kept in a secure location, with access limited to individuals authorized by the Investigator. The Investigational Device Accountability Log will be used to account for all investigational devices received, dispensed and returned and must be maintained by the site until the conclusion of the study at which time the original will be retrieved by NeoSync, Inc. and a copy kept at the site. Following accountability of the investigational devices by NeoSync, Inc., all investigational devices will be returned to NeoSync, Inc. Any discrepancies noted will be investigated, resolved, and documented prior to return of device. The courier shipping form should be faxed on the day of shipment to ensure tracking by the Sponsor. The device is to be sent back to NeoSync, Inc. in its original packaging.

7 VISITS AND PARAMETERS

7.1 Examination Schedule

Subjects will be examined and evaluated according to the following schedule of visits:
Screening and Baseline (($\leq$Day 0)
Week 1 (Treatment Day 1-5) Treatment Visit(s)
Week 1 (Treatment Day 5) Evaluation Visit
Week 2 (Treatment Day 6-10) Treatment Visit(s)
Week 2 (Treatment Day 10) Evaluation Visit
Week 3 (Treatment Day 11-15) Treatment Visit(s)
Week 3 (Treatment Day 15) Evaluation Visit
Week 4 (Treatment Day 16-20) Treatment Visit(s)
Week 4 (Treatment Day 20) Evaluation Visit
Week 5 (Treatment Day 21-25) Treatment Visit(s)
Week 5 (Treatment Day 25) Evaluation Visit
Week 6 (Treatment Day 26-30) Treatment Visit(s)
Week 6 (Treatment Day 30) Evaluation Visit

Optional Open Label Treatment and Evaluation Visits
Week 7 (Open Label Treatment Day 1-5) Treatment Visit(s)

Week 7 (Open Label sTMS Treatment Day 5) Evaluation Visit
Week 8 (Open Label Treatment Day 6-10) Treatment Visit(s)
Week 8 (Open Label sTMS Treatment Day 10) Evaluation Visit
Week 9 (Open Label Treatment Day 11-15) Treatment Visit(s)
Week 9 (Open Label sTMS Treatment Day 15) Evaluation Visit
Week 10 (Open Label Treatment Day 15-20) Treatment Visit(s)
Week 10 (Open Label sTMS Treatment Day 20) Evaluation Visit
Week 11 (Open Label Treatment Day 21-25) Treatment Visit(s)
Week 11 (Open Label sTMS Treatment Day 25) Evaluation Visit
Week 12 (Open Label Treatment Day 26-30) Treatment Visit(s)
Week 12 (Open Label sTMS Treatment Day 30) Evaluation Visit

The first treatment (Day 1) may occur on the same day as the baseline visit (Day 0) if all study criteria are met and randomization procedures are complete, or subjects will be asked to return on a subsequent day to begin the weekly treatment schedule. Subjects will come to the clinic for 5 daily treatment sessions per treatment week for a total of 30 treatment sessions over 6 treatment weeks. A consistent Monday through Friday weekly treatment schedule will be highly encouraged. However, a visit interval of 5-10 calendar days will be allowed for each treatment week to accommodate visit scheduling adjustments when needed. Treatment will be discontinued at the end of Week 6 (30 treatment sessions). Subjects will be clinically evaluated for safety and efficacy at the end of each of the six weekly treatment courses. Subjects, who have not remitted at the Week 6 evaluation visit, may be eligible to receive open label sTMS during the follow-up phase. If so, additional weekly treatment evaluation visits shall be performed at the end of treatment Week 7, 8, 9, 10, 11 and 12. Subjects who do not meet response criterion (relative to pretreatment baseline, Day 0) following 3 weeks (15 treatments) of open label treatment may be offered additional concomitant antidepressant therapy for the final 3 weeks of open label treatment.

7.2 CLINICAL PARAMETERS

The clinical parameters to be evaluated are:

1. **Electroencephalogram (EEG):** Screening, Baseline
   EEG testing will be performed with patient laying still, relaxed, with eyes closed.
2. **Demographics:** Screening
   Demographic data to be captured for all subjects includes age, gender, race, and education level
3. **Vital Signs:** Baseline, Week 6 Evaluation Visit
   Subjects' heart rate and blood pressure will be collected at Baseline and at the time of study treatment completion.
4. **Weight:** Baseline, Week 6 Evaluation Visit
   Subject's weight will be recorded at Baseline and at the time of study treatment completion.
5. **Pregnancy Test:** Screening
   Female subjects of child bearing potential must have a negative urine pregnancy screen (HCG) to participate in the trial. Such subjects will also be required to use acceptable forms of birth control; such as prescribed birth control pills, IUD, or hormonal injection during the course of the study. Method of birth control for female subjects of child bearing potential will be recorded by study staff at the beginning of the trial. A follow-up urine pregnancy screen will be obtained at any time in the study if doubt exists that she might be pregnant. Any woman who becomes pregnant will be discontinued from the study immediately and referred for appropriate treatment.
6. **Urine Toxicology Panels:** Screening
   A urine toxicology dipstick screen will be performed at screening visit in order to rule out use of unprescribed psychoactive medications. All subjects with a positive test must be withdrawn from the study unless a subsequent negative test is obtained (this may only occur once prior to randomization). These subjects will be informed that urine samples may be obtained on additional occasions during

the study, but will not be told how many samples nor about the time at which the samples will be collected. Sites may conduct an optional urine toxicology screen if the Investigator feels it is indicated at any time during a subject's study participation.

7. **Mini Mental Status Exam Version 2 (MMSE-2):** Screening
   The Mini Mental Status Exam is a standard clinical evaluation of the severity of cognitive impairment, commonly used in Screening and evaluation for age-related dementia and Alzheimer's disease. The MMSE-2-Standard Version will be used in this trial.
8. **Medical/Psychiatric History:** Screening
   An assessment of a subject's past medical and psychiatric history will be performed via clinician interview to determine pre-existing conditions and verify appropriateness for the trial.
9. **MINI:** Screening
   The MINI is a structured diagnostic interview, developed to assess the diagnoses of psychiatric subjects according to DSM-IV-TR criteria in less time than other diagnostic interviews such as the Structured Clinical Interview for DSM-IV-TR disorders (SCID). The psychometric characteristics of the MINI make it a good choice for research purposes (van Vleit 2007). Any other primary Axis I diagnosis will exclude the subject from the study.

10. **Antidepressant Treatment History Questionnaire (ATHQ):** Screening
    The ATHQ is a semi-structured inventory used to rigorously characterize antidepressant treatment in terms of dosing adequacy, treatment duration, subject compliance and outcome. It has been shown to demonstrate predictive validity for the outcome of somatic treatments for depression, and hence is a valid alternative to a prospective treatment trial to establish antidepressant treatment resistance.
11. **HAM-D/MADRS:** Screening, Baseline , Week 1-6 Evaluation Visits, Open Label Week 7-12 Evaluation Visits
    The clinical evaluator will interview the subject during the screening and baseline appointments using a combined structured interview guide for the HAM-D/MADRS.
    Total score of HAM-D_{17} at Screening and Baseline should be 17 or greater for subjects to qualify for the study, with a decrease in total score $\leq$5 points from Screening to Baseline. In addition, subjects must score greater than or equal to a 2 on Item 1 of the HAM-D at the same visits to qualify.
12. **IDS-SR:** Baseline, Week 1-6 Evaluation Visits, Open Label Week 7-12 Evaluation Visits
    Subjects will be asked to complete a 30 item self-rated scale at screening and baseline and at each evaluation visit thereafter.
13. **C-SSRS:** Screening, Baseline, Week 1-6 Evaluation Visits, Open Label Week 7-12 Evaluation Visits, and when specific Adverse Events are present
    The Columbia Suicide Severity Rating Scale is an easy-to-administer yet comprehensive measure that assists with the tracking of such thoughts, from a wish to die to an actual plan, and behaviors, from preparing for an attempt to an actual attempt. This scale will be administered at specific time points in the trial. Additionally, if a subject reports a new Adverse Event of depression worsening, suicidal ideation or suicide attempt at any time during the trial, a C-SSRS will be completed and appropriate actions should be taken to ensure the safety of the subject.
14. **Adverse Events:** Screening, Baseline, Week 1-6 Treatment and Evaluation Visits, Open Label Week 7-12 Treatment and Evaluation Visits
    All adverse events, including the following, will be assessed by the Investigator, and recorded in the subjects study chart and on the appropriate case report form pages.
15. **Concomitant Medications**: Baseline, Week 1-6 Treatment and Evaluation Visits, Open Label Week 7-12 Treatment and Evaluation Visits
    All medications prescribed and/or taken by the subject will be collected.
    Any changes to these medications may be updated at any visit.
16. **Verification of Blinding Questionnaire:** Week 1 and 6 Evaluation Visits

Each subject, sTMS Administrator, and Rater will be asked to guess whether they believe the subject was randomized to active treatment or sham group. In addition they will be asked to provide a reason why they believe that they were randomized to the group they chose and their confidence level. Assessment of these data will be summarized at the completion of the trial.

17. **Laboratory Assessments**: Screening (Optional)
    If the Investigator believes there is a need to assess a subject's safety for participating in the study based on the subject's history prior to enrolling, he/she may conduct blood tests for review prior to initiation of study treatments.
18. **Physical Exam:** Screening(Optional)
    Physical exams may be done if the study physician feels it is indicated (e.g. because of medical history). This exam may include neurological assessments if applicable.
19. **Electrocardiogram (ECG):** Screening (Optional)
    Electrocardiograms may be performed at Screening if the study physician feels it is warranted based on the subject's medical history or physical exam.

A flowchart of all study procedures can be found in Appendix I.

7.3 Clinical Parameters by Visit

Initial Screening/Baseline Visit

Potential study participants will be screened for eligibility per the protocol eligibility criteria. The Screening/Baseline visits may be split into two or more days. After informed consent has been signed and washout from previous medications is complete (when necessary), the following assessments will be performed as part of the subject eligibility assessment:

- MINI
- ATHF
- Mini Mental Status Exam (MMSE-2)
- Medical and psychiatric history
- Concomitant medication history
- Adverse Events
- Demographics
- NeoSync EEG
- Vital Signs (HR, BP)
- Weight
- Pregnancy Test (HCG)
- Urine Toxicology Screen
- HAM-D/MADRS
- IDS-SR
- C-SSRS
- Standard 12 lead ECG (optional)
- Physical Examination (optional)
- Laboratory Assessments (optional)

Randomization into the Trial

Upon successful completion of Screening and Baseline visits to establish eligibility, subjects will be randomized into the trial. A PPM will be selected and assigned to the subject. This PPM can only be used with either an active or sham device as they are already encrypted and assigned to a randomization arm per the pre-generated randomization schema. The subject's EEG will be recorded. The EEG will be

processed and used to determine the treatment parameters stored on the subject's PPM. The PPM should be labeled with the Sub ID. That PPM must be used with that device for all treatments.

Double-Blind Treatment Visits (Week 1-6)

After the subject has been deemed to be acceptable for inclusion in the trial and randomized to a treatment group, they may begin scheduled treatments. They will go to the physician's office 5 days per treatment week to complete the treatment procedure. In addition, subjects will be assessed for changes in adverse events, concomitant medications, or worsening of symptoms that may need physician intervention at each of the treatment visits. The first treatment visit may occur after randomization at the baseline visit given sufficient time.

Double-Blind Evaluation Visits (Week 1-5)

In addition to the treatment visits, an evaluation will be conducted on the same day as the last treatment (5^{th} treatment session, within 10 calendar days) of each weekly treatment cycle. The following assessments will be performed as part of that evaluation:

- HAM-D/MADRS
- IDS-SR
- C-SSRS
- Adverse Events
- Concomitant Medications
- Treatment Blinding Questionnaire(s) (Week 1)

Week 6 /Early Termination Visit

If assessments are done as part of an early discontinuation visit, subject should be asked to come in for the post-treatment follow-up visit.

- Vital Signs
- Weight
- HAM-D/MADRS
- IDS-SR
- C-SSRS
- Adverse Events
- Concomitant Medications
- Treatment Blinding Confirmation Questionnaire(s)
- Determination of eligibility for open label sTMS treatment

Open Label Evaluation Visits (Week 7-12)

In addition to the treatment visits, an evaluation visit will be conducted on the last day of each weekly treatment cycle. The following assessments will be performed as part of that evaluation:

- HAM-D/MADRS
- IDS-SR
- C-SSRS
- Adverse Events
- Concomitant Medications

8 DISCONTINUATION

8.1 WITHDRAWAL FROM STUDY

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. The Investigator, the IRB and NeoSync, Inc. also have the right to withdraw subjects or terminate the trial for the following reasons:

- Occurrence of unacceptable risk to the subjects enrolled in the study, including significant worsening of depression.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

The Investigator may use the weekly clinical evaluation to determine if the subject's symptoms or quality of life have significantly deteriorated to the point where withdrawal from the study would be in the subject's best interests.

A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:

- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities.
- Insufficient adherence to protocol requirements.
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or appropriate regulatory authority.

Subjects who withdraw from the study for any reason will not be replaced. Subjects who voluntarily withdraw from the study will be asked to complete the Week 6/Early Termination assessments. Subjects who are withdrawn due to adverse events will be followed until resolution or stabilization of the adverse event.

8.2 REASONS FOR DISCONTINUATION OF SUBJECTS

Subjects may decide to discontinue their participation in the study for various reasons such as unmanageable side effects, lack of efficacy, withdraw of consent, etc. The PI may also decide to withdraw the subject for reasons including: protocol noncompliance, safety concerns, etc.

Sites will attempt to gather information for all subjects that discontinue from the study whenever possible. The sites shall, at minimum, collect details regarding the subject's primary reason for discontinuing, HAM-D, MADRS, current medication use, and adverse events. Other scales may be collected, based upon the subject's availability.

8.3 SUBJECTS LOST TO FOLLOW-UP

In the event that a subject does not return for his/her next scheduled visit, sites must make every attempt to contact the subject to attempt to retain them in the study. Site staff should contact the subjects in order to either continue his/her study participation, or to ensure safe discontinuation from study and transfer care to the subject's personal physician/psychiatrist. Sites will gather as much information as possible for any subject that discontinues his/her study participation. If a subject does not show up for a scheduled visit the site should make the following efforts to continue the subject in the study and/or gather discontinuation status information:

- At least three follow-up phone calls to attempt to contact subject. Documentation of all phone call attempts in the subject's source documentation.
- Phone calls should be made at different times in the day, and different days of the week.
- Send a certified letter to each subject that does not return phone calls.

8.4 SUBJECT STUDY COMPLETION

Any subject who remains in the trial to the endpoint analysis (Week 6 Evaluation Visit) will have final evaluations completed in line with the Week 6 visit schedule of events. Based upon the clinician's assessment of subject's current status (e.g. response, side effect profile, insurance situation), a decision will be made as to the best treatment plan for the subject.

If the subject does not reach a clinical assessment definition of "remission" (HAM-D_{17} score ≤ 7) by the time of their Week 6 Evaluation Visit, they are eligible to be considered for an additional 6 weeks of open label sTMS treatment. This open label treatment is completely optional and shall be considered based upon the clinician's judgment on the best course of therapy. Alternatively, the subject may begin a course of antidepressant medications or may choose to return to their primary physician for follow-up care. If the subject does participate in the open label sTMS treatment phase, they will be evaluated weekly during the 6 weeks of therapy. Information about the subjects' transition will be collected along with their current symptoms, adverse events, etc. at the final study visit.

9 EVALUATION OF SAFETY

An adverse event (AE) is defined as any untoward medical occurrence in a subject treated with an investigational product that does not necessarily have to have a causal relationship with the treatment under investigation. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product whether or not considered related to the investigational product.

A Serious Adverse Event (SAE) is defined as an adverse event that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly or birth defect

An unanticipated adverse device event (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol and/or Instruction For Use (IFU) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subject.

All adverse events that do not meet any of the criteria for SAEs or UADEs should be regarded as non-serious adverse events.

Progression of disease, in this case major depressive disorder, reflects lack of therapeutic efficacy and should not be treated as serious adverse events. However, other events or complications meeting the criteria for serious adverse events should be considered as a serious adverse event and should be reported immediately to NeoSync regardless of presumed relationship to the investigational device.

9.1 ADVERSE EVENT ASSESSMENT

All adverse events, including the following, will be assessed by the Investigator via interview, and recorded in the subjects study chart and on the appropriate case report form pages.

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- Medical condition which emerges during the study, having been absent at baseline
- Medical condition present at baseline, which appears to worsen during the study

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the investigational product.

Each AE must be described as follows: the date of onset, date of resolution, severity, frequency of the event (single episode, intermittent, continuous), action taken (none, medical and/or surgical), relationship to investigational device, and seriousness criteria must be recorded. Each adverse event must be recorded separately.

Severity will be assessed using the following definitions:

Mild	Aware of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

The relationship to investigational device will be assessed by the Investigator using the following definitions:

Not Related	Evidence exists that the adverse event definitely has a cause other than the investigational device (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
Possibly Related	A temporal relationship exists between the event onset and administration of investigational device. Although the adverse event may appear unlikely to be related to the investigational device, it cannot be ruled out with certainty; and or the event cannot be readily explained by the subject's clinical state or concomitant therapies.
Probably Related	A temporal relationship exists between the event onset and administration of investigational device, and appears with some degree of certainty to be related based on known therapeutic and pharmacologic actions of the investigational device. It cannot be readily explained by the subject's clinical state or concomitant therapies.
Definitely Related	Strong evidence exists that the investigational device caused the adverse event. There is a temporal relationship between the event onset and administration of the investigational device. There is strong therapeutic and pharmacologic evidence that the event was caused by the investigational device. The subject's clinical state and concomitant therapies have been ruled out as a cause.

9.2 ADVERSE EVENT REPORTING

All subjects who have been exposed to the investigational device will be evaluated at baseline and future visits by a clinician for adverse events via interview. All adverse events will be evaluated beginning with onset, and evaluation will continue until the last day of the study, until resolution or recovery is observed

or until the Investigator determines that the subject's condition is stable, whichever is earlier. The Investigator will take all appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form.

If more than one distinct adverse event occurs, each event should be recorded separately. The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study. For this study, the endpoint is defined as the last administration of study treatment.

9.3 Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

All Serious Adverse Events (SAE) and Unanticipated Adverse Device Effects that occur during the study, including death, must be reported within one working day by telephone to the study's Medical Monitor, and followed up in writing within 24 hours. The urgency for reporting SAE is four-fold: (1) to facilitate discussion (and implementation, if necessary) by the Sponsor and the Investigator of appropriate follow-up measures; (2) to facilitate Investigator reporting of unanticipated problems involving risk to human subjects to the IRB; (3) to facilitate the Sponsor's rapid dissemination of information regarding AEs to other Investigators/sites in a multi-center study; and (4) to enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority. Serious adverse events should be reported by phone and facsimile to NeoSync, Inc.

Within the following 48 hours, the Investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study Sponsor.

10 STUDY OUTCOMES

10.1 Primary Efficacy Outcome

The primary endpoint will be clinical response, defined by 50% or greater reduction on the HAM-D_{17} total symptom scores following 6 weeks of treatment.

10.2 Secondary Outcomes

Additional outcomes will include the following:

- The change in symptom scores on the HAM-D_{17} through 6 weeks of treatment
- The change in symptom scores on the MADRS through 6 weeks of treatment.
- Clinical response, defined by 50% or greater reduction on the MADRS total symptom scores following 6 weeks of treatment.
- Effectiveness of blinding questionnaire

10.3 Safety Data

Safety will be assessed by the following:

- The incidence and severity of all adverse events (including, but not limited to, serious adverse events and no-related adverse events)
- Changes in C-SSRS through 6 weeks of treatment.

11 STATISTICAL METHODS

11.1 Population for Analysis

The Intent-to-Treat (ITT) Population will consist of all subjects who are randomized to a study group.

The Per-Protocol (PP) Population is comprised of subjects who receive treatments according to the recommended protocol schedule without any major protocol violation. Major protocol violations include but are not limited to:

- Receiving treatments other than those specified in the study protocol.
- Treatments not administered according to study protocol.
    - Subjects cannot miss more than 1 dose in a treatment week and their weekly visit interval cannot exceed 10 calendar days. Any subject who misses more than 6 doses in the 6 week treatment period (maximum of 60 days) is not considered compliant with the treatment and will not be included in the analysis.
- Receiving concomitant medications that are not allowed per the study protocol.
- HAM-D17 not available at Week 6.

The PP population analysis will serve as the primary analysis population.

The Safety Population will consist of all subjects who received at least one study treatment.

For the six-week open label phase, all efficacy and safety summaries will be based on the combined sTMS-treated subject population, which consists of all subjects who have entered the six-week open label phase. For the open-label phase, all efficacy analyses will be performed on the Observed Cases (OC) dataset only. That is, no imputation for missing data will be used, and only data observed during the follow-up phase will be summarized.

11.2 SUBJECT DEMOGRAPHICS/OTHER BASELINE CHARACTERISTICS

Descriptive statistics for background and demographic variables such as age, sex, race, ATHF level and HAM-D17 total score and subscores at baseline will be presented for the ITT and PP populations. The standard descriptive statistics such as mean, standard deviation, median, quartiles, minimum, and maximum will be used to summarize the continuous variables. For discrete variables, the frequency and percentage of subjects in each category will be calculated.

The demographic profile of subject enrolled in the present study will be compared in an exploratory descriptive manner to the non-Naïve cohort of subjects enrolled in the previous NEST study to assess comparability of study populations.

For patients entering the follow-up open-label phase, descriptive statistics for background and demographic variables will be presented according to previous double-blind treatment for the all sTMS-treated subject population.

11.3 TREATMENTS (STUDY PROCEDURES, OTHER CONCOMITANT THERAPIES)

A data listing of the study treatment administered will be provided. The cumulative number and percentage of subjects exposed to study treatment by time interval and descriptive statistics of duration of exposure to study treatment will be provided by treatment group. The number and percentage of subjects receiving concomitant medications and significant non-drug therapy will also be summarized.

For subjects who receive open label sTMS treatment, data on study treatment administered and duration of exposure to study treatment will be summarized for the all sTMS-treated subject population using similar displays as for the double-blind treatment. These data will be categorized into two groups: those who had received sTMS during the double-blind treatment phase and those who received sham during the double-blind treatment phase.

11.4 ANALYSIS PLAN

Definition of Primary Endpoint

The primary endpoint is clinical response, defined by 50% or greater reduction on the HAM-D17 total symptom scores through 6 weeks of treatment.

Statistical Hypotheses

We will test the null hypothesis that the active sTMS treatment group does not differ from the sham group in the proportion of subjects who show 50% or greater improvement from baseline to Week 6 on the HAM-D_{17} total score. The corresponding alternative hypothesis is that the active sTMS treatment group has a greater proportion of patients than the sham group with respect to the proportion of subjects who show 50% or greater improvement from baseline to Week 6 on the HAM-D_{17} total score. The hypotheses can be expressed numerically as:

H0: $\pi A - \pi S = 0$
and
Ha: $\pi A - \pi S \neq 0$

where πA is the proportion of subjects who show 50% or greater improvement in mean HAM-D_{17} total score from baseline (Day 0) to Week 6 for the active treatment and πS is the equivalent value for the sham-controlled group.

Sample Size Calculation

The calculation of sample size requirements for this confirmatory study is based on the results observed in the PP analysis of non-Naïve subjects enrolled in the previous NEST trial. In that population, 34% of subjects treated with active sTMS were categorized as responders, whereas only 8% of sham treated subjects responded. Assuming true population response rates of 34% for sTMS and 8% for Sham, power analysis indicates that a PP sample size of 92 subjects (46 subjects per treatment group evaluable at week 6) yields 81% power to demonstrate superiority of sTMS, where the statistical test is Fisher's exact test at a two-sided 0.05 level of significance. A total of 120 subjects will therefore be enrolled in the study to account for potential drop-outs and noncompliance prior to Week 6.

Adaptive Sample Size Re-estimation

Due to uncertainty regarding the expected sham response rate and resulting treatment effect differential, this study will utilize an adaptive design that allows one interim sample size re-estimation after a minimum of 70 subjects have been enrolled and completed 6 weeks of treatment (or dropped out prior to 6 weeks). The pre-specified maximum allowable adjusted sample size following re-estimation will be 240 enrolled, or two times the initial planned sample size of 120 enrolled, based on practical resource constraints and the desire to achieve a minimum differential of 12% between active and sham response rates. The re-estimation of sample size will be conducted by an independent biostatistician following a pre-specified plan as described by Mehta and Pocock, 2010.

Specifically, at the interim stage the conditional power (CP) for obtaining a significant beneficial effect of sTMS over sham with respect to the primary endpoint will be calculated. This conditional power will be calculated using formula (6) in Mehta and Pocock (2010) under the assumption that the interim estimate of the risk difference is the true population risk difference. The study will not be stopped for overwhelming efficacy or futility at this interim stage. Based on Table 1 of Mehta and Pocock (2010), if the CP $\leq$ 36% or CP $\geq$ 90%, the study will continue to its original planned sample size of 120 enrolled subjects. Otherwise if 36% < CP <90% (the Mehta and Pocock "promising zone"), then the sample size may be increased in order to obtain 90% CP, up to a maximum of 240 enrolled subjects. This approach to sample size increase does not inflate the overall Type I error.

The sponsor and investigators will remain blinded to the interim results for the duration of the ongoing study.

11.5 General Statistical Considerations

The data analysis will be performed after all subjects have completed the Week 6 visit or have withdrawn from study prior to completion of 6 weeks of follow-up. The standard descriptive statistics such as mean,

standard deviation, median, quartiles, minimum, and maximum will be used to summarize the continuous variables. For discrete variables, the frequency and percentage of patients in each category will be calculated.

All statistical tests will be two-sided with a significant level of 0.05 unless otherwise specified. All confidence intervals will be two-sided with a confidence level of 95%, unless otherwise specified.

Primary Efficacy Analysis

The primary efficacy analysis will be a test of the hypotheses:

H0: $\pi A - \pi S = 0$
and
Ha: $\pi A - \pi S \neq 0$

where πA is the proportion of subjects who show 50% or greater improvement in mean HAM-D_{17} total score from baseline (Day 0) to Week 6 for the active treatment and πS is the equivalent value for the sham-controlled group. The test of the null hypothesis will be based on Fisher's exact test at a two-sided 0.05 level of significance. In addition, the observed response rates and two-sided 95% confidence intervals of the risk difference between treatments will be presented, calculated using the Wilson method as discussed in Newcombe (1998).

To assess homogeneity of results across study centers, the number and percentage of primary responders in each study center will be reported by treatment group. An assessment of treatment-by-center interaction will be carried out at the 0.15 level of significance using the Breslow-Day test. Study centers with less than 10 subjects per center will be pooled with other center(s) by geographic region. The pooling will be detailed in the statistical analysis plan and will be carried out before the blind is broken.

This efficacy analysis will be performed on the ITT and PP (primary) analysis sets. For the ITT, the main analysis will exclude missing data. There will be no missing primary endpoint data in the PP population, by definition. Due to the confirmatory intent of this study, the PP analysis set will be used for initial sample size estimation, for sample size re-estimation, and to assess consistency in a descriptive manner with the previous NEST results showing superiority of active over sham response rates for non-naïve subjects receiving treatment as prescribed.

Additional Endpoint Analyses

The following analyses will be carried out for each of the ITT and PP (primary) populations. There will be no imputation for missing data or adjustments for multiple comparisons.

Additional Endpoints to be studied are:

- The change in mean symptom scores on the HAM-D_{17} through 6 weeks of treatment
- The change in mean symptom scores on the MADRS through 6 weeks of treatment.
- Clinical response, defined by 50% or greater reduction on the MADRS total symptom scores through 6 weeks of treatment.
- Effectiveness of Blinding questionnaire

Descriptive statistics (sample size, mean, median, quartiles, standard deviation, minimum, maximum) of the mean change in HAM-D_{17} and MADRS from baseline to Week 6 will be presented. Change from baseline in the HAM-D_{17} and MADRS total scores will be compared across treatment groups using a MMRM model with terms for treatment, investigative center, visit, and the treatment by visit interaction (visits in the open-label phase will be excluded for the primary double-blind analysis). The model will also include baseline HAM-D_{17} (or MADRS) score as a covariate and subject will be a random effect. An unstructured covariance matrix will be used for the within-subject correlation. Kenward-Rogers'

approximation will be used to estimate degrees of freedom. The LSMEANS statement for the treatment-by-visit interaction will be employed to examine differences across treatments at specific time points, with the focus being on the Week 6 change from baseline. Parameter estimates will be presented and two-sided 95% confidence intervals will be constructed using model estimates for the mean and residual error. Tests of hypotheses will be two-sided and will be based on the contrasts between active sTMS and sham within the model.

For MADRS response rate through 6 weeks of treatment, the number and percentage of responders will be calculated and will be compared in a similar manner as the primary endpoint. Tests of hypotheses will be two-sided and will be based on the contrasts between active sTMS and sham within the model.

For the Effectiveness of Blinding Questionnaire, descriptive statistics (sample size, mean, standard deviation) of the treater, rater, and patient blinding index will be presented at each visit (Treatment Day 5 and Treatment Day 30 [end of double-blind phase]) for each treatment group and both treatments combined as described by Bang et al (2004). A mean close to 0 indicates random blinding (or random guessing); a mean closer to 1 than 0 may indicate failure in blinding (majority of "guesses" were correct); a mean closer to -1 than 0 indicates mainly incorrect guesses were made.

11.6 Safety Data

The assessment of safety will be based mainly on the frequency of adverse events recorded. Other safety data (e.g., vital signs and ECG) will not be collected systematically but will be considered as appropriate. All safety analyses will be performed on the Safety Population as defined above.

Adverse events will be summarized by presenting the number and percentage of subjects having any treatment emergent adverse event (TEAE; defined as an AE that started or worsened in severity following randomized treatment), and having ay TEAE within each MedDRA system organ class and within each MedDRA preferred term. Patients with multiple occurrence of an event will be counted once within the given system organ class and preferred term. This analysis will be repeated for serious TEAEs. TEAEs will further be categorized for each individual AE by severity and relationship to study treatment.

The incidence of treatment-emergent adverse events by MedDRA system organ classes and preferred terms will be compared between active and sham treatment using Fisher's Exact test.

Other information collected will be listed as appropriate.

Statistical tests performed on safety data to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration. Safety summaries will be performed for each of the active and sham treatment for all study subjects in the Safety Population.

12 STUDY MONITORING

12.1 Study Monitoring Plan

This study will be monitored according to the NeoSync, Inc. monitoring plan to ensure its scientific integrity, the quality of data, the safety of human subjects, and compliance with the ethical principles that have their origin in the Declaration of Helsinki, the ICH guideline for Good Clinical Practice (GCP), applicable local regulatory requirements, and Sponsor regulations, guidelines, and policies. Specifically, monitoring assures that:

- Study staff adhere to the protocol;
- Trial data are entered completely and accurately on the CRFs;
- Device Records accurately account for all trial devices shipped to the site;
- Devices are stored properly;
- Regulatory requirements for conducting clinical trials are followed;
- The Investigator's facility, including staffing, remains adequate to conduct the clinical trial;

- The clinical trial progresses according to schedule;
- IRB approval/favorable opinion and laboratory certification are current.

Monitoring visits will be scheduled to take place during the clinical trial at intervals specified in the NeoSync monitoring plan, upon request of the Investigator, and whenever they are deemed necessary by the CRA. The Investigator must allow direct access to the source documents for this purpose. For all sites, a final monitoring visit will be made upon completion of the clinical trial after locking the database (trial close-out visit). Subject recruitment/trial progress will be monitored. The items monitored include enrollment, discontinuations, and completions. This information will be updated every week. To assure the accuracy and completeness of the data, the CRA will compare CRFs with subjects' medical records (source data verification) during the on-site monitoring visits. The Investigator must allow direct access to the source documents for this purpose.

The following minimum information should be recorded in the subject's study records:
- Participation in the clinical trial
- Each visit/contact
- Selection criteria (i.e. a statement that they were all checked)
- Medical history
- Prescription of and adherence to treatment
- Concomitant medication
- Assessments and tests
- Adverse events
- Discontinuation of participation

The following data will be captured directly at the source:
- Laboratory, ECG

For data captured at the source and those entered directly on the CRF, a check on inconsistencies will be carried out. Data requiring clarification will be brought to the attention of the Investigator. Documentation on data verification and correction will be retained as an integral part of the trial documentation.

The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities, and has adequate space to conduct the monitoring visit.

12.2 CONFIDENTIALITY

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:
- What protected health information (PHI) will be collected from subjects in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

12.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, device dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, and x-rays.

12.4 Case Report Forms

Data will be collected at each site using an electronic case report form (eCRF). The study case report form (eCRF) is the primary data collection instrument for the study. Backup paper CRFs will be available for rare instances where access to the eCRF is not available. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, answer "N/D". If the item is not applicable to the individual case, answer "N/A". On paper CRFs, all entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT WRITE OVER, ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

12.5 Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 10 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 10 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

12.6 Protocol Deviations

Deviations to the protocol will be documented by each site. Each site will follow their individual IRB guidelines for proper reporting of protocol deviations.

12.7 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB members and their affiliate to the Sponsor.

12.8 Informed Consent

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject

undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the Investigator-designated research professional obtaining the consent.

13 RISK/BENEFITS

13.1 RESEARCH RISKS

Risks associated with participation in this trial include possible lack of positive response to the treatment or worsening of depressive symptoms. There is no guarantee that the treatment will lead to improvement in all subjects.

13.2 OTHER RISKS

The NeoSync sTMS device generates a weak magnetic field that is considered to be a small fraction of the exposure you would have from a single scan of your brain with an MRI machine. In previous studies with this device, the participants reported minimal side effects. In the prior NEST study, there was no significant difference in the rate of adverse reactions or early discontinuations in the active and sham treatment groups. Adverse events reported in both the "sham" and "active" treatment groups that were considered "possibly" related to the procedure were: Stiff Neck, Back Pain, Headache, Lightheadedness, Dizziness, Blurred Vision, and Insomnia. All of these events resolved and none resulted in discontinuation from the trial.

Other risks of this study are minor. Occasionally some emotional discomfort may occur while filling out questionnaires or being interviewed about matters pertaining to mood, functioning and other experiences. Subjects may experience minor discomfort during blood draws for laboratory tests. In addition, there may be minor skin irritation caused by the application of EEG electrodes.

13.3 STUDY ALTERNATIVES

The alternatives to participation in this study include either receiving no treatment, or receiving treatment prescribed by a physician not affiliated with this study. The primary risk of untreated MDD is prolonged disability and suffering, or if the condition worsens, possibly attempting or completing suicide. This principal risk of treatment outside of this study is side effects from prescribed treatment or non-response.

13.4 POTENTIAL BENEFITS

For Subjects

Benefits to subjects from participation in this trial include a thorough evaluation for MDD at no cost and possible relief from symptoms of MDD.

For Society

The potential benefits of this project to society could include enhanced knowledge about the treatment of MDD, enhanced methods for treatment of MDD, and greater help for people with MDD in the future.

13.5 RISK BENEFIT RATIO

The risk benefit ratio of this study is favorable. Risks of adverse events associated with the use of this device are minimal. Risk of potential non-response associated with lack of efficacy is managed through oversight by a trained physician and results from previous studies that demonstrated potential efficacy and safety of this treatment. Patients will be under the care and supervision of experienced research psychiatrists and will be seen in the office five (5) days per treatment week for treatment and assessment of worsening of symptoms/adverse events. Although two previous sham controlled studies provide evidence of sTMS efficacy, inclusion of a sham control for the present confirmatory study was deemed necessary by the FDA to further support regulatory clearance of this device.

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15 APPENDICES

APPENDIX I: STUDY FLOWCHART

APPENDIX II: INVESTIGATOR'S QUALIFICATIONS AND RESPONSIBILITIES (INCLUDING INVESTGATOR PROTOCOL SIGNATURE PAGE)

APPENDIX III: SPONSOR'S COMMITMENTS

APPENDIX I
STUDY FLOWCHART

ACTIVITY	SCREEN	BASELINE (DAY ≤0)	WK1 TX DAY 5	WK2 TX DAY 10	WK3 TX DAY 15	WK4 TX DAY 20	WK5 TX DAY 25	WK6/ EARLY TERM TX DAY 30	WK7 OPEN LABEL TX DAY 5	WK8 OPEN LABEL TX DAY 10	WK9 OPEN LABEL TX DAY 15	WK 10,11,12 OPEN LABEL TX DAY 20,25,30
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Mini Mental Status Exam (Version 2)	X											
MINI	X											
ATHF	X											
Blinding Questionnaire			X					X				
Randomization		X										
NeoSync EEG	X	X										
Med/Psych History	X											
Vital Signs		X						X				
Labs[a]	X											
Pregnancy Test (HCG)[b]	X											
Urine Drug Screen[b]	X											
Weight		X						X				
Physical Exam[a]	X											
Demographics	X											
ECG[a]	X											
HAM-D/MADRS	X	X	X	X	X	X	X	X	X	X	X	X
IDS-SR		X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Med[c]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[c]	X	X	X	X	X	X	X	X	X	X	X	X

a Optional
b Must be performed at Screening and may be performed at any subsequent visit at the discretion of the Investigator
c In addition to the assessment visits outlined here, All subjects will have 5 treatment visits per week during treatment period changes in adverse events and concomitant medications should be recorded when made known to the site..
Note: The first treatment session may begin on the same day as baseline visit, after subject meets all criteria and is randomized to a treatment arm.

APPENDIX II
INVESTIGATOR'S QUALIFICATIONS AND RESPONSIBILITIES

Each Investigator must be a licensed physician who has completed a residency in psychiatry. The Investigators have the following responsibilities:

1. Subject Selection

The Investigator is responsible for assuring that all subjects entering the study conform to the subject selection criteria.

2. Informed Consent

The Investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective subjects prior to their enrollment in the study. The Investigator is responsible for obtaining written Informed Consent in compliance with 21 CFR 50 for each subject, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record, a copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor, and a copy will be given to the subject.

3. Institutional Review Board (IRB) Approval

The Investigator must obtain approval for his participation in this protocol from the IRB for the institution at which the procedure will be performed, prior to entering any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB for approval prior to initiation of the study. Assurance that the IRB approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The Investigator is responsible for performing the subject evaluations as described in the study protocol. All information generated by the subject evaluation will be recorded on the Subject Case Report Forms provided by the Sponsor.

Investigator(s) will not deviate from the study protocol without prior approval of NeoSync, Inc. unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

The Investigator shall maintain all subject records for whichever of the following periods is shortest:

- A period of 10 years has elapsed since the formal discontinuation of clinical development of the investigational product.
- A period of 10 years after last approval of a marketing application in their country and there are no pending or contemplated marketing applications in their country.

6. Investigational Material Accountability

The Investigator must maintain accurate records of the receipt of all investigational material shipped by NeoSync, Inc., including the date and code numbers received. In addition, accurate records must be kept on the amount and date that investigational material, by code number, was dispensed or returned for each subject in the trial. The Investigator must assure that study supplies be dispensed only to subjects enrolled in the study and under the direct supervision of the Investigator or Co-Investigators.

Records of all investigational supplies received, used and returned must be kept by the principal Investigator. All unused investigational supplies as well as all labeled containers will be returned to the

Sponsor as soon as practical upon completion of the treatment regimen for each subject. Investigational material accounting procedures must be completed before the study is considered terminated.

Investigator Protocol Signature Page

My signature below attests to the fact that I have read the protocol and agree to adhere to all directions/specifications/guidelines within the protocol. This includes but is not limited to: subject inclusion criteria, subject exclusion criteria, procedures for obtaining informed consent, subject screening procedures, enrollment procedures, treatment procedures, laboratory and diagnostic procedures, data collection and reporting procedures, and procedures for recording and reporting adverse events and serious adverse events.

I attest that I am familiar with FDA "Good Clinical Practice Guidelines" and other regulatory guidelines. I agree to conduct the investigation in accordance with the final trial protocol, all applicable regulations, and any conditions of approval imposed by the reviewing IRB/Human Studies or Ethics Committee. I will ensure that the requirements of obtaining informed consent are met and assume responsibility for the conduct and activities of the study staff under my direction at the study site, including but not limited to: sub-investigators, research coordinators, research nurses, research assistants, and any additional staff involved in the process and procedures in the study.

Additionally I agree to submit a copy of the informed consent intended to be used to obtain subject informed consent in this study to the Sponsor for written approval prior to submitting the informed consent to the Institutional Review Board.

_____

Print Name of Investigator

_____ _____

Investigator's Signature *Date*

This protocol contains confidential proprietary information with respect to NeoSync's products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.

_____ _____

Investigator's Signature *Date*

APPENDIX III

SPONSOR'S COMMITMENTS

NeoSync, Inc., Inc. is committed to:

Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.

Protecting the rights, health, safety and welfare of study subjects.

Insuring that informed consent will be obtained from all subjects and/or their legal representative prior to participation in the study.

Informing the clinical Investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.

Providing the clinical Investigators with the study protocol and Case Report Forms to document the study evaluation variables for each subject entered into the study.

Providing training to the personnel at each investigational site on the device, study protocol and other study documentation.

Preparing all reports required per relevant sections of 21 CFR part 812 and other reports required by the local IRB.

Maintaining all records required per relevant sections of 21 CFR part 812.

Performing routine site monitoring to insure compliance with all applicable health authority regulations governing the conduct of clinical research studies

Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.

Ensuring equity of consideration among all Investigators in multicenter studies in all matters of publications, meeting presentations, etc.

Certifying that IRB approval of the protocol and completion of the Investigator's Agreement will occur prior to treatment at any investigational site.