NCT02586688

44-02219-000 A Randomized, Sham-Controlled Trial Evaluating the Safety and Effectiveness of NeuroStar Transcranial Magnetic Stimulation (TMS) Therapy in Depressed Adolescents

Regulatory Sponsor:	Neuronetics, Inc 3222 Phoenixville Pike Malvern, PA 19355
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Study Product:	NeuroStar TMS Therapy® System using NeuroStar XPLOR® research configuration

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1 Contact Information/Approvals

1.1 *Emergency Contact*

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2 Medical Monitor Signature

I have read and approve this protocol. This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Medical Monitor's Signature	Date of Signature (DD Mmm YYYY)

Mark A. Demitrack, MD

Medical Monitor's Name (print)

3 Investigator Agreement

I have read this protocol and agree that it contains all necessary details for conducting the study as described.

I will conduct this investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and any conditions of approval imposed by the Institutional Review Board (IRB) and FDA.

I will provide a copy of my current curriculum vitae.

I will provide a summary of my relevant clinical experience (including dates, location, extent and type of experience) for the conduct of this trial.

By signing this document, I attest to the fact that I have not been involved in an investigation or other research that was terminated, or if so, I will provide an explanation of the circumstances that led to termination.

I will maintain all confidentiality.

I will supervise all testing of the device involving human subjects.

I will ensure that all study personnel are appropriately trained and that they have access to all relevant documents related to the investigations, as furnished by the sponsor.

I will discuss all relevant study-related information with study personnel to ensure that they are fully informed about the device and the studies.

I will assure that all requirements of informed consent are met for subjects participating in these studies.

I understand that this study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Investigator's Signature	Date of Signature (DD Mmm YYYY)

Investigator's Name (print)

4 Institutional Review Board (IRB)

The name, address, and phone number of the IRB used by each site participating in this study is identified below.

IRB: _____

Address: _____

_____

Phone No.: _____

IRB: _____

Address: _____

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Phone No.: _____

IRB: _____

Address: _____

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Phone No.: _____

5 Disclosure Statement

This protocol contains information that is confidential and proprietary to the sponsor. It is being provided to you for the sole purpose of evaluating and/or conducting a clinical trial for the sponsor. You may disclose the contents of this document only to study personnel under your supervision, IRBs, or duly authorized representatives of the U.S. FDA or other regulatory authority for this purpose under the condition that they maintain confidentiality.

The contents of this protocol may not be used in any other device trial, disclosed to any other person or entity, and/or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsor of any such disclosure.

Any information that may be added to this protocol is also confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this protocol.

6 List of Abbreviations

^{1}H-MRS	Proton Magnetic Resonance Spectroscopy
3T	3 Tesla
AC	Anterior Cingulate
AE	Adverse Event/Adverse Experience
AMI	Autobiographical Memory Interview
APB	Abductor Pollicis Brevis
ATHF	Antidepressant Treatment History Form
ATR	Antidepressant Treatment Record
CDRS-R	Childhood Depression Rating Scale – Revised
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression – Severity of Illness
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia – Suicide Severity Rating Scale
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAMD	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intention-to-Treat
L-DLPFC	Left Dorsolateral Prefrontal Cortex
MADRS	Montgomery Asberg Depression Rating Scale
M.I.N.I.	Mini International Neuropsychiatric Interview
M.I.N.I. KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NIH	National Institutes of Health
PHI	Protected Health Information
PI	Principal Investigator
QIDS-A17-SR	Quick Inventory of Depressive Symptoms – Adolescent Version – Self Report
TMS	Transcranial Magnetic Stimulation
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
TASS	Transcranial Magnetic Stimulation Adult Safety Screen
TEEQ	Treatment Expectations and Experience Questionnaire
YMRS	Young Mania Rating Scale

7 Study Summary

Title	A Randomized, Sham-Controlled Trial of the Safety and Effectiveness of NeuroStar Transcranial Magnetic Stimulation (TMS) Therapy in Depressed Adolescents
Running Title	NeuroStar® TMS Adolescent MDD RCT
Protocol Number	44-02219-000
Methodology	Randomized, sham-controlled, triple-blinded; crossover open-label acute treatment and post treatment follow up. (Investigator Blinded to criteria for eligibility to entry into crossover study phase)
Overall Study Duration	42 months
Subject Participation Duration	Screening to Randomization: 1 week Phase I (Randomized, Blinded): 6 weeks (Active TMS vs. Sham) Phase II (Non-Randomized, Open-label): 6 weeks of open-label acute treatment (for Phase I subjects who did not receive protocol-defined clinical benefit). (Note: The definition of protocol defined clinical benefit is concealed from study staff.) Taper (End of Phase I or Phase II): After acute treatment is completed (prior to exit of study at end of phase or prior to entry into Phase III), subject will receive 3 weeks of taper treatments (week 1:3, week 2:2, week 3:1 Phase III (Long term follow up): 6 month follow up with retreatment course for symptom re-emergence (for Phase I and II subjects who received protocol-defined clinical benefit)
Objectives	Primary: To evaluate the antidepressant effects of daily, active TMS (when compared with sham treatment) in adolescents meeting criteria for Major Depressive Disorder, single or recurrent episode (Phase I). Secondary: To evaluate the acute and long term safety of TMS treatment in adolescent MDD subjects. To evaluate the durability of benefit of TMS treatment over the course of 6 months in subjects who received clinical benefit from acute treatment course(s) (Phase III). To evaluate the benefit of daily, active, open-label TMS in Phase I subjects who did not receive protocol-defined clinical benefit; as new acute treatment (sham to active) or as extended treatment course (blinded active to open label active) (Phase II)

	Structural MRI (conducted at specific sites only): To utilize standard morphometric measures to determine structural changes in the brain associated with TMS treatment.
Number of Subjects	Phase I: Total of 100 enrolled (50 Active/50 Sham) across sites Phase II: Subjects from phase I who did not receive protocol-defined clinical benefit from acute treatment will be offered open-label treatment (estimated to be 42 subjects) Phase III: Subject who did meet protocol-defined clinical benefit after acute treatment in Phase I or Phase II will be followed for 6 months post taper (estimated to be 37 subjects) Structural MRI subset: Approximately 25% of subjects of the Phase I population.
Diagnosis and Main Inclusion Criteria	• Male or female outpatients, age 12-21, meeting DSM-5 diagnosis of Major Depressive Disorder, single or recurrent course of illness, of moderate or greater symptom severity • CGI-S score ≥ 4 • $HAMD_{24}$, item 1 ≥ 2 and total score at least 20 at screening • At the end of the baseline visit, subject must have a HAMD24 score of ≥ 18 and change in score may not be ≥ 25% decrease from that seen at the screening visit • Duration of current episode of depression ≥ 4 weeks and ≤ 3 years • Resistance to antidepressant treatment in a discrete illness episode defined by the Antidepressant Treatment Record (ATR): - Resistance to treatment defined by ATR level 1 through 4 in current episode. If insufficient number of trials in the current episode, then must also have failed ≥1 and ≤ 4 trials in a previous episode - Subjects who have been unable to complete an antidepressant trial of adequate dose and duration due to intolerance to antidepressant therapy may be included if they have demonstrated intolerance to ≥ 4 antidepressant medications within one discrete illness episode (current or a previous episode as defined above) • For any subject currently receiving antidepressant medication, the clinician must determine that insufficient benefit is being received from this treatment and it is clinically appropriate to discontinue the existing antidepressant.
Exclusion Criteria	• Subjects associated directly with this study or indirectly by a parent or sibling being affiliated with the study. • Subjects diagnosed by the investigator with one or more of the following conditions (current, unless otherwise stated): depression secondary to a general medical condition or substance-induced; seasonal pattern of depression; history of substance abuse or dependence within the past year (except nicotine or caffeine); any psychotic disorder (lifetime), including schizoaffective disorder, or major depression with psychotic features in this or previous episodes; amnestic disorder, mental retardation, bipolar disorder; eating disorder (lifetime); obsessive compulsive disorder (lifetime); or

	posttraumatic stress disorder (lifetime) • Any psychiatric disorder, which in the judgement of the Investigator may hinder the subject in completing the procedures required by the study protocol. • Subject with a clinically defined neurological disorder or insult including, but not limited to any condition likely increase the risk of seizure; such as, space occupying brain lesion; any history or family history of epilepsy; history of cerebrovascular accident; transient ischemic attack within two years; cerebral aneurysm; dementia; brain surgery or history of stroke. • Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure or history of significant head trauma with loss of consciousness for ≥ 5 minutes. • A true positive response to any question on the TASS • Inability to locate and quantify a motor threshold as defined in the protocol • History of treatment with ECT or TMS Therapy for any disorder • Use of any investigational drug within 4 weeks of the baseline visit • Use of any excluded medication(s) listed on the Concomitant Medication List (Appendix D) within 1 week of the baseline visit • Significant acute suicide risk, defined as follows: Suicide attempt within the previous 6 months that required medical treatment or ≥ 2 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 inform a family member or call his/her 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. • Conductive, ferromagnetic, or other magnetic-sensitive metals implanted in the subject's head within 30 cm of the treatment coil excluding the mouth that cannot safely be removed. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. • Active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. • Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease • Known or suspected pregnancy • If sexually active female, not on an approved method of birth control. • Unstable psychotherapy (therapy must be for at least 3 months prior to entry into the study, with no anticipation of change in the frequency or treatment focus of the therapeutic sessions over the duration of the study) • Positive urine drug screen (a positive screen at screening may be repeated once prior to randomization upon approval from the Sponsor) • Clinically significant laboratory abnormality or medical condition, in the opinion of the Investigator would hinder the subject in completing the procedures required by the study.
Study Device	NeuroStar TMS Therapy® System using NeuroStar XPLOR® research configuration

Duration of Exposure	**Phase I (Randomized, Blinded):** For subjects randomized to the active treatment, stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. Repositioning of coil, per NeuroStar User Manual, and prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable. During the first week of treatment only, in the event that the subject cannot tolerate the treatment at these dose parameters, dose intensity may be titrated downward to 110% of the motor threshold, with all other dose parameters remaining the same. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A maximum total of 36 treatments will be completed within 9 weeks of Phase I (including the 6 treatments administered during the 3 week taper phase). If the subject meets criteria (blinded to Site personnel) to enter Phase II, they will not complete the 3 week taper phase, resulting in a maximum total of 30 treatments. **Phase II (Non-Randomized, Open-label):** Subjects who do not achieve ;protocol-defined clinical benefit to treatment in Phase I will be offered the opportunity to undergo acute TMS treatment using the known-active therapy coil in Phase II. A maximum total of 36 treatments will be completed within 9 weeks of Phase II (including the 6 treatments administered during the 3 week taper phase). Therefore, subjects who are randomized to active treatment during Phase I and subsequently enroll into Phase II will receive up to a total of 66 active treatments using stated study parameters within the 15 week combined timeframe (including one taper phase). Subjects who are randomized to sham treatment during Phase I and subsequently enroll in Phase II will receive up to a total of 36 active treatments using stated study parameters within the 15 week combined timeframe (including one taper phase). **Phase III (Long Term Follow up):** Subjects who achieve protocol-defined clinical benefit from treatment in Phase I or Phase II will be followed for 6 months after treatment. If a subject experiences re-emergence of depressive symptoms, an acute TMS retreatment course will be initiated. The TMS retreatment course will continue up to 6 weeks until symptom score is at or below Phase III entry score. Each successful retreatment is followed by a 3 week taper. Subjects could receive retreatment on more than one occasion; therefore, any subject could receive up to 72 treatments in Phase III over 6 months, in addition to Phase I and II exposure.
Reference Therapy	Subjects in Phase I who are randomized to sham treatments will have schedules, systematic assessments, and treatment approaches that are identical to subjects randomized to active treatments. Subjects, treaters, and clinical raters ***will not*** know whether the treatment is active or sham in nature (triple-blinded). The sham coil is identical in its appearance to the active coil. Furthermore, the sham

	coil operates with an acoustically matched profile that renders the auditory experience of the treatments virtually indistinguishable to subjects or researchers. The sham coil also creates a mild percussive sensation that may be felt by the subject and further assists in simulating the active condition. The blinded randomization of patients in the Phase I acute phase to the active or sham condition will remain blinded for the duration of all study phases including Phases II and III.
Concomitant Therapy	*Permitted:* Zaleplon, zolpidem, or zopiclone (1 dose nightly) as needed for treatment emergent insomnia or lorazepam (up to 2 mg daily) for treatment emergent anxiety, may be administered for up to 14 doses during Phase I and an additional 14 doses during Phase II. For Phase III, these medications may be administered for up to 10 days, on ≤5 occasions. The use of alternative hypnotics or anxiolytic compounds requires prior approval from the Sponsor. Hormonal contraceptives are allowed if the subject has been on a stable dose for at least 3 months. The use of alternative hypnotics or anxiolytic compounds requires prior approval from the Sponsor. Short-term treatments for headaches, allergies, colds, or flu-like symptoms require prior approval from the Sponsor. *Prohibited:* Any medication administered for the treatment of any psychiatric or neurologic disorder or any other known CNS-active drugs, including herbal, over-the-counter, and homeopathic medications, MAOIs, other antidepressants, antipsychotics, stimulants and mood stabilizers.
Statistical Methodology	Statistical analysis plan for Primary objective and secondary objectives : • Primary efficacy outcome, HAMD24, will be examined in a frequentist analysis (i.e., meta-analysis) combining the data obtained in this study with data borrowed from two prior randomized controlled trials conducted in adults tested using the same procedures outlines in this protocol (O'Reardon, et al., 2007; George, et al., 2010). • The model for this analysis will include the following terms: treatment (active vs. sham), baseline score (continuous), medication resistance level as determined using the Antidepressant Treatment Record (ATR), (ATR=1 'Lo' vs. ATR=2-4 'Hi'), and Study (adolescent study, and adult studies O'Reardon, et al, 2007 and George, et al, 2010) as fixed effects, and, interaction terms for "study-by-treatment" and "ATHF medication resistance level-by-treatment". A random effect of "site nested within study" will also be included to assess any potential site effects. • In the absence of a statistically significant interaction between Study and Treatment on the primary efficacy outcome variable at a pre-specified alpha level = 0.10, the continuity of efficacy across the age range 12 to 70 will be established, and the main effect for treatment is statistically significant at the alpha level = 0.05. • A sample size of 50 patients per treatment condition in the adolescent study and an alpha level of 0.10 to test the Study by Treatment interaction, will detect a statistically significant Study by Treatment interaction if the mean treatment group difference, in favor of active, is greater than the upper bound of 5.5 points or less than the lower bound of -0.8 points. In the absence of a statistically significant interaction between Study and Treatment, the lower bound of the observed treatment group difference must be greater than 1.7 in favor of the active

	treatment in order to borrow data from the adult studies in a meta-analysis with the data from the adolescent study.

8 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States and Canadian government regulations and Good Clinical Practices, as documented in the study reference manual.

8.1 *Background*

NeuroStar TMS Therapy System Mechanism of Action

The NeuroStar TMS Therapy® System is a computerized electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex. Since the NeuroStar TMS Therapy System produces a time varying magnetic field, its intended effect derives fundamentally from Faraday's Law, which asserts that a time-varying magnetic field produces an electrical current in an adjacent conductive substance. During TMS, the conductive substance of interest is the brain, in particular the region of the cortex that lies beneath the NeuroStar TMS Therapy System treatment coil.

The electric current induced in this region of the cortex travels in a path orthogonal to the direction of the alternating magnetic field with the point of maximum field strength and greatest current located directly beneath the center of the coil, which is the NeuroStar TMS Therapy System component that rests against the patient's head and transmits magnetic pulses to the patient's brain. The induced current is tangential to the scalp at the cortical surface, and diminishes in magnitude with increasing depth.

In the targeted area of the motor cortex, where field strength achieves the stimulation threshold, it is postulated that neuronal depolarization occurs. This type of magnetic field is not intended to induce a seizure during therapeutic use. The peak magnetic field strength achieved with each pulse in the cortex is approximately 0.5 Tesla.

Although the mechanism of action is unknown, it is hypothesized that the NeuroStar TMS Therapy System causes direct neuronal depolarization in brain regions immediately adjacent to the magnetic coil, and also results in changes in functional activity in areas of the brain that are synaptically connected to the brain regions experiencing direct neuronal depolarization. It is thought that these actions may cause various physiologic changes in the brain which are associated with the symptomatic relief of depression in patients.

Efficacy and Safety of TMS and the NeuroStar TMS Therapy® System in Major Depression in Adult Patients

The efficacy and safety of the NeuroStar TMS Therapy System in adult patients with major depressive disorder (MDD) who failed to receive satisfactory improvement from prior antidepressant medication was established in two randomized controlled trials (O'Reardon2007; Janicak 2008; George 2010).

Clinical efficacy outcomes of the use of NeuroStar TMS Therapy in adult patients with major depression in real world clinical practice was demonstrated in a multisite naturalistic study in 42 US centers under conditions of general clinical use (Carpenter, 2012; Janicak2013).

A company-independent, randomized controlled trial funded by the National Institute of Mental Health, evaluated the safety and efficacy of TMS using a clinical trial version of the NeuroStar TMS Therapy System in adult patients (N=197, 4 sites) with moderate to severe major depressive disorder and who failed to benefit from 1 through 4 adequate antidepressant medication trials, as defined using the Antidepressant Treatment History Form (ATHF), or who could not tolerate 3 or more antidepressant medications (George 2010).

The study evaluated 197 outpatients across 4 sites, ages 21-70 years, most with a recurrent course of major depression (~97%), with the maximum duration of the current episode of depression of ≤3 years. Patients had received a median of 1.6 total prior antidepressant medications at an adequate dose and duration in the current episode or a median of 4 treatment attempts at any dose and duration.

The primary outcome measure was remission using the HAMD24 (HAMD24 total score ≤3 or 2 consecutive HAMD24 total scores <10) through 6 weeks of acute treatment. A statistically significant benefit of active TMS as compared to sham treatment for the HAMD24 remission outcome (Active TMS: 13.4% vs Sham TMS: 5.0%, P=0. 0173) was observed in the ITT study population (N=197). An adjusted odds ratio of achieving remission with active TMS was 4.05 (95% confidence interval (CI), 1.28-12.83) as compared to sham TMS. The baseline to endpoint change score outcome using the HAMD24 also favored active TMS compared to sham treatment (-2.11, 95% CI: -4.30, 0.08; P=0.0588). Baseline to endpoint outcomes for patients treated with active TMS were statistically significant as compared to sham treatment as measured using the MADRS (P=0.0136), CGI-S (P=0.0181) and the patient-rated IDS-SR (P=0.0008). For the categorical endpoints, higher rates of remission were observed for patients receiving active TMS as compared to sham treatment as measured using the MADRS (P=0.0170) and the patient-rated IDS-SR (P=0.1199), and for response (50% improvement from baseline) for all three measures (HAMD24, P=0.0104; MADRS, P=0.0063; IDS-SR, P=0.0145). Standardized effect size estimates for the continuous outcome endpoints range from 0.43 to 0.67, indicating a moderate to large effect size in this patient population. Study 101 evaluated the safety and efficacy of NeuroStar TMS Therapy in 301 adult outpatients across 23 sites with moderate to severe major depressive disorder and who failed to benefit from 1 through 4 prior antidepressant medication trials administered at an adequate dose and duration, and verified using the ATHF (O'Reardon2007; Janicak, 2008). The patient population was similar to patients enrolled in the independent NIMH-funded trial. Outcome on the primary efficacy endpoint (MADRS change from baseline at 4 weeks) favored NeuroStar TMS Therapy (P=0.057) over sham treatment for the ATHF 1 through 4 population. A subgroup analysis of the overall study population demonstrated that the device was safe and effective for patients who had failed to achieve satisfactory improvement from one prior antidepressant medication (N=164 patients, P=0.0006, MADRS, primary efficacy endpoint) in the current episode.

Study 19-50001 was a multisite naturalistic study in 42 US centers that evaluated the acute efficacy and 12-month durability of NeuroStar TMS Therapy under conditions of general clinical use (Carpenter, 2012; Janicak, 2013; Dunner 2014). This study enrolled adult patients (N=307) with MDD who failed to benefit from any number of antidepressant medications administered at an adequate dose and duration (mean of 2.5, range 0-14) in the current episode.

There was a statistically significant improvement from baseline in CGI-S total score (CGI-S, −1.9 ± 1.4, P < .0001, primary efficacy outcome) at end of acute treatment. A similar pattern and magnitude of clinical improvement was observed in the two patient self-reported outcome measures, the PHQ-9 (−8.7 ± 7.2, P <0.0001) and the IDS-SR (−18.3 ± 14.9, P<0.0001). Categorical response and remission rates were consistent in clinical magnitude on all three outcome measures i.e., CGI-S (58.0% response; 37.1% remission), PHQ-9 (56.4% response; 28.7% remission), and IDS-SR (41.5% response; 26.5% remission).

Study 19-50001 also evaluated the durability of acute benefit with NeuroStar TMS Therapy® during 12 months of follow-up in patients maintained on antidepressant medication and/or with periodic TMS reintroduction for symptom worsening (Dunner, 2014). Overall, 36.2% of patients required retreatment with TMS over 12 months. Among acute treatment remitters, 29.5% of patients experienced relapse over the subsequent 12 months of follow-up.

The safety of the NeuroStar TMS System for the treatment of patients with MDD was demonstrated in Neuronetics studies as reported by Janicak and colleagues (2008). These studies evaluated safety by the analysis of spontaneously reported adverse events as well as targeted measures of cognitive function and auditory threshold. The most frequent device-related adverse event reported was cutaneous discomfort at the site of application, which was reported in approximately 30% of patients. There were no negative effects on cognitive or auditory function. George and colleagues (George 2010) reported safety data in their study that were consistent with the information reported by Janicak (2008).

Efficacy and Safety of TMS and the NeuroStar TMS Therapy® System in Major Depression in Adolescent Patients

This research proposal is intended to provide the first randomized, blinded, sham-controlled study of repetitive transcranial magnetic stimulation (TMS) in depressed adolescents. This study will be the first to compare active treatment with a placebo (sham) treatment condition in adolescents who have not responded to at least one adequate course of antidepressant pharmacotherapy. Thus far, TMS has proven to be a safe treatment approach with early promise as an effective and well-tolerated treatment option in youth, but it has not yet been tested under the scientific rigor of a blinded, sham-controlled trial.

Although the exact mechanism of action remains unknown, TMS stimulates cortical neurons using pulsed magnetic fields generated by rapidly changing currents in a coil of wire placed on the scalp. By using advanced imaging techniques that analyze the magnetic resonance spectroscopy (MRS) patterns of TMS response in depressed adolescents, this proposal will serve as a landmark in advancing the scientific understanding of two fields – neurostimulation and the practice of child and adolescent psychiatry. This research protocol will fundamentally change how TMS is viewed as a treatment intervention in depressed adolescents.

Croarkin and colleagues (Wall, 2011) have published previous trial data demonstrating the safety and efficacy of open-label TMS in depressed adolescents using the NeuroStar TMS Therapy System. To date, this is the largest known trial in the United States demonstrating the tolerability and therapeutic potential of TMS in depressed adolescents. Data on the efficacy and safety of TMS in adolescent depression is discussed further in Section 8.3 below.

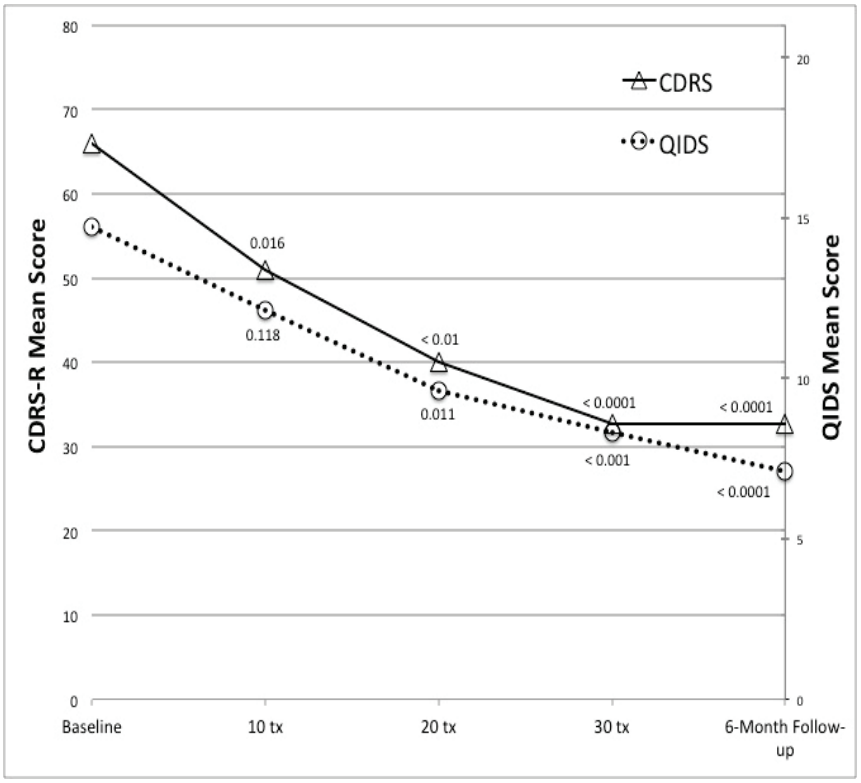
8.2 *Investigational Device*

The NeuroStar XPLOR® TMS Therapy System is a clinical research option for the NeuroStar TMS Therapy® System that provides features necessary to conduct randomized, controlled trials and other TMS research. The XPLOR research configuration consists of three coils: a known-active coil identical to the NeuroStar TMS Therapy System treatment coil and two identical, "blinded" coils. One of the blinded coils provides active treatment identical to the known-active NeuroStar TMS Therapy System treatment coil; the sham coil provides acoustically indistinguishable (from active) pulses and a gentle percussive sensation that simulates scalp sensations produced during active treatment.

8.3 *Clinical Data to Date*

Efficacy of TMS for the treatment of adolescent depression, for all TMS devices including the NeuroStar TMS Therapy® System, has been reported in two pilot clinical studies and in multiple case reports (Walter 2001; Bloch 2008; Wall 2011). These open-label studies describe the treatment of 24 patients, ages 10-18. The 2011 Wall et al. open-label trial is the only study that used the NeuroStar TMS Therapy System. This study reported on the treatment of 7 antidepressant-resistant adolescents and demonstrated a robust response rate noted by 5 of 7 subjects achieving remission of depression,as rated using the Childhood Depression Rating Scale – Revised (CDRS-R). Furthermore, CDRS-R mean depression severity scores were significant by treatment 20 as compared to baseline with similar efficacy demonstrated using the patient reported Quick Inventory of Depressive Symptoms – Adolescent Version (QIDS-A17-SR) (Figure 1). Placebo effects in open-label trials of adolescents are a well-known phenomenon. However, as shown in Figure 1, the adolescents treated in this protocol were shown to demonstrate enduring mood improvement for at least 6 months following their final acute treatment (session 30). Furthermore, 7 of 8 subjects completed the entire treatment course, with 1 patient exiting the study after only 5 minutes of treatment due to scalp discomfort and a perceived lack of improvement.

Figure 1 – CDRS-R and QIDS-A17-SR Mean Score Change from Baseline in Depressed Adolescents in an Open-label TMS Trial (Wall, et al. J Clin Psychiatry, 2011. 72(9): p. 1263-1269)



8.4 *Study Rationale and Risk/Benefits*

Study Rationale

A large percentage of adolescents suffering from Major Depressive Disorder (MDD) do not adequately benefit from currently-available medications, psychotherapy, and/or social support treatments. In fact, it is estimated that current treatment approaches, considered separately, fail to provide adequate clinical improvement in 40% of adolescents with MDD. Moreover, these treatment approaches produce complete remission in only 30% of adolescent patients (March 2004, March 2007, Brent 2008, Walkup 2010). Unfortunately, adolescents with persistent symptoms of depression are more likely to experience inpatient psychiatric hospitalization, psychosocial maladjustment, and suicidality (Croarkin 2010). Consequently, they are more likely to receive additional psychopharmacologic agents that generally offer little additional benefit and increase the risk of adverse effects.

The current literature inclusive of evidence across all TMS devices describes a total of approximately 1,300 adult subjects safely treated with TMS. In this published literature, the two largest sham-controlled, randomized clinical trials (with a combined sample of about 500 patients) used the NeuroStar TMS Therapy® System, in similar patient populations and with the identical treatment parameters and regional brain localization for placement of the device on the head. These studies both demonstrated the safety and efficacy of NeuroStar TMS monotherapy applied to the left dorsolateral prefrontal cortex (L-DLPFC) in depressed adults (O'Reardon 2007; George 2010). As discussed above, TMS has been applied to a much smaller number of adolescent depressed patients. In four separate studies using varying clinical characteristics, devices, and stimulus dosing, significant improvement was demonstrated in 12 of 18 patients with no evidence of significant treatment-related adverse events other than scalp discomfort, boredom during the treatment, and mild headaches (Walter 2001; Loo 2006; Bloch 2008; Wall 2011). In recent years, TMS treatment parameters have advanced with regard to an increase in the number of stimulations per session and in the percentage of motor threshold at which the stimulations are applied, to the current standard in clinical care where a specified treatment parameter set has been established for routine clinical care, with a treatment site over the left dorsolateral prefrontal cortex.

Anticipated Risks

Seizures

Repetitive transcranial magnetic stimulation is generally regarded as safe and without any serious or lasting adverse effects (Wasserman 1998; Rossi 2009). Inadvertent induction of a seizure is the most medically significant potential safety concern. However, with the adoption and widespread use of recommendations delineating a safe margin for both intertrain intervals and for other relevant TMS dosing parameters as disseminated in the 1998 TMS consensus safety guideline from the National Institute of Neurological Disorders and Stroke (NINDS), the risk for seizures is significantly mitigated in routine clinical practice. In Neuronetics' post market surveillance experience, the incidence of inadvertent seizure induction is <0.1% per patient (Neuronetics, data on file). This study will comply with NINDS guideline standards for TMS (Wasserman 1998; Rossi 2009) and current practice established for the FDA-cleared labeled use of the NeuroStar TMS Therapy® System. It is important to note that there is no evidence in the literature or in Neuronetics' post market surveillance data to indicate that a single seizure during TMS makes subsequent seizures more likely in an otherwise non-seizure-prone individual. Nevertheless, it is true that there are potential consequences of a seizure, regarding employment or insurability in the future. If a subject does experience a seizure related to this investigation, a letter from the site Principal Investigator will note that the seizure was produced under experimental conditions, and there is no reason to expect the subject to experience another seizure in the future.

Safety Monitoring for Potential Seizure Risk

Safety monitoring for the potential risk of seizure is addressed in several ways in this protocol. All subjects will be assessed during the screening phase for neurologic disease, concurrent medication use, or other clinical factors that may contribute to the risk of seizure. The Transcranial Magnetic Stimulation Adult Safety Screen (TASS) will be used as a screening tool to assure rigorous review of these clinical factors. Stimulation parameters have been selected to optimize the likelihood of clinical efficacy, while maintaining a safety level within the guidelines consistent with the 1998 NINDS workshop recommendations (Wasserman 1998).

All clinical personnel involved in the motor threshold determinations and the TMS treatment sessions will be familiar with the ISTS Consensus Statement on Managing the Risks of Repetitive Transcranial Magnetic Stimulation, with specific attention to the requirements of medical supervision and first-responder capability in the event of a seizure as outlined in that document. Specifically, all personnel will be familiar with the procedures for subject screening for risk factors prior to treatment, individual risks and potential benefits for specific subjects, appropriate discussion of the risks and potential benefits of study participation as outlined in the informed consent document, the stimulation parameters to be used in this study, monitoring subjects for the potential development of seizures by continuous visual inspection during the course of each treatment session (especially the more subtle signs and symptoms of frontal lobe seizures), and first responder management in the event of a seizure. All sites will be required to have immediate (i.e., within minutes) availability of more sophisticated medical support, including access to an emergency room, in the event that a seizure is not a self-limited event, access to antiepileptic medications, and to life support equipment including oxygen, suction, blood pressure monitoring and cardiopulmonary (CPR) equipment.

As stated above, for all subjects who may experience a seizure during the study, the Investigator will provide a letter documenting that the seizure was experimentally produced.

All personnel involved in the administration of TMS in this study will be required to participate in individual site initiation visits and/or complete other sponsor training requirements and be able to demonstrate understanding of these issues to sponsor study personnel prior to initiation of subject enrollment at that site.

If a seizure occurs during the active treatment phase of the study, that subject will be discontinued from the study.

Mood considerations

There is a risk that the TMS treatment may not be effective for some subjects and that their depression may worsen. Concerns for theoretical mood destabilization, including induction of mania or worsening of suicidality, will be carefully considered throughout the course of treatment (at every treatment visit); and subjects, their families, and investigators may elect to discontinue the treatment protocol and withdraw from the study at any point. Furthermore, safety considerations consistent with current standard of care in child and adolescent psychiatric practice will be employed including contacting the primary mental health care provider, referral to on-call child and adolescent psychiatric services, referral to the emergency room, and/or hospitalization if necessary.

Several studies in the adult population and limited studies in the adolescent population have so far demonstrated the feasibility of TMS to treat depression without any indicators of exacerbation of depression or suicidality (Loo 2006; Janicak 2008; George 2010; Wall 2011). However, pediatric use of antidepressant *pharmacotherapy* has corresponded with warnings about increases in suicidal ideation and

behavior in youths and young adults. No compelling data are available to indicate whether the net result of treatment of depressed youths with these compounds is an overall increase or an overall decrease in the hazard of completed suicide; there is limited and inconclusive evidence in either direction (Rapaport 2006; Gibbons 2007; Libby 2007; Cheung 2008; Maalouf 2010).

Exacerbation of depression that results in hospitalization or increased suicidality, or any emergent symptoms that are deemed clinically significant by the treating physician, will be considered a Serious Adverse Event (SAE), regardless of relatedness to TMS treatment.

Management plan for treatment-emergent mania, exacerbation of depression, and/or suicidality

During the consent process, subjects and families will be educated about the possibility of significant changes in mood, suicidal thinking, and/or behaviors during the treatment. These changes could include emergence of mania, worsening of depression, and/or suicidal thinking and behaviors. Both the subject and parent(s) will be told to initiate contact with their study doctor, if they experience any significant mood or behavior changes including suicidal ideation. Principal Investigator contact information is included in each site's consent/assent document. Furthermore, during the active treatment phases of the protocol, subjects will have assessments weekly where changes of psychological symptoms will be queried (see Appendix A-C for schedules of events). Ongoing monitoring for worsening of depression and emergence of suicidal ideation and/or behaviors will be evaluated using the HAMD, C-SSRS, and CGI-S.

Suspected treatment-induced mania will be evaluated using the Young Mania Rating Scale (YMRS). A YMRS score of ≥ 20 will prompt administration of the M.I.N.I./M.I.N.I. KID to determine whether or not the subject meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for mania. A YMRS score of 20 or greater will be considered an adverse event (AE) and will be monitored using the YMRS; the emergence of DSM-5 verified mania will be treated as a serious adverse event (SAE) and will also be monitored using the YMRS.

Exacerbation of depression, suicidality or induction of mania would constitute an SAE and the subject would be discontinued from the study. See Section 17 for SAE handling. Subject would then be referred for clinical follow-up outside of the study.

Other potential side effects of TMS that may be experienced *during* treatment

In the adult controlled registration studies using the NeuroStar TMS Therapy® System, the adverse event verbatim terms were collected at each clinical visit and subsequently coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and reported by MedDRA preferred terms. The most commonly occurring adverse events in the randomized controlled trial described in O'Reardon, et al (2007) are shown in Table 1, for those events occurring with an incidence of 5% or greater in the active TMS treatment group and twice the rate for the sham TMS treatment group. Headache occurred equally in subjects in both treatment groups. Similar rates of adverse events were reported in the controlled trial using the NeuroStar TMS Therapy System described in George, et al., 2010. Post market surveillance has been consistent with these events reported, with no additional types of events reported for adolescent subjects.

Table 1. Adverse Events with an Incidence in Active TMS at a Rate of > 5% and at Least 2x Sham in the Safety Exposure Study Population

Body System - Preferred Term	Active TMS (N=165) N (%)	Sham TMS (N=158) N (%)
Eye disorders		
- Eye pain	10 (6.1)	3 (1.9)
Gastrointestinal disorders		
- Toothache	12 (7.3)	1 (0.6)
General disorders and site administration conditions		
- Application site discomfort	18 (10.9)	2 (1.3)
- Application site pain	59 (35.8)	6 (3.8)
- Facial pain	11 (6.7)	5 (3.2)
Musculoskeletal and connective tissue disorders		
- Muscle twitching	34 (20.6)	5 (3.2)
Skin and subcutaneous tissue disorders		
- Pain of skin	14 (8.5)	1 (0.6)

There is the potential risk of alteration in auditory threshold. As a result of the rapid changes in the magnetic field during TMS administration, the coil produces an audible, high-energy clicking sound, which may be associated with temporary increases in auditory threshold. During previous studies with the NeuroStar TMS Therapy® System (O'Reardon 2007; George 2010; Carpenter 2012), all subjects were required to use hearing protection at a protection rating of ≥30 db. No change in hearing was found with air conduction threshold testing in the two randomized clinical studies (Janicak 2008 and George 2010) when this method of ear protection was used. As a safety precaution, auditory assessments will be conducted during this study per the schedule of events

Treatment plan for other side effects of TMS experienced *during* treatment:

Repositioning of coil, consistent with the guidelines in the NeuroStar User Manual, and prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable or painful. During the first week of treatment only, in the event that the participant cannot tolerate the treatment at the stipulated study dose parameters, dose intensity may be titrated downward to 110% of the motor threshold, with all other dose parameters remaining the same.

Treatment plan for other potential side effects experienced *following* treatment:

Subjects reporting headaches during or following study treatment will be encouraged to take acetaminophen or ibuprofen prior to the daily treatment. To reduce the risk of temporary or permanent hearing loss due to noise emitted from the stimulator, subjects will wear protective ear plugs during treatment. All subjects will be monitored, and appropriate treatment will be recommended including the possibility of stopping TMS. Any other potential side effects will be managed symptomatically with treatment(s) deemed appropriate by the study site Principal Investigator. All symptomatic interventions will be recorded in the subject's case file and, if applicable, adverse event CRF.

****Treatment with the Neurostar TMS Therapy System may involve other risks that are not known at the present time. The long-term effects of TMS are not known.****

Structural Head MRI

As this study only involves up to four MR scans (Phase I Baseline; End of Phase I/Phase II Baseline; End of Phase II; End of Phase III [LTFU]), the risk is assessed as minimal. No contrast material or exposure to ionizing radiation will occur for the conduct of this protocol.

To minimize any potential risks from the scans, the physician will ensure that the subject does not meet any contradictions for an MRI. Subjects who are uncomfortable in enclosed places (claustrophobic) may experience some discomfort. The MRI staff will be in contact with subjects at all times throughout the scanning process, and if necessary the scan can be stopped at any time. The total scanning time will be approximately 30 minutes per scanning session.

Overall Risk Analysis Statement

Based on available data, the potential benefits of this study outweigh the risks. Depressed adolescents who fail to respond to medication are at increased risk for suicide and prolonged disability related to depressed mood during a critical developmental stage. The preliminary data suggest that TMS has antidepressant effects – in both the adult and the pediatric populations. The risks of TMS are slight relative to electroconvulsive therapy (ECT), a treatment sometimes used in this population, or pharmaceutical therapy with multiple medications. If TMS proves to be an effective alternative to ECT and/or combination pharmaceutical therapy, depressed adolescents not responding to medication would have an effective treatment alternative with fewer side effects and risks. The protocol procedures are considered to be safe, and are well within previously established TMS guidelines.

Potential Benefits

The NeuroStar TMS Therapy® System, that delivers repetitive transcranial magnetic stimulation, is a medical device that was cleared by the United States FDA since October 2008 for the treatment of MDD in adults who fail to achieve satisfactory improvement from prior antidepressant medication. It is a promising alternative to treatments such as ECT or pharmacotherapy for subjects presenting with treatment-resistant cases of MDD. The TMS procedure is non-invasive, does not require anesthesia, and may be delivered in an outpatient setting.

9 Study Objectives

9.1 *Primary Objective: Phase I*

The primary objective of this study is to evaluate the safety and efficacy of TMS as a monotherapy antidepressant in a prospective, randomized, sham-controlled study in adolescents with MDD who have not responded sufficiently to at least one antidepressant medication trial administered at a clinically adequate dose and duration.

9.2 *Secondary objectives*

Phase I

To evaluate the acute safety of TMS in adolescent subjects.

Phase II

To evaluate the benefit of daily, active, open-label TMS in Phase I subjects who did not receive protocol-defined clinical benefit from their assigned treatment condition in Phase I; either as new acute treatment (sham to active) or as extended treatment course (blinded active to open label active).

Phase III

To evaluate the long term safety of TMS in adolescent subjects.

To evaluate the durability of the acute clinical benefit of TMS treatment over the course of 6 months among subjects who received protocol-defined clinical benefit from their initial acute treatment course(s).

10 Study Design

10.1 *General Design*

Screening

Subjects will undergo medical, psychological and neuropsychological assessments to assure compliance with all inclusion and exclusion criteria. Eligible subjects will enter Phase I, randomized acute treatment. See Appendix A for schedule of events.

TMS Treatment

All treatments and motor threshold determinations will be completed by physicians or other health care providers who have been trained to the process based on the NeuroStar User Manual and certified by the Neuronetics study staff. All processes are consistent with the clinical use of the NeuroStar TMS Therapy® System.

Motor Threshold (MT) Determination: MT Location and MT Level

The motor threshold location will be determined by visual confirmation of the location on the motor cortex that controls the abductor pollicis brevis (APB) muscle of the thumb. The resting MT level is the minimum power to produce a stimulation response 50% of the time.

Phase I (Randomized, Triple-Blinded): Active Treatment

Stimulation will occur over the left dorsolateral prefrontal cortex at 120% magnetic field intensity relative to the subject's resting motor threshold, at 10 pulses per second for 4 seconds, with an off time, or intertrain interval, of 26 seconds. Repositioning of the coil, per the NeuroStar User Manual, and prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable or painful. During the first week of treatment only, in the event that the subject cannot tolerate the treatment at these dose parameters, dose intensity may be titrated downward to 110% of the motor threshold, with all other dose parameters remaining the same. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6 weeks of treatment initiation.

Phase I (Randomized, Triple-Blinded): Sham Treatment

Subjects randomized to sham treatments will have identical schedules, systematic assessments, and treatment approaches to their active treatment counterparts. Neither the adolescents nor the investigators (clinical raters or treaters) will know whether the treatment is active or sham in nature. The sham coil is identical in its appearance to the active coil. Furthermore, Neuronetics, Inc. has created an acoustic matching profile that renders the "sound" of the treatments virtually indistinguishable to subjects or researchers. The acoustic signal creates a painless percussive sensation that will be felt by the subject and will assist in simulating the active condition.

Structural Head MRI Subset (Limited study sites)

Structural MRI comparisons will be acquired for subjects. A consistent MRI technician at each study site will be requested for each of the study scans. Each subject will have a baseline scan and additional scans at the completion of each treatment phase (Phase I and Phase II, if applicable) and at six months post treatment (end of Phase III) or at study discontinuation whichever comes first. The maximum number of scans during the study will be four.

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

Subjects who do not meet Investigator site blinded criteria for protocol-defined treatment benefit following Phase I treatment will be offered the opportunity for 30 treatments using the known-active coil. The treatment parameters and methods of assessment in Phase II will be identical to those in Phase I. The only difference will be that the coil used for Phase II will be active and known to the subject and investigators. See Appendix B for schedule of events. The blind will not be broken from Phase I at entry into Phase II.

Taper Phase:

At completion of acute treatment (Phase I or II) and following each retreatment in Phase III, each subject will undergo tapering of the TMS treatment course over three weeks. During week 1, the subject will have 3 treatments (e.g. Mon, Wed, Fri). During week 2, the subject will have 2 treatments (e.g. Mon, Fri) and during week 3, the subject will have 1 treatment (e.g. Fri).

Phase III (Non-Randomized, Open –Label Follow up):

Subjects who at the completion of Phase I or II meet blinded criteria for protocol-defined treatment benefit will be followed for 6 months. If symptom worsening occurs (as defined by increase in CGI-S by 1 or more points from Phase III entry score, for 2 consecutive weeks), an acute course of known active TMS will be offered for up to 6 weeks, until symptoms return to the level recorded at entry into Phase III. Clinical assessments will occur biweekly over the phone and monthly at the study site, throughout the duration of the follow up phase. See Appendix C for schedule of events.

10.2 *Efficacy and Safety Assessments*

Phase I

See Appendix A for schedule of events.

Outcome Assessments

Trained physicians and raters will administer all diagnostic assessments and clinical interviews determining study eligibility during screening and prior to randomization. All study staff will be trained on study procedures by Neuronetics staff.

Outcome screening will occur after both the Informed Assent/Consent Document and the HIPAA Authorization are signed. Baseline assessments will occur prior to the first TMS treatment session. Outcome measures in Phase I will be assessed at the end of treatment weeks 4 and 6. The following outcome assessments will be completed: HAMD/MADRS structured interview, CDRS-R, CGI-S, and QIDS-A17-SR.

Safety Assessments

A physical and complete medical and psychiatric history will be obtained at the screening visit.

Vital signs including height, weight, blood pressure and heart rate will be collected at the baseline visit and at week 6.

Laboratory determination will be measured at screening and include: Blood chemistry, hematology, urine drug screen, and urine pregnancy for female subjects.

Subjects will be evaluated clinically for adverse events at each visit. Serious adverse events (SAEs) will be recorded as they occur and reported to Neuronetics by the study site within one business day of notification.

Cognitive function assessments will be conducted at the baseline visit and at week 6. The following tests from the NIH Toolbox Cognition Battery are used for this study:

- Education
- Handedness
- Attention
    - Flanker Inhibitory Control and Attention Test
- Episodic Memory
    - Picture Sequence Memory Test
    - Auditory Verbal Learning Test (Rey)
- Executive Function
    - Dimensional Change Card Sort Test
    - Flanker Inhibitory Control and Attention Test
- Language
    - Picture Vocabulary Test
    - Oral Reading Recognition Test
- Processing Speed
    - Pattern Comparison Processing Speed Test
- Memory
    - List Sorting Working Memory Test

The C-SSRS will be completed weekly during TMS treatment to assess worsening of illness and suicidality. The YMRS will be completed at baseline and will be repeated based on reported change in symptoms.

Air conduction thresholds will be assessed for both left and right ears at the baseline visit and at week 6.

Phase II

See Appendix B for schedule of events. The schedule of efficacy and safety measures for Phase II will be identical to that of Phase I.

Phase III

See Appendix C for schedule of events.

Outcome measures for Follow up Phase III, including HAMD/MADRS structured interview, QIDS-A17-SR, CDRS-R, and CGI-S, will be assessed per schedule of events.

Subjects will be evaluated clinically for adverse events at each visit and at the bi-weekly phone call. The bi-weekly calls are done as a safety check to assess worsening of illness between monthly visits. The phone call will be documented as a progress note and placed with the subjects' source documentation. SAEs will be recorded as they occur and reported to Neuronetics by the study site within one business day of notification.

The C-SSRS will be completed weekly during TMS retreatment session(s). The YMRS will be completed if the interval assessment of spontaneous adverse events indicates the potential occurrence of symptoms of mania or hypomania. In addition, in all subjects receiving TMS retreatment, air conduction thresholds will be assessed for both left and right ears at baseline and at the end of the retreatment block.

Vital signs (including height, weight, blood pressure and heart rate), cognitive function assessments and air conduction thresholds for both ears will be assessed at the end of six-month follow-up.

10.3 *Structural Head MRI (Limited study sites)*

Analyzed by standard morphometric measures to determine structural changes in the brain associated with TMS treatment. See Appendix A-C for schedule of events.

11 Subject Selection, Enrollment and Withdrawal

All adolescents and their guardians (if applicable) will be provided a careful assent and consent discussion prior to enrollment. Since this is a sham-controlled trial, all subjects would need to understand that during Phase I of the trial, they will be randomized to either the active treatment condition or the sham treatment condition. They will also be informed about the opportunity to receive open, active TMS treatment (during Phase II) if they did not receive protocol-defined clinical benefit during Phase I.

11.1 *Inclusion Criteria*

Table 2 – Inclusion Criteria

Inclusion Criteria	Determinant
Primary diagnosis of unipolar major depressive disorder, in a current major depressive episode, without psychotic features	M.I.N.I./M.I.N.I. KID (ages up to <18) or (ages ≥ 18) to confirm DSM-5 criteria
Duration of current episode of depression ≥4 weeks and ≤3 years (the definition of an episode is demarcated by a period of ≥ 2 months when the subject did not meet full criteria for the DSM-5 definition of major depressive episode	Physician evaluation, M.I.N.I./M.I.N.I. KID
CGI-S ≥ 4	CGI-S
Age is at least 12 and less than 22 years	Self-report and review of medical record
Resistance to antidepressant treatment in a discrete illness episode as defined by the Antidepressant Treatment Record (ATR): • Resistance to treatment defined by ATR level 1-4 in current episode. If insufficient number of trials in the current episode, then must also have failed ≥ 1 and ≤ 4 trials in a previous episode	Physician evaluation and review of medical record

• Subjects who have been unable to complete an antidepressant trial of adequate dose and duration due to intolerance to antidepressant therapy may be included if they have demonstrated intolerance to ≥ 4 antidepressant medications within one discrete illness episode (current or a previous episode as defined above) For any subject currently receiving antidepressant medication, the clinician must determine that insufficient benefit is being received from this treatment and it is clinically appropriate to discontinue the existing antidepressant.	
HAMD24 Item 1 ≥ 2 and total score ≥ 20	HAMD24
Subjects able to commit to protocol schedule	Subject and family agreement
Willing to provide informed assent (adolescent) and informed consent (family) for subject < 18 years old or legal requirements of the state Willing to provide informed consent by subject ≥18 years old or legal requirements of the state	Consent/assent discussion
Signed HIPAA authorization by subject or parent (for subject < 18 years old)	HIPAA authorization

Interim Inclusion Criteria	Determinant
At the end of the baseline visit, subject must have a HAMD24 score of ≥ 18 and change in score may not be ≥ 25% decrease from that seen at the screening visit	HAMD24

11.2

11.3 *Exclusion Criteria*

Table 3 – Exclusion Criteria

Exclusion Criteria	Determinant
Subjects directly affiliated with the study or their immediate families (parent or sibling, whether by birth or legal adoption)	Physician interview
Subjects currently on concurrent medication listed as excluded on the Concomitant Medication list (Appendix D) and/or use of an investigational drug within 4 weeks of the baseline visit.	Physician evaluation and review of medical record
Active substance use	Urine drug test (at screening; second test allowed prior to randomization as permitted by Sponsor)
Prior TMS, vagus nerve stimulation (VNS), or ECT	Medical history
Contraindication to MRI (only for Structural Head MRI subset subjects)	Physician evaluation; medical history; MRI Safety Screening Questionnaire

Contraindication to TMS Conductive, ferromagnetic, or other magnetic-sensitive metals implanted in the subject's head within 30 cm of the treatment coil excluding the mouth that cannot safely be removed. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators.	Physician evaluation and review of medical record
Cardiac pacemakers, implanted medication pumps, intracardiac lines	Physician evaluation and review of medical record
A true positive response to any question on the TASS questionnaire	Physician evaluation
History of neurological disorder or insult including but not limited to the following that may increase risk of seizure: • Antecedent seizures • Any condition likely to be associated with increased intracranial pressure • Space occupying brain lesion • History of cerebrovascular accident • Transient ischemic attack within 2 years • Cerebral aneurysm • Dementia • Brain surgery • Head trauma with loss of consciousness for ≥5 minutes • History of stroke • History and/or family history of epilepsy	Physician evaluation and review of medical record
Unstable medical conditions, including: • Hematological or infectious (e.g., human immunodeficiency virus-HIV) disorders. • History of autoimmune, endocrine, viral, or vascular disorder • Unstable cardiac disease, uncontrolled hypertension, or sleep apnea • Current anticoagulant, immune suppressive, and/or chemotherapy or those who have received any of these therapies within 3 months before enrollment in the study.	Physician evaluation; medical history
Clinically significant laboratory abnormality, in the opinion of the Investigator	Physician review of screening laboratory tests
Individuals diagnosed with the following conditions (current unless otherwise stated): • Depression secondary to a general medical condition, or substance induced: • Seasonal pattern of depression as defined by DSM-5 • Any psychotic disorder (lifetime), including history of schizophrenia, schizoaffective disorder, other psychosis, psychotic features in this or previous episodes, amnestic	M.I.N.I. or M.I.N.I. KID (age <18) to confirm DSM-5 criteria Physician Examination and conference with family member/guardian to confirm findings (age <18 or legal requirements of the state)

disorder, • Mental retardation, • Substance dependence or abuse within the past year (except nicotine or caffeine), • Bipolar disorder, • Obsessive compulsive disorder (lifetime), • Post-traumatic stress disorder (lifetime), • Eating disorder (lifetime).	
Any psychiatric disorder, which in the judgement of the Investigator may hinder the subject in completing the procedures required by the study protocol.	M.I.N.I. KID (ages up to <18) or M.I.N.I. (ages ≥ 18) to confirm
If participating in psychotherapy, must have been in stable treatment for at least 3 months prior to screening into the study with no anticipation of change in the frequency or focus of therapeutic sessions over the duration of the study.	Physician evaluation; medical history
Significant acute suicide risk, defined as follows: • Suicide attempt within the previous 6 months that required medical treatment; or • History of attempt within the past 2 months or ≥2 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 inform a family member or call his/her 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.	Physician evaluation, M.I.N.I./M.I.N.I.-KID
Any other relevant medical, personality, or psychosocial issues specific to the subject that the PI determines to be reason for exclusion from the study	Physician evaluation; medical history
Pregnant or suspected pregnancy	Urine pregnancy test
If sexually active female, not on an accepted method of birth control. See Appendix D, Concomitant Medication List	
Inability to locate and quantify a motor threshold	Motor Threshold determination

11.4 *Subject Recruitment, Enrollment and Screening*

Subject Recruitment

Several resources will be utilized for recruitment of potential subjects including:

- from within the clinical and referral practices of the clinical study site
- referrals from other care providers within the treatment communities
- radio advertisements
- invitation letters sent to parents of potentially eligible subjects
- print advertisements, including but not limited to brochures, flyers, Craig's List, and listings in research classifieds
- trial listing with ClinicalTrials.gov

- trial listing on university and clinical study site website
- social media

All advertising materials will be reviewed and approved by the site's IRB prior to use.

Potentially interested adolescents and their families may be provided with printed subject educational materials to aid them in making an informed decision regarding their willingness to participate in this study.

Subject Enrollment

At the time of the enrollment visit, potential subjects and their parent(s) will be provided with a written copy of the current IRB-approved informed consent/assent form from the site at which they will be receiving study treatments. All adolescents and their guardians will be provided a careful assent and consent discussion prior to enrollment. Due to the nature of a sham-controlled trial, all subjects will need to understand that during Phase I of the trial, they will be randomized to either the active treatment condition or the sham treatment condition. They will also be informed about the opportunity to receive open, active TMS treatment during Phase II if they did not receive protocol-defined clinical benefit during Phase I. For subjects who reach the age of maturity (18 years or legal requirements of the state) during their participation in the study, written consent will be obtained from the subject at the next visit following their birth date.

Subject Screening

Following the informed consent process, enrolled subjects will begin the study eligibility screening process. Verification of inclusion and exclusion will be completed by the study physician to ensure that the subject is eligible for the study and that it is safe for them to participate. Subjects must have discontinued all antidepressants and psychotropics for at least one week (or until all traces are eliminated from the subject's system) prior to administering the $HAMD_{24}$/MADRS and any other efficacy assessment.

11.5 *Early Withdrawal of Subjects*

When and How to Withdraw Subjects

Subjects may withdraw voluntarily from the study at any time. They may be withdrawn from the study by the Investigator if a subject:

- experiences a seizure,
- experiences a DSM-5-confirmed treatment-induced mania,
- is non-compliant with study procedures; or
- the randomization code is broken for this subject.

The Investigator may also withdraw a subject if he/she believes that for safety reasons it is in the best interest of the subject to be withdrawn.

Discontinuation information [e.g., date and the reason(s) for discontinuation] must be recorded in the subject's CRF (i.e., Study Completion Form). Subjects who discontinue prematurely should complete the Week 6 assessment procedures within 2 days following their last TMS treatment session. See the Schedule of Events for the specific procedures to be performed at this discontinuation visit.

Subjects withdrawn from the study due to an AE will be followed up for 30 days or until resolution. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal. An effort

will be made to determine why a subject does not return for the required visits or is dropped from the study. This information will subsequently be recorded on the subject's CRF.

Subjects will be encouraged to remain compliant with all expected study visits. Non-adherence to expected study visits will be documented and may result in removal from the study. This will be clearly discussed during the consent/assent process and reinforced throughout the study through regular screening for issues with compliance.

12 Study Device

12.1 *Description*

The NeuroStar TMS Therapy® System is a computerized electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex. It is a non-invasive tool used for the treatment of subjects with MDD who have not achieved sufficient clinical benefit from antidepressant pharmacotherapy. The NeuroStar TMS Therapy System has been FDA-cleared for use in adult subjects. NeuroStar XPLOR® is a clinical research option for the NeuroStar TMS Therapy System that provides features necessary to conduct randomized controlled trials and other TMS research. The active treatment modality is essentially the same for both the NeuroStar TMS Therapy System and NeuroStar XPLOR.

The NeuroStar XPLOR TMS System consists of the following equipment and software:

- Mobile Console (includes processor module, power module, mast, gantry, halo, and display arm)
- System Software; the XPLOR option also includes a dedicated system software application (software version 1.7.5 or greater) with its own dedicated database of subject treatment history, TMS TrakStar® application, and TrakStar database that operates only with the corresponding XPLOR Software, maintaining isolation, security, and data integrity of the research.
- TMS TrakStar® Data Management System software
- Therapy Coils included with the XPLOR option is a set of three TMS coils:
    - a blinded sham or placebo coil; the sham coil is acoustically matched to protect the integrity of the blind,
    - a blinded active coil, and
    - a standard treatment coil that can be used for performing motor threshold level determination or open-label treatment.
- Head Support System (includes laser positioning aid and coil positioning guide)
- Treatment Chair
- Positioning Cushions (to enhance comfort and positioning of the subject in the required posture for the duration of the treatment session)

The NeuroStar TMS Therapy System also requires supplies and disposables for each treatment session:

- Head Cushion Liner
- Head Side Pad Liner
- Head Positioning Straps
- Earplugs
- SenStar® Treatment Link (a single-use medical device)
- Used SenStar Treatment Link Return box

12.2 *Subject Identification*

Each subject will be assigned a unique subject identification upon signing the informed consent form. This number will consist of an assigned 2-digit study site identifier, and a unique, 3-digit subject identifier. For example, the first subject screened at site 01 would be subject 01-001.

Subjects should be identified to the Sponsor only by their assigned number and initials except where requested on the CRFs and source documents. The Investigator must maintain a master list linking subject names and the identifying information indicated above.

12.3 *Randomization*

A randomization schedule will be generated by Neuronetics or a designated contract research organization. Subjects will not be randomized until all entry (inclusion and exclusion) criteria have been met and all pre-study procedures have been satisfactorily completed. Eligible subjects will be randomly assigned to receive one of the two treatment regimens (active TMS treatment or sham TMS treatment), and the next available randomization number for the subject's stratum will be recorded in the screening log and on the subject's CRF. Randomization numbers may not be reassigned. A permuted-block procedure will be used to randomly assign the treatment conditions, with a fixed block size for each stratum.

12.4 *Masking*

All site personnel will be masked to the treatment assignment for each subject. Specific aspects of the trial design are intended to optimize the integrity of the masking and all staff will be trained to the procedures for masking during the site initiation visit.

In addition to those procedures, each Investigator will be provided with individually sealed and numbered envelopes, corresponding to subject randomization numbers. In the case of an emergency, an envelope may be opened to identify the TMS treatment assignment for a particular subject. In all circumstances, the Investigator will notify Neuronetics prior to unmasking the TMS treatment for any subject, if possible. In the event that the emergency circumstances preclude first notifying Neuronetics immediately, the Investigator should contact Neuronetics within one business day and provide the reason(s) for unmasking and date of opening of the envelope must be documented in the subject's files.

The unmasking must also be documented on the Adverse Event page of the CRF, and in the subject's source documents. Additionally, the Investigator must submit a written explanation describing the unmasking within 5 working days. All other randomization envelopes must be returned unopened to Neuronetics at the completion of the trial.

13 Preparation and Administration of Investigational Device

Administration of TMS treatment will be consistent with procedures outlined in the NeuroStar® User Manual and User training documentation.

13.1 *Motor Threshold Determination Procedure – per NeuroStar User Manual*

Subjects in Phase I randomized to active treatments will receive treatment parameters that have been safely and feasibly utilized in adult randomized, controlled trials and in the 2011 Wall et al. open-label trial in adolescents. Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment for the first week only, the intensity of the magnetic field can be reduced, as needed, to 110% for tolerability. Upward titration with goal of return to maximum

intensity (not to exceed 120% MT) will occur as tolerated by each subject by the end of the first week of treatment. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. Up to a total of 30 treatments will be completed within 6 weeks of treatment initiation.

13.2 *Treatment*

Subjects in Phase I randomized to sham treatments will have identical schedules, systematic assessments, and a treatment approach to active treatment. Neither the subject nor Investigators will know whether the treatment is active or sham in nature. The sham coil will be identical in its appearance to the active coil. Furthermore, Neuronetics, Inc. has created an acoustic matching profile that renders the "sound" of the treatments virtually indistinguishable to subjects or researchers. The acoustic signal creates a painless percussive sensation that will be felt by the subject and will assist in simulating the active condition.

Subjects in Phase II will receive treatment that is identical in schedule and parameters to that of Phase I with the exception that the known-active therapy coil will be used for all treatments. Up to a total of 30 treatments will be completed within 6 weeks.

Subjects in Phase III will be monitored for symptom re-emergence. In the event that the subject's CGI-S score worsens by 1 point or more from the value observed at Phase III entry, then the subject must be rescheduled for repeat clinical assessment within 1 week. If this symptom change is confirmed at that visit, then the subject is considered to have met criteria for clinical deterioration. TMS re-introduction treatment should occur with the known active coil using the same protocol parameters. A Motor Threshold determination must also be performed immediately prior to administration of the first TMS treatment to a subject in any TMS treatment block. During each active TMS retreatment block, subjects are assessed every other week with the same efficacy measures used in the Week 6 visit and the C-SSRS. During a TMS retreatment block, TMS should be discontinued when the CGI-S score has returned to the value observed at Phase III entry. Subjects must be withdrawn from the study if they meet criteria for relapse as defined:

- Meeting diagnostic criteria for major depression, confirmed on two occasions within a two week period, or
- Failure to experience symptomatic improvement by restoration of CGI-S score to its Phase III entry value upon the completion of an TMS retreatment block

13.3 *Packaging and Labeling*

The NeuroStar XPLOR® Therapy System will be clearly labeled with the following warning:

"CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use"

13.4 *Blinding of Study*

The blinded TMS coils will arrive from Neuronetics and will be identical in appearance and labeled generically (e.g., Coil X, Coil Y). The device will recognize one coil as active and the other coil as sham. Once a subject has been randomized, the device will "link" the subject's treatment with the corresponding coil. The device will remain inactive if the "incorrect" coil is used for a subject, adding an additional safeguard for each subject and the integrity of the study and allowing the study treaters to remain blinded to the nature of the subject's treatment assignment.

Subjects will be randomly assigned to a coil and will receive all treatments during Phase I of the trial using this coil. Neither the subject nor the study staff (including those administering TMS treatments and those administering mood, cognitive, safety, and imaging assessments) will know whether the subject is

receiving active or sham treatment. Subjects and Parents (if subject < 18 years old or does not meet the local or state legal age requirement) will complete a Pre/Post-Treatment Expectations and Experience Questionnaire (PRE-TEEQ-A/PRE-TEEQ-P and POST-TEEQ-A/POST-TEEQ-P) that queries their initial expectations of trial outcome and final impression of the trial.

In Phase II and III, all treatments will be provided with the known-active coil.

To minimize any source of bias, unblinding of the study will not be done until all subjects have completed all study phases. However, unblinding will occur if the Data and Safety Monitoring Board, consistent with their assigned charter and associated stopping rules, determines that it necessary to do so.

As an additional measure to ensure the integrity of the blinded coil assignment, the study coils at each location may be retrieved by Neuronetics study personnel and new study coils re-assigned.

13.5 *Receiving, Storage, Distribution and Return*

Receipt of Investigational Devices

NeuroStar XPLOR® TMS Therapy System will be delivered to the Investigator and installed by Neuronetics.

Upon receipt of the NeuroStar and study treatment supplies, an inventory will be performed and a device accountability log completed by designated study staff at each site. The designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies or damaged or unusable devices in a given shipment will be documented in the device accountability log. The Investigator at each study site will notify Neuronetics immediately of any discrepancies or damaged or unusable products.

Storage

The supplies and disposables required for each treatment will be stored in a supply station separate from clinical practice stock at each site.

Distribution of Study Device

Subjects in Phase I will be randomly assigned to one of the blinded treatment coils at time of enrollment, as outlined in protocol section 13.2. All subjects in Phase II and III will be treated with the known-active, non-blinded therapy coil. All subjects will be treated using a new single-use treatment disposable, or SenStar® Treatment Link, from their treatment site at the start of every new treatment. The treatment packs and SenStar Treatment Links will be stored in an area that is separate from clinical practice stock. Regular reconciliation of SenStar Treatment Links received from Neuronetics, SenStars used during study treatments, and SenStars remaining will be performed. This reconciliation of the inventory will be logged in the Device Accountability Log, signed, and dated. Any discrepancies noted will be documented, Neuronetics will be notified, and an investigation will be conducted to determine the cause of the discrepancy. Any SenStars disposed of for any reason other than use for the study will be documented in the Device Accountability Log at the time of disposal.

Return or Destruction of Study Device

The NeuroStar® devices purchased from Neuronetics, Inc. will remain at the study sites at the completion of the study. NeuroStar devices and/or XPLORs that are loaned to the study site for purposes of participating in this study will be returned to Neuronetics at conclusion of the study by Neuronetics personnel. SenStars® that are remaining in the site study research inventory at the completion of the study will be packaged and returned to Neuronetics.

14 Study Procedures

14.1 *Study Overview*

Adolescents will be screened and enrolled in the study and randomized in a blinded manner to either the active treatment or sham treatment group. Neither the subjects nor the investigators will know whether the treatments are active or sham in nature. All subjects will have baseline mood, safety, and cognitive assessments. Subjects at sites conducting the Structural Head MRI subset will have baseline imaging. All subjects will then undergo 30 TMS treatments within the 6 week timeframe. Mood, safety, and cognitive assessments will be performed at regular intervals throughout the study (see Appendix A for schedule of events). After the final treatment (i.e., treatment #30 or at early withdrawal), the mood and cognitive assessments will be performed for all subjects.

The treatment and assessment schedules for Phase I are identical for both the active and the sham treatment cohorts. For subjects in the Structural MRI subset, MRI scans will also occur after the final treatment for Phases I and II and again at the 6-month follow-up visit.

14.2 *Subject Compliance Monitoring*

Non-adherence to the assigned treatment regimen is defined as missing ≥3 treatments in daily sequence, or missing more than 20% of the total number of treatment sessions occurring during the 6 weeks of acute treatment (does not include taper treatments) as outlined in the schedule of events (i.e., 100% compliance = 30 total treatments). However, if the subject does miss a treatment, the subject must not go more than 3 calendar days without a treatment session. Treatments missed during the taper visits are considered protocol deviations. Subjects who are unable to comply with this schedule may be withdrawn from the investigational treatment portion of the study. If a subject receives more than the prescribed number of pulses (i.e. 3000 pulses of good contact), this would be considered an overdose and documented on the SAE form and reported to Neuronetics.

14.3 *Prior and Concomitant Therapy*

Reasonable efforts will be made to determine all somatic therapies for depression received by the subject in the past 2 years. All other medications and therapies received within six months of study enrollment will also be determined. All relevant information will be recorded on the subjects CRF. The ATR will be used in this study to verify the inclusion criteria pertaining to treatment resistance and intolerance. (See Study Reference Manual for details of the administration of the ATR.)

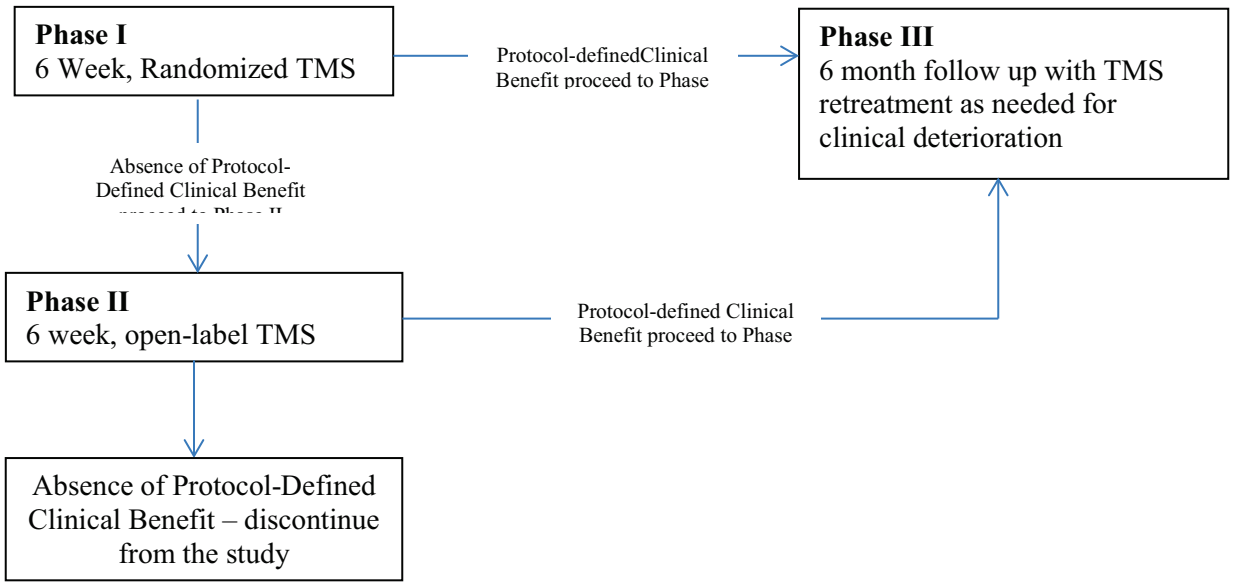
Permitted Concomitant Therapy

Zaleplon, zolpidem, or zopiclone (1 dose nightly) as needed for treatment emergent insomnia or lorazepam (up to 2 mg daily) for treatment emergent anxiety, may be administered for up to 14 doses during Phase I and an additional 14 doses during Phase II. For Phase III, these medications may be administered for up to 10 days, on ≤5 occasions. The use of alternative hypnotics or anxiolytic compounds requires prior approval from the Sponsor. Hormonal contraceptives are allowed if the subject has been on a stable dose for at least 3 months. Short-term treatments for headaches, allergies, colds, and flu symptoms will be allowed during the study provided the medications utilized have no established psychotropic effects that would be expected to confound interpretation of study outcome measures. These medications may include non-sedating, over-the-counter, or prescription antihistamines, analgesics and decongestants. All questions regarding the acceptability of specific medications must be approved by the Sponsor.

Prohibited Concomitant Therapy

Any medication administered for the treatment of any psychiatric or neurologic disorder or any other known CNS active drugs, including herbal, over-the-counter, and homeopathic medications, MAOIs, other antidepressants, antipsychotics, stimulants and mood stabilizers are prohibited during this study (See Appendix D, Concomitant Medication Exclusion List). Use of Zaleplon, zolpidem, zopiclone or lorazepam for more than the permitted days (see above) or beginning a new regimen of hormonal contraception may lead to excluding the subject from the study.

14.4 *Phases – Randomized, Triple-Blinded*



15 Statistical Plan

15.1 *Sample Size and Power Calculation*

There are no large, randomized controlled trials of the use of transcranial magnetic stimulation (TMS) in the treatment of adolescent major depressive disorder that can be used to estimate effect size. Therefore, several different sources of evidence were used to estimate the expected effect size of treatment as proposed in this protocol. First, evidence was reviewed from the study by Wall and colleagues, who reported preliminary data from a small patient population of adolescents treated with the NeuroStar TMS Therapy System in an open label study design (Wall, 2011). This study is especially relevant because it is the only available evidence using the specific TMS device (i.e., the NeuroStar TMS Therapy System) that will be utilized in the NeuroStar TMS Adolescent MDD RCT, and it used the identical stimulation parameters and duration of treatment proposed in this study protocol. In that report, eight adolescent patients participated who had previously failed to benefit from treatment with 2 or more antidepressant medications and were currently in stable treatment with a single ineffective (selective serotonin reuptake inhibitor, SSRI) antidepressant medication. Seven of 8 patients, ages 14-18 years, completed all 30 treatments in this study. The primary outcome measure was the Children's Depression Rating Scale-Revised (CDRS-R) which showed significant improvement from baseline (mean [SD]) (69.6 [6.6]) at treatment 10 (50.9 [12]), $P<0.02$, treatment 20 (40.1 [14]), $P<0.01$, treatment 30 (32.6 [7.3]), $P<0.0001$, and at 6-month follow up (32.7 [3.8]), $P<0.0001$.

Using this data, the mean change in CDRS-R total score was estimated to be approximately 33, with a standard deviation of 7.3. It is presumed that a treatment difference of 8.0 points on the CDRS-R scale between randomized treatment conditions may be anticipated in a sham-controlled study, and that a conservative estimate for a pooled standard deviation is 10.0 points, which results in an estimated standardized effect size of 0.80. This is considered to be the upper bound of an expected magnitude of treatment benefit in an adolescent depression study population. Under these assumptions, it is presumed

that a sample size of approximately N=35 patients per treatment group, with an alpha level = 0.05 would provide approximately 90% power to detect a treatment difference between active and sham TMS groups.

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

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

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

15.2 *Analysis Plan*

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

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

As noted elsewhere in this protocol, the sites will remain blinded to which efficacy measure has been declared as the primary outcome and to the point of efficacy declaration in order to improve the study's signal detection ability. Point of declaration and the primary outcome measure will be documented in the study master file prior to unblinding of the dataset. The null hypothesis will be tested in an analysis of covariance of the LV, using baseline score, and ATR medication resistance level as fixed effect covariates, adjusting for site differences using a random effect. As discussed elsewhere, the ATR medication resistance levels will group subjects categorically by number of medications which have shown an adequate degree of resistance for that subject. These resistance levels will be grouped into two categories in statistical model, 0-1 in the current episode or 2-4 in the current episode, unless the final distribution of ATR scores in the study population suggests another allocation would be more statistically appropriate. All tests are two-sided, at the 5% level. The primary outcome should be available and meaningful for nearly all subjects, so the main analysis will be by strict intention-to-treat as defined above. An analysis of observed cases only will be performed as a secondary outcome measure. A site by treatment interaction analysis will be done as a secondary analysis to see if there is significant heterogeneity in the effect of TMS across sites. In particular, we will examine site-specific treatment effects (with confidence intervals) to test for evidence of true reversal of effect.

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

In addition to testing the hypothesis noted above in the study alone, a meta-analysis will be used to establish evidence of efficacy. Specifically, in addition to the evidence to be obtained in this study protocol, there are already two large, randomized, multisite sham-controlled studies of the use of the NeuroStar TMS Therapy® System in adult patients (ages 18-70 years of age) with major depressive disorder. These data are statistically important to consider in the interpretation of the data to be collected in the adolescent study population using the NeuroStar® TMS device. Therefore, a frequentist analysis will be used to demonstrate the effectiveness of the NeuroStar TMS Therapy System across ages 12-70 by borrowing data from the two adult studies to be used in a meta-analysis with the adolescent study data. This approach effectively allows meaningful computational use of the preponderamce of adult study evidence with the adolescent study datato permit a "sample-sparing" adolescent study design. This approach is clinically justified by the substantial evidence of safety and effectiveness already shown in the adult patient population, the biological and clinical continuity of the disease state from adolescence to

adulthood, the shared mechanism of action of transcranial magnetic stimulation across age groups, and because of the significant unmet need in treatment options available for adolescent patients with major depressive disorder.

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

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

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

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

If the criteria described above for pooling the adolescent study with the adult studies are not satisfied, the adolescent study must stand alone. If the results of the analysis of the adolescent study shows a statistically significant treatment group difference in favor of the active treatment at a pre-specified alpha level = 0.05, then this study alone will be sufficient to establish efficacy in the adolescent population.

A listing of the efficacy outcome measures and their intended sequence of testing in priority order are listed here. Note that the point of declaration of efficacy for the primary outcome measure is concealed from the Investigator and hence, is not specifically noted in this listing. All tests are to be performed on the intent to treat sample unless specifically noted. Please refer to the Schedule of Events for a listing of study timing for collection of primary and secondary outcome measures.

Table 4. Prioritized Order of Testing of Primary and Secondary Outcome Measures

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

The integrity of the masking of the efficacy treatment conditions will be evaluated by exploratory analyses of the efficacy measures with subjects grouped by prominent self-reported spontaneous adverse events. In addition, subjects and Parents will complete a Pre/Post-Treatment Expectations and Experience Questionnaire (PRE-TEEQ-A/PRE-TEEQ-P and POST-TEEQ-A/POST-TEEQ-P) that queries their initial expectations of trial outcome and final impression of the trial.

Neurocognitive safety outcome measures will be compared from end of each phase to Phase I baseline and previous phase completion assessments.

16 Safety and Adverse Events

16.1 *Adverse Event Definitions*

An *adverse event* is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person who has received treatment with a Neuronetics device or in a Neuronetics clinical study. The event need not be causally related to the Neuronetics device or Neuronetics clinical trial. An AE includes, but is not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (i.e., a dose higher than that described in the protocol) of a Neuronetics device, whether accidental or intentional;
- An AE occurring from abuse (e.g., use for non-clinical reasons) of a Neuronetics device;
- An AE that has been associated with the discontinuation of the use of a Neuronetics device; a *preexisting condition* is a clinical condition (including a condition being treated) that is diagnosed before an informed consent form is signed and is documented as part of the subject's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE (TEAE). An AE is considered to be treatment emergent if (1) it was not present when the active phase of the study began and is not a chronic condition that is part of the subject's medical history, or (2) it was present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increased during the active phase.

The treatment phase of the study begins at the time of the first administration of a TMS treatment (active or sham). A *serious adverse event* (SAE) is defined by Neuronetics as an AE that:

- Results in death:
- Is life threatening (see below)
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life
- Necessitates medical or surgical intervention to preclude such impairment
- Results in a congenital anomaly or birth defect

Additionally, *important medical events* that may not result in death, be life-threatening, or require hospitalization, may be considered SAEs, based upon appropriate medical judgment.

Life threatening refers to immediate risk of death as the event occurred or use or continued use of the device or other medical product might have resulted in the death per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death.

Hospitalization is to be considered only as an admission. Hospitalization or prolongation of a hospitalization constitutes an AE to be classified as serious.

Note that hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

An adverse event of special interest is a device-specific adverse event designated by Neuronetics for transmission in the same time frame as an SAE, even if it does not meet serious reporting criteria. For this protocol, seizure should be reported as an adverse event of special interest.

If there is any doubt whether the information constitutes an SAE, the information should be treated as an SAE for the purpose of this study.

16.2 *Timing for Reporting of Serious Adverse Events*

Any SAE, regardless of causal relationship, must be reported immediately to the Neuronetics medical monitor (within one business day) by faxing a completed serious adverse event form to the fax telephone number listed in Section 1.2 of this protocol and then confirming by telephone that the fax was received. Compliance with this time requirement is essential so that the Sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Neuronetics medical monitor within one business day after the information is received by the Investigator by faxing a completed serious adverse event form to the fax telephone number listed in Section 1.2 of this protocol and confirming by telephone that the fax was received. The subject should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

Any emergency must be reported to Neuronetics immediately (within one business day) by contacting the medical monitor listed in the front of this protocol (Section 1.2).

For all other inquiries and information about this study, contact the Neuronetics representative identified in Section 1.12 of this protocol.

16.3 *Reportable Events*

An AE or SAE can occur from the time that the subject signs the informed consent form to 30 days from the subject's last study visit regardless of relationship to the protocol or TMS device. This includes events that emerge during the prestudy screening phase. All AEs and SAEs will be recorded on source documents and recorded on the subject's CRFs. All AEs and SAEs that occur after the prestudy screening period will be recorded on the subject's CRFs, which will be provided to the Sponsor. The Neuronetics medical monitor will instruct the Investigator to follow all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilizes.

The Investigator will provide all relevant documentation pertaining to an SAE (e.g., additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to Neuronetics in a timely manner. Reports relative to the subject's subsequent course must be submitted to the Neuronetics until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Other information reportable to Neuronetics, while not meeting the definition of an AE, is reportable to Neuronetics with the timeliness of an SAE. This includes:

- Seizure
- Pregnancy occurring during the study period in which the subject was exposed to the TMS device;
- Overdose (e.g., a dose higher than that prescribed by a healthcare professional for clinical reasons) with or without AEs;
- Abuse (e.g., use for non-clinical reasons) with or without an AE;
- Inadvertent or accidental exposure with or without an AE;
- Device malfunction that would likely result in death, serious injury or other significant adverse event.

16.4 *Reporting Procedures*

At each required study visit, all AEs that have occurred since the previous visit will be recorded in the adverse event record of the subject's CRF. The information recorded should be based on the signs or

symptoms detected during the physical examination and clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

The following AE information must be included (when applicable): the specific condition or event and direction of change; whether the condition was preexisting (i.e., an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (e.g., in severity and/or frequency); the dates and times of occurrence; severity; causal relationship to the investigational device; action taken; and outcome.

Causal relationship options and definitions are as follows:

- *Definitely related*: Event can be fully attributable to administration of the investigational device.
- *Probably related*: Event is most likely to be explained by administration of the investigational device, rather than the subject's clinical state or other agents/therapies.
- *Possibly related*: Event is as likely explained by administration of the investigational device, as by the subject's clinical state or other agents/therapies.
- *Probably not related*: Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the investigational device.
- *Definitely not related*: Event can be fully explained by the subject's clinical state or other agents/therapies, rather than the investigational device.

When assessing the relationship between an investigational product/protocol and an AE, the following parameters are considered:

- Temporal relationship between the investigational device/protocol and the AE
- Biologic plausibility of relationship
- Subjects' underlying clinical state or concomitant agents/therapies
- Where applicable, whether the AE abates on discontinuation of the investigational device (dechallenge)
- Where applicable, whether the AE reappears on repeat exposure to the investigational device (rechallenge)

SAEs that are not investigational device-related may nevertheless be considered by the participating Investigator or the medical monitor (or designee) to be related to the conduct of the clinical study, i.e., to a subject's participation in the study.

16.5 *Adverse Event Reporting Period*

For this study, the treatment follow-up period for adverse events is defined as 30 days following the last study visit. Follow up will be documented in the subjects study file.

16.6 *Unblinding Procedures (Breaking the Blind)*

While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject's safety. In the event of a serious adverse device effect, the Investigator will carefully assess whether breaking the blind will critically affect how a subject is treated in response to the adverse effect and whether this knowledge outweighs the implications to the scientific soundness of the study. In the case of most serious adverse effects, treatment would be discontinued and symptoms treated symptomatically irrespective of the knowledge of whether the

treatment received was active or sham in nature. In these instances, having this information would not significantly alter the treatment of the adverse effect(s).

As an additional safeguard against bias, the DSMB has been charged with making the final recommendations for breaking the study blind. If the DSMB recommends unmasking the study, Neuronetics, Inc. will be contacted and the key to active or sham treatment will be obtained. Notation regarding the nature of the treatment the subject had been receiving will be documented in the subject's source document.

If the decision to break the blind is made immediately upon learning of the adverse event, this information will be reported to the FDA and reviewing IRB at the time of initial adverse event reporting. If the unblinding occurs after the initial reporting, the FDA will be notified of the action within ten working days from the time of breaking the blind. The reviewing IRB will be notified according to their reporting guidelines if the decision is made to break the study blind after the initial reporting.

If unblinding occurs at one site, the other sites WILL NOT be given the randomization key unless directed to do so by the FDA; Neuronetics, Inc.; reviewing IRB; or the DSMB.

16.7 *Stopping Rules*

Specific occasions when study treatment may be stopped are explained Section 8.4 in the discussion of Anticipated Risks.

Because of the anticipated low level of adverse events of TMS, the DSMB will be charged with reviewing adverse events at least every six months. Serious adverse events will be reviewed on a monthly basis, unless a more urgent review is requested. Only under extreme circumstances or if it were determined that a high level of side effects was due to TMS, would the DSMB be charged with breaking the study mask.

16.8 *Medical Monitoring*

The regulatory sponsor has oversight for the overall safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be assembled to oversee the safety of the study, subjects, and the scientific validity and integrity of data collected as part of the study. This DSMB will include members from academic sites independent of the study sites and will consist of at least one non-study, board-certified psychiatrist and one biostatistician.

The responsibilities and decision points for the DSMB will be captured in the DSMB charter.

17 Data Handling and Record Keeping

17.1 *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 who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

17.2 *Source Documents*

Source data comprise 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, pharmacy 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, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the source data recorded on the source documents.

17.3 *Case Report Forms*

The Sponsor will provide case report forms (CRFs) for each subject enrolled into the study to ensure consistent data collection.

Data will be captured at each participating site by qualified study staff who will perform primary data collection from source-document reviews to case report forms (CRF). Data will be collected for this study utilizing one or a combination of the following methods:

1. Data may be transcribed from the Electronic Medical Record (EMR-an electronic source that must be available for review) onto the CRF. A copy of the EMR will be printed and placed in the subjects case file as source documentation.
2. Data may be captured directly onto the CRF and transcribed into the EDC system by Neuronetics, BUT paper documentation must be retained and available for review.

Data reported in the CRF should be consistent with the source documents or the discrepancies should be explained.

Data Management

Neuronetics and/or Study Sites will enter data from the CRFs into an electronic data capture (EDC) system that is compliant with 21 CFR (Code of Federal Regulations) Part 11 FDA (Food and Drug Administration) requirements. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. Data will be transmitted via the internet to a central hosting site, utilizing state-of-the-art encryption mechanisms to ensure security and confidentiality.

Details of the study treatments including treatment parameters, such as MT for each subject, will be retained within the TMS device by the XPLOR software. In addition, a printed report of the treatments

will be stored as part of the subject's source documents. Details from the study treatments will be entered into EDC.

Case files will be created for each subject where completed CRFs will be stored.

Data Security and Confidentiality

Database and Web servers will be secured through controlled physical access. For security reasons, and in compliance with regulatory guidelines, EDC system access is granted to the user who owns the sign on identification and password in use. Access codes are non-transferrable. Personnel who have not undergone training may not access the study eCRF's until appropriate training is completed and documented. The eCRF data elements do not reside on the users work station; they are transmitted to a secure central database (host site) as forms are completed or updated. Protocol-specified source documents (e.g. hospital discharge summaries, operative/procedural reports) will be retrieved as necessary. Copies of all study-related documentation will be retained at the site.

Case files will be located in a secured area at each study site. All completed CRFs will be de-identified and subjects will be referred to using only their assigned study subject identifier and initials. Information stored in the source documents will be safe-guarded according to institutional guidelines.

Data Quality Assurance/Data Clarification Process

The EDC database will have consistency checks programmed into the system to assist the Sponsor with informing investigators of potential data issues as the data entry progresses. The exception log for entries will be reviewed by the Sponsor to identify potential training and/or data integrity issues. Neuronetics (or designee) will perform site monitoring, including review of the CRFs with verification to the source documentation to verify accuracy of CRF data. During monitoring visits, the site will make their computer and/or high speed internet access available to the study monitor so that he or she may verify the data entries with the source documentation as needed. If data integrity issues are suspected they will be reported to the Sponsor immediately.

Request for data clarification or correction will be forwarded to the study site for resolution.

17.4 *Records Retention*

The site PIs will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Records will be retained per local regulations and local site policy and also in accordance with part 21 CFR 312.62(c) which states "for a period of 2 years following the date a marketing application is approved for the drug/device for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified." Furthermore, Neuronetics will be notified in writing of the relocation of any study related records.

18 Study Monitoring, Auditing, and Inspecting

18.1 *Study Monitoring Plan*

This study will be monitored by Neuronetics or designee according to the monitoring plan included in the study reference manual.

18.2 *Auditing and Inspecting*

The site investigator will permit study-related monitoring, audits, and inspections by the IRB, the Sponsor, and government regulatory agencies, of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The site investigators will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

19 Ethical Considerations

This study is to be conducted according to United States and Canadian government regulations and Institutional research policies and procedures.

Although this study is considered more than minimal risk to adolescents, TMS treatments offer a potential direct benefit for the individual subject. In addition, the schedule of mood assessments and daily assessment during the interventional portion of the study for any adverse events has been developed for the purpose of monitoring the subject's well-being.

This protocol and any amendments will be submitted to a properly constituted local IRB, in agreement with local requirements, for formal approval of the study at each participating site. The decision of the IRB concerning the conduct of the study will be documented in writing to the regulatory sponsor before commencement of this study.

All families and subjects for this study will be provided a consent/assent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent/assent form will be submitted with the protocol for review and approval by the site IRB for the study. The formal consent of a subject, using the approved IRB consent/assent form, must be obtained before that subject undergoes any study procedure. This form must be signed and dated by the subject, the subject’s legally-authorized representative, and the individual obtaining informed consent/assent.

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Appendix A. Phase I Schedule of Events

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

a. A minimum of 7 days may elapse between the screening and baseline visits; a maximum of 5 days may elapse between the baseline visit and the first treatment day of Week 1. All baseline assessments must be completed and laboratory results received before 1st TMS treatment.

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

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

d. If subject <18 yrs of age or the legal age requirement of the state

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

f. Subject must have been off of any antidepressants for at least one week.

g. Laboratory determinations to include standard hematology, and blood chemistry.

h. If subject is female of childbearing potential, a urine pregnancy test will be performed in the office at screening.

i. Performed on a subset of subjects at participating sites,

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

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

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

m. Taper occurs only if exiting the study or transitioning directly to Phase III.

Appendix B. Phase II Schedule of Events

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

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

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

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

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

e. **Performed on a subset of subjects at participating sites**

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

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

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

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

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Appendix C. Phase III Schedule of Events

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix D. Concomitant Medication List

CONCOMITANT MEDICATION LIST

This list should not be considered exhaustive. In general, drugs that are categorized into one of the drug categories listed in the table below should be treated similarly. Contact Neuronetics if questions arise.

CLASS: Drug	PRN	Chronic
ANTIASTHMA DRUGS		
Theo-Dur (theophylline)	**N**	**N**
Bronchodilators		
Alupent (metaproterenol), Proventil (albuterol), Ventolin (albuterol)	**Y**	**Y**
Steroids		
Inhaled (Beclovent [beclomethasone], Azmacort [triamcinolone], Vanceril [beclomethasone])	**Y**	**Y**
Oral	**C**	**N**
Leukotriene antagonists		
Accolate (zafirlukast), Zyflo (zileuton), Singulair (monoleukast)	**N**	**Y**
ANTICOAGULANTS		
Coumadin (warfarin)	**N**	**Y** (w/ stable protime)
ANTICHOLINGERGICS		
Cogentin (benztropine), Artane (trihexyphenidyl), etc.	**N**	**N**
Phenylpropanolamine (PPA) and pseudoephedrine	**N**	**N**
ANTIHISTAMINE and DECONGESTANTS		
Sedating		
Anticholinergic (Benadryl [diphenhydramine], chlorpheniramine, brompheniramine, Atarax [hydroxyzine]) (not for psychiatric indications)	**N**	**N**
Non-sedating		
Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)	**Y**	**Y**
Hismanal (astemizole)	**N**	**N**
ANTI-INFECTIVE AGENTS		
Antibacterial antibiotics (Penicillin, sulfa, etc.)	**Y**	**Y**
Antifungal agents *(ketoconazole, fluconazole, etc.)*		
Topical creams and ointments	**Y**	**Y**
Oral antifungals (single-dose for vaginitis OK)	**Y**	**N**
Antiviral agents		
Zovirax (acyclovir), Famvir (famcyclovir), Valtrex (valacyclovir)	**Y**	**Y**
Antiretroviral drugs (e.g. AZT, protease inhibitors)	**N**	**N**
ANTI-NEOPLASTIC AGENTS	**N**	**N**
SKELETAL MUSCLE RELAXANTS		
Lioresal (baclofen), Flexeril (cyclobenzaprine), Parafon Forte	**N**	**N**

CLASS: Drug	PRN	Chronic
(chlorzoxazone), Robaxin (methocarbamol), Soma (carisoprodol)		
ANALGESICS AND ANTIPYRETICS		
Nonsteroidal anti-inflammatory agents (aspirin, ibuprofen, naproxen)	**Y**	**Y**
Opiate Agonists / Partial Agonists (including Ultram [tramadol])	**N**	**N**
Miscellaneous analgesics & antipyretics (acetaminophen, paracetamol)	**Y**	**Y**
CARDIOVASCULAR DRUGS (All drugs in this category must be stable for at least 3 months)		
CARDIAC DRUGS		
Calcium Channel Blockers for coronary disease or angina (see also "Antihypertensives") (Calan [verapamil], Cardizem [diltiazem], Norvasc [amlodipine], Procardia [nifedipine])	**N**	**Y**
Antiarrhythmics		
Cordarone (amiodarone), lidocaine (note: local anesthesia injection OK), Mexitil (mexiletine), Norpace (disopyramide), Procan (procainamide), quinidine, Tambocor (flecainide)	**N**	**N**
Digoxin (blood levels must be monitored)	**N**	**Y**
ANTI-HYPERTENSIVE AGENTS (All anti-hypertensives must be stable dose x 1 month)		
ACE Inhibitors (Vasotec, Capoten, Zestril)	**N**	**Y**
Angiotensin receptor blockers (Cozaar)	**N**	**Y**
Calcium Channel Blockers	**N**	**Y**
Diuretics	**Y**	**Y**
Phentolamine	**N**	**N**
Beta-Adrenergic Blockers *(see also* ***Anti-Migraine****)*		
Low lipid solubility/CNS penetration (Corgard [nadolol], Tenormin [atenolol])	**Y**	**Y**
High lipid solubility/CNS penetration (Inderal [propranolol], Lopressor [metaprotereno]), (low lipid solubility preferred)	**Y**	**Y**
Peripherally-acting alpha adrenergic agents		
Cardura (doxazosin), Hytrin (terazosin), Minipress (prazosin)	**Y**	**Y**
Centrally-acting alpha adrenergic agents		
Aldomet (methyldopa), Catapres (clonidine)	**N**	**N**
All others *(quanethidine, reserpine, etc.)*	**N**	**N**
ANTILIPEMIC AGENTS		
Niacin (no slow-release preparations), Lipitor (atorvastatin), Lopid (gemfibrozil), Mevacor (lovastatin), Zocor (simvastatin)	**N**	**Y**
VASODILATING AGENTS		
Hydralazine	**N**	**Y**
minoxidil (topical OK)	**N**	**C**
ANTI-CONVULSANTS	**N**	**N**

CLASS: Drug	PRN	Chronic
PSYCHOTHERAPEUTIC AGENTS		
Antidementia drugs (donepezil, etc.), Antidepressants, Antipsychotics (Thorazine, Prolixin, etc.), Miscellaneous Psychotherapeutic Agents	**N**	**N**
Anxiolytics (per protocol)	**Y**	**N**
Stimulants	**N**	
Sedatives and Hypnotics		
Barbiturates, Benzodiazepines (except those allowed per the protocol), Other hypnotic agents	**N**	**N**
Ambien (zolpidem; per protocol), chloral hydrate (per protocol), Sonata (zaleplon; per protocol), Lunesta (eszopiclone; per protocol), Rozerem (ramelteon; per protocol)	**Y**	**N**
ANTIMANIC AGENTS		
Anticonvulsants, lithium	**N**	**N**
HORMONES & SYNTHETIC SUBSTITUTES		
Corticosteroids (methylprednisolone, prednisone)	**Y**	**C**
Mineralocorticoids (Florinef [fludrocortisone])	**N**	**C**
Topical steroids (creams, ointments, eyedrops)	**Y**	**Y**
pregnenolone	**N**	**N**
Androgens	**N**	**N**
DHEA, testosterone, danazol	**N**	**N**
Contraceptives		
Hormonal *(dose must be stable for at least 3 months)*: Oral, Vaginal Ring, Patch, Injections, Norplant (levonorgestrel)	**N**	**Y**
Intrauterine device	**Y**	**Y**
Latex condom, diaphragm and or cervical cap with spermicide	**Y**	**Y**
Estrogen replacement *(postmenopausal, stable dose for ≥3 months)*	**N**	**Y**
Thyroid *(stable dose for ≥3 months and thyroid function tests within normal limits. Clinical significance to be determined by the physician)*	**N**	**Y**
ANTIDIABETIC AGENTS		
Oral hypoglycemic agents	**N**	**Y**
Insulin's	**Y**	**Y**
DERMATOLOGIC AGENTS		
Topical steroid preparations, Rogaine (topical minoxidil), Miscellaneous creams, ointments, etc.	**Y**	**Y**
VITAMINS	**Y**	**Y**
OVER-THE-COUNTER SUPPLEMENTS		
chromium picolinate, DHEA, melatonin, pregnenolone, St. John's Wort	**N**	**N**

CLASS: Drug	PRN	Chronic
GASTROINTESTINAL DRUGS		
Cisapride (propulsid)	**Y**	**Y**
Antiemetics		
Over-the-counter (e.g., Emetrol [dextrose], Coke syrup)	**Y**	**Y**
Phenothiazines & related drugs (Compazine [prochloroperazine], Phenergan [promethazine], Reglan [metoclopramide], Tigan [trimethobenzamide]), Anzemet (dolasetron), Kytril (granisetron), Zofran (ondansetron)	**C**	**N**
Marinol (dronabinol),	**N**	**N**
Antacids		
AlternaGel (aluminum hydroxide), Amphojel (aluminum hydroxide), Basaljel (aluminum carbonate), Bicitra (sodium citrate), Maalox (calcium carbonate), MagOX (magnesium oxide), Mylanta (magnesium hydroxide), Tums (calcium carbonate), UroMag (magnesium oxide)	**Y**	**Y**
Antidiarrhea agents		
Arco-Lase (trizyme), Furoxone (furazolidone), Motofen (difenoxin), Sandostatin (octreotide acetate)	**N**	**N**
Imodium (loperamide), Lomotil (diphenoxylate), Pepto-Bismol (bismuth subsalicylate)	**Y**	**N**
Cathartics & Laxatives		
Colace (docusate), enemas, Metamucil, Perdiem, Senokot, Soflax, Unifibre	**Y**	**Y**
Dialose (docusate)	**Y**	**Y**
Antisecretory agents		
H2 Blockers	**N**	**N**
Axid (nizatidine), Pepcid (famotidine), Zantac (ranitidine)	**Y**	**Y**
Proton pump inhibitors		
Prevacid (lansoprazole), Prilosec (omeprazole)	**Y**	**Y**
Miscellaneous gastrointestinal drugs		
Carafate (sucralfate)	**Y**	**Y**
Reglan (metoclopramide)	**N**	**N**
Levsin (L-hyoscyamine sulfate)	**Y**	**Y**
ANTI-MIGRAINE		
DHE 45 (dihydroergotamine), Imitrex (sumatriptan), methysergide, Midrin (isometheptene mucate), Zomig (zolmitriptan)	**N**	**C**
Fiorinal (butalbital, ASA, caffeine), Cafergot (ergotamine)	**Y**	**C**
Nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, Toradol, etc.)	**Y**	**Y**
Beta-blocking drugs		
Corgard (nadolol), Tenormin (atenolol), Other beta-blockers (e.g., Inderal [propranolol])	**Y**	**Y**
SKIN & MUCOUS MEMBRANE AGENTS	**Y**	**Y**

CLASS: Drug	PRN	Chronic
MISCELLANEOUS DRUGS		
Acutane, All over-the-counter diet pills, Ionamin (phentermine resin), Lioresal (baclofen), Wellbutrin (bupropion), Zyban (bupropion)	**N**	**N**
Allopurinol, colchicine	**Y**	**Y**
Fosamax (alendronate)	**N**	**Y**
Gold compounds, hydroxychloroquine, and methotrexate for severe arthritis	**N**	**C**
Smoking cessation aids (Nicorrette, nicotine patches)	**C**	**C**
Chantix (varenicline)	**N**	**N**

ENDNOTES

N = Never to be used in this study.
Y = Can be used in this study for either PRN or Chronic use as indicated in the table.

C = Call for Sponsor approval. Approval for these medications is generally granted if the patient is otherwise acceptable, including stable medical condition, no undue risk, no other "marginal" considerations in the medical history or concomitant medications. Or may be used during the long-term maintenance phase with certain restrictions.