Protocol Title: An Open Label Trial of TMS Therapy for Bipolar Depression

Funding Agency: Philanthropic Funds
Equipment Donation by Neuronetics, Inc.

Principal Investigator: Scott T. Aaronson, MD
Director, Clinical Research Programs
Sheppard Pratt Health System
6501 N. Charles Street
Baltimore, Maryland 21204

Treatment: Neuronetics Neurostar TMS Therapy® System

Sheppard Pratt IRB Approval Date: November 18, 2015

NCT Number 02640950

TABLE OF CONTENTS

Objectives

Transcranial Magnetic Stimulation (TMS) is an increasingly accepted neurostimulation- based treatment for major depressive disorder. While there is a growing anecdotal database supporting its use in bipolar depression we propose to collect open label efficacy and safety data in a small population of patients with clinically verified bipolar disorder.

Aims and Hypotheses

The primary aims of this study are:

1. To provide clear open-label evidence that a standard course of TMS therapy can be effective for patients who have a diagnosis of bipolar depression and are currently on mood stabilizing medication.
2. To investigate the safety of TMS in a population at risk for activation from neuromodulation. In particular to observe if these patients are at risk for changing from a depressive state to a mixed or manic state.

Specific Hypotheses are that:

1. TMS will provide effective antidepressant treatment in patients with bipolar depression both type I and II.
2. TMS will show a shorter time to response in bipolar depressed patients compared with the available data in unipolar depressed patients.
3. TMS can be safely given in bipolar depression without inducing a manic or mixed episode switch in patients who are receiving adequate concurrent mood stabilizing medication.

Background

The current FDA approved evidence base for the treatment of bipolar depression is limited to three atypical antipsychotics, one of which is paired with an SSRI. (Nierenberg et. al. 2015). The data analyzed from the STEP-BD study supports the notion that the use of antidepressants added to mood stabilizers provides no improved outcome but may carry the risk of precipitating or supporting a mixed or manic episode. (Sachs et. al., 2007, El-Mallakh et. al. 2015) A problem in developing safe and effective treatment paradigms for bipolar depression is that the population is so heterogeneous and subgroups may require different pharmacological interventions (Altshuler et. al. 2003, Goldberg et. al. 2015)

Transcranial magnetic stimulation has had a growing impact on the treatment of major depressive disorder. There is increasing use of this modality as insurers have increasingly provided support. Sheppard Pratt has been a leader in the adoption of TMS and our clinical TMS program using the Neuronetics NeuroStar

TMS Therapy® System (See Appendix 1) has treated over 200 patients over the past six years. While there is a clear evidence base for the use of TMS in MDD, there is as yet only a small anecdotal base for its use in bipolar depression (Connolly 2012, Nola 2013, Woźniak-Kwaśniewska 2015).

We are currently doing a retrospective look at our experience in treating bipolar depression with TMS which has represented about 15% of our patient base. (Aaronson data in review) A preliminary evaluation of our database shows that we have treated 45 patients with bipolar depression (See Appendix 2). Four patients had their course stopped by their clinician due to side effects; none of them met the criteria for mania or mixed state. Five patients had their course completed by a different TMS provider (closer to their home) and two had incomplete data. For the 34 patients who completed a course of treatment, 26 (76.5%) met response criteria by Montgomery-Asberg Depression Rating Scare (MADRS) score and 12 met remission criteria (35%). These results are numerically superior to our experience in unipolar depression where our response rate is 62% and our remission rate is 31%. In general the treatment has been well tolerated and effective. Most of these patients have a long history of either poor efficacy or safety in the use of antidepressants and inadequate antidepressant response to the use of mood stabilizers or atypical antipsychotics.

A unique aspect of TMS for the bipolar depression patient is the ability to use the neurostimulation during the depressive episode without providing it as a chronic intervention as is the case with medication. The existing database is scant. While several trials are listed at clinicaltrials.gov, most of these data have remained unpublished. There is a current multi-center study, that uses the Brainsway H-Coil Deep TMS system, but the trial is still enrolling and likely years away from publication.

Given that Sheppard Pratt has an active, research based, clinical program, we would like to collect data prospectively and formalize diagnostic criteria, outcome measures and adverse events for this under-studied population. We will also be collaborating with the Mayo Clinic Rochester site.

Study Overview and Hypotheses

We propose to screen patients with bipolar depression I or II, who are already on acceptable mood stabilization. They may or may not be on antidepressants at the time of screening but subjects on antidepressants would be taken off them before completing the screening phase. Those patients who have a depression of at least moderate severity without significant symptoms of activation or mania will be started on a course of open label TMS treatment of up to 35 sessions. Safety and efficacy assessments will be done weekly. Patients will complete a course of treatment when they meet remission criteria (MADRS score < 10) or at the end of 30 treatments, whichever comes first. Patients who are still judged to be improving between treatment 25 and treatment 30 will be eligible to complete up to five addition treatments as the discretion of each site's principal investigator.

Patients who meet response criteria (MADRS score decreases by at least 50%) will complete the full course of 30 to 35 TMS sessions. Patients will be withdrawn for safety concerns, particularly the onset of activation suggestive of mania or a mixed state.

Patients who meet response or remission criteria will be followed monthly for up to six months to evaluate the durability of response. They will be on standard mood stabilizing medications and psychotherapy per their clinician's discretion.

The primary study hypotheses are:

1. TMS will provide effective antidepressant treatment in patients with bipolar depression both type I and II.
2. TMS will show a shorter time to response in bipolar depressed patients compared with the available data in unipolar depressed patients.
3. TMS can be safely given in bipolar depression without inducing a manic or mixed episode switch in patients who are receiving adequate concurrent mood stabilizing medication

The secondary hypothesis is:

1. The majority of treatment responders will show adequate durability of response with remitters showing better durability.

Study Design

Prescreening - Prospective study patients will be prescreened to determine the possible presence of bipolar depression and their willingness to be in a treatment study. The PI will introduce the study to the patient and give the patient an IRB-approved informed consent to read. The patient will have the opportunity to ask any questions about the trial and if desired, may take the consent form home to discuss with family, their physician, or others. Those who pass prescreening and want be in the study will be scheduled for a screening visit.

The study will be divided into three phases, Screening, Treatment and Follow-up.

<u>Phase I: Screening</u>

At screening all prospective subjects will sign the informed consent. A copy of the signed informed consent will be given to each participant. At the time of admission to the study, the patient's current treatment provider, if any, will be consulted, with the patient's permission, about the patient's participation in the study. After informed consent is obtained, patients will be eligible to be screened for inclusion in the study.

Screening will consist of several activities designed to validate that patients are suffering from bipolar illness, are currently in the depressed phase, and have been depressed in the current episode for at least four weeks but not longer than three years. The main screening tool will be the Mini International Neuropsychiatric Interview (M.I.N.I.)) (Sheehan 1998). The Montgomery-Asberg Depression Scale (MADRS), the Young Mania Rating Scale (YMRS) and the Clinical Global Impression of Severity of Illness (CGI-S) rating will be done to confirm the patients' depression level and the absence of mania. As well, patients will be evaluated for the presence of any medical or psychiatric conditions that would either make it unsafe for them to participate in the trial (i.e., an unstable medical condition) or confound evaluation of the course of their bipolar condition (i.e., the presence of psychosis, substance abuse, or an eating disorder). Please see inclusion and exclusion criteria for specific qualifying parameters. When all inclusion criteria have been met and none of the exclusion criteria are present, patients are eligible to enter Phase II. They will be kept on mood stabilizing agents but will be tapered off of antidepressants. . As part of this initial evaluation, the study physician will evaluate the course of each subject's illness to determine the optimal medications to use during the course of TMS. If the subject, the referring physician or the study physician feels that it would be unsafe or unwanted to stop the antidepressant medication, the subject will be dropped from study participation and returned to routine clinical care. The course of TMS treatment will not start until two weeks after the antidepressant has been completed. This phase will last 1 to 28 days in order to accommodate possible changes in medication.

The subject's referring clinician will be advised of their patient's participation and asked not to change medications during the open label TMS treatment. The referring clinician will be invited to follow along or transfer care to the study physician until the subject completes or discontinues open label treatment, at which point care will return to the referring clinician who will be provided with a transfer note by the study staff.

Phase II: Open Label TMS Treatment

Once study patients are on stable medication and it is confirmed that they meet the entry criteria for Phase II they will begin a standard course of five times a week TMS treatment for six weeks. They will be assessed at each treatment visit for side effects, concomitant medication use, and once per week for severity of depression and evidence of any symptoms suggestive of mania or agitation. Any suggestion of mania or activation will be assessed by the study physician who will evaluate to determine if the subject can remain in the study or needs other intervention to manage emerging symptoms.

The MADRS, the 17-item Hamilton Depression Rating Scale (HAM-D_{17}), the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16), the

YMRS, the C-SSRS (Columbia Suicide Severity Rating Scale) and CGI-S will be performed once per week. The CGI-Improvement Scale
(CGI-I) will be done weekly starting at Visit 3. Treatment will continue until remission criteria is reached (MADRS score <10) or 30 treatments have occurred, whichever comes first. If improvement is continuing between treatment 25 and 30, treatments may be extended up to 35. Patients who are discontinued due to onset of manic or mixed symptoms will be followed until resolution of these symptoms. Patients who meet response criteria (MADRS score drops by at least 50%) or remission criteria will be followed in Phase III.

Phase III: Six Month Follow Up

Patients' meeting response or remission criteria will be followed monthly for up to six months by in-person visits or phone interviews. The MADRS, CGI-S and CGI-I scales will be administered at each encounter. Relapse will be defined as a MADRS score of 20 or above for two consecutive weeks. Patients who meet relapse criteria will have an early termination visit the following week and referred for standard clinical treatment.

Study Population
It is estimated that up to approximately 30 patients will participate in the study at the Sheppard Pratt site with 20 addition patients enrolling at the Mayo Clinic Rochester site Patients must have Bipolar I or Bipolar II depression as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 criteria) and be taking a mood stabilizer acceptable to the principal investigator. They will not be allowed to take antidepressant medication. Their depression must be at least moderate in severity without significant symptoms of activation or mania.

Patients treated may come from the Retreat assisted living, outpatient services, outpatient practices of local psychiatrists, the Sheppard Pratt day hospital, or inpatient units. Patients enrolled at Mayo Clinic will come from their Mood program, Mood Clinic, Inpatient practice and the community. It is unlikely that current inpatients will qualify for this study as most of them will have co-morbidities, psychotic symptoms or mixed presentations which would exclude them.

Inclusion and Exclusion Criteria – Phase II
Patients must meet fulfill all of the following inclusion criteria in order to enter Phase II of the study:

1. Must be at least 18 years old.

2. Must meet **DSM-5** criteria for bipolar (either I or II) depression by clinical interview and M.I.N.I. The duration of the current depressive episode must be at least 4 weeks and no longer than 3 years in length.

3. Should have a MADRS score of at least 20 at screening, an YMRS score of less than 12 and a CGI score of at least 4.

4. Must have signed the informed consent document and have a level of understanding sufficient to provide informed consent and to communicate with the investigator and site personnel.

5. Must be on a mood stabilizer acceptable to the study physician which is consistent with their diagnosis. The mood stabilizer must be at a stable dose for at least four days before starting TMS treatment.

6. If female of childbearing potential, patients must
   a) have a negative urine pregnancy test at screening, and
   b) not be nursing or planning a pregnancy, and
   c) be on a medically acceptable method of birth control acceptable to the principal investigator.

   Choices of contraception that meet the study requirements are
   - Intrauterine device
   - Hormonal contraception (estrogen-containing birth control pills, Vaginal ring, patch, injections or implants)
   - Latex condom with spermicide
   - Diaphragm with spermicide
   - Cervical cap with spermicide

   Females of childbearing potential who are abstinent can enroll in the study.

Patients will *not* be enrolled in Phase 2 of the study if they meet any of the following exclusion criteria:

1. May not be directly affiliated with Sheppard Pratt Clinical Research Programs or be immediate family of Research Programs personnel.

2. Must not have another primary Axis I diagnosis.

3. The subject must not have stopped an antidepressant less than two weeks before starting TMS treatment or unable to discontinue antidepressant therapy.

4. Should have no previous history of psychosis or substance dependence or abuse within the six months prior to Screening

5. Presence of an Axis II disorder felt by the investigator to potentially interfere with study compliance would exclude a potential participant.

6. Should not have prior intolerance of TMS or significant lack of response to adequate trials of TMS.

7. Should not have a lifetime history of lack of response to ECT or VNS.

8. Should not have any medical condition likely to interfere with safe study participation.

9. Women of child-bearing potential who are not using a medically accepted means of contraception when engaging in sexual intercourse are excluded, as well as women who are pregnant or breast-feeding.

10. Positive urine screen for any substance of abuse will exclude a patient, with the exception of benzodiazepines. A satisfactory explanation in the opinion of the investigator along with a negative repeat screen prior to Visit 2 is possibly acceptable.

11. Current suicide risk, as evidenced:

    a) It is the judgment of the investigator that the patient may be at risk for suicide
    b) The patient has rated a "yes" to question 4 or question 5 on the Screening C-SSRS
    c) The patient has attempted suicide within the past 12 months prior to Screening.

12. History of head injury, epilepsy or seizure disorder, non-removable metallic implants or objects in or around the head.

Inclusion Criteria – Phase III
Patients who meet MADRS criteria for response or remission will enter Phase III, the six month follow-up phase of the study.

Patient Withdrawal
Patients will be told verbally and in the informed consent that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled.

The investigator may discontinue a patient from the study for the following reasons:

- Non-compliance with 5-day TMS treatment schedule. Patients must complete at least 4 consecutive days of treatment per week.
- It is the judgment of the investigator that the patient may be at risk for suicide
- The patient has rated a "yes" to question 4 or question 5 on the C-SSRS "Since Last Visit" version
- Patient meets relapse criteria (MADRS score ≥ 20 for two consecutive weeks
- Onset of manic or mixed symptoms
- Pregnancy
- Intercurrent illness, adverse event or any other reason concerning the well-being of the patient.

Patients who voluntarily withdraw from the study or who are discontinued from the study will be asked to complete an early termination visit. The early termination visit will be done one week after study withdrawal. A MADRS and CGI will be performed by the investigator. Patients will be referred back to their treating psychiatrist for standard clinical care.

Treatment

Treatment will be done using the Neuronetics NeuroStar TMS Therapy® System. This treatment modality was approved by the Food and Drug Administration for the treatment of Major Depressive Disorder in 2008.

Neuronetics will be providing supplies so there will be no per use charges for patients who are unable to use third party insurance for this study. All subjects at the Sheppard Pratt site will receive TMS treatment at no cost.

Open Label Treatment with TMS

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. All qualified study patients will receive open label TMS treatment, five times a week for a total of 30 treatments or until they meet remission criteria.

Rationale for Use of Mood Stabilizers

The goal is to make this study as naturalistic as possible. Clinical experience to date is that we have not seen TMS treated bipolar patients becoming manic but there is some risk of activation. Patients with bipolar type I will require mood stabilization within the clear therapeutic range. As there is no clear evidence for what bipolar II patients require for adequate stabilization, the criteria for adequate treatment will be more liberal and patient specific at the discretion of the principal investigator.

Concomitant Therapy

In general, concomitant medications with primarily central nervous system activity will be kept to a minimum outside of the required mood stabilizing agent. All concomitant medications taken during the study will be recorded on the case report forms. Patients will be instructed to contact the investigator or study coordinator before taking any new prescribed medications, over-the-counter medications or supplements.

Subjects will be allowed to take up to 10 mg of Ambien per night for sleep.

Treatment Compliance

The goal of treatment is: 1) at least four treatments per week and 2) no more than 3 consecutive days without a treatment. Patients unable to adhere to this schedule will be discontinued.

Efficacy Measures and Safety Evaluations

Primary Efficacy Measure:

- Montgomery-Asberg Depression Rating Scale (MADRS)

Change from baseline to endpoint in MADRS total score will be the primary efficacy measure. The MADRS is a widely used rating scale for severity of mood related symptoms (Montgomery and Asberg, 1979). The scale consists of 10 items and ranges from 0 to 60. Higher scores denote more severe symptoms. The MADRS score (as opposed to the HAMD) is more sensitive to detect changes in the psychic rather than physical symptoms of depression.

Secondary Efficacy Measures:

- HAMD-17

The 17-item Hamilton Depression Rating Scale will be used as a secondary rating scale. This scale weights the physical symptoms of depression more than the psychic symptoms (Hamilton, 1960).

- QIDS-SR16

The Quick Inventory of Depressive Symptoms-Self Rating is a 16 item scale in which patients evaluate the severity of their depression. It is able to give an impression from the patients' point of view as to whether or not they are improved and provides a contrast to the clinician-rated scales (Rush 2003).

- C-SSRS

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation (Posner. The "baseline" version of the instrument will be administered at the screening visit. The "since-last-visit" version will be administered at all other visits.

- YMRS

The Young Mania Rating Scale is the most often used scale to assess the degree of manic symptoms a patient has (Young et al., 1978). This scale will be used to screen out patients in mixed or manic states at enrollment and will be used during the trial to assess if the TMS treatment may be inducing mania.

- CGI Severity and CGI Improvement

These are global assessment scales of the severity of a patient's illness on a seven-point scale and degree of change from baseline on a seven-point scale (Guy, 1976). The CGI improvement scale is often the most sensitive marker to recognize status change in patients.

Safety Evaluations

The investigator or his designee is responsible for the medical care of study patients during the study. The investigator remains responsible for following, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient will be followed until the event is resolved or explained.

Adverse Events

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's medical condition(s). During the study, site personnel will again note any change in the existing conditions and the occurrence and nature of any new adverse events.

If a patient experiences an adverse event after the informed consent is signed, but before study drug is given, the event will be noted as a pre-existing condition unless the investigator believes that the event may have been caused by a protocol procedure.

The Data Safety Management Board (DSMB) and the IRB for this study will evaluate all adverse event reports including data from both sites.

Serious Adverse Events

A serious adverse event is defined as any event that:

1. Results in death
2. Results in initial or prolonged inpatient hospitalization
3. Is a life-threatening experience (immediate risk of dying)
4. Results in persistent or significant disability/incapacity
5. Is a congenital abnormality/birth defect
6. Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Unexpected adverse drug experiences (those not consistent with current package labeling information) will also be reported.

The causality of serious adverse events and unexpected adverse drug experiences will be assessed by the investigator(s). The IRB will be sent a report of any serious adverse event or unexpected adverse drug experience within 24 hours of the event becoming known. Reports to the DSMB will be handled in the same manner.

Statistical Methods

- Sample Size

We are looking to collect sufficient data to demonstrate the efficacy and safety of TMS in bipolar depression. As this is an open label trial we will aim to treat 30 patients to achieve a reasonable sample size.

- Primary Efficacy Analysis

The primary outcome measure will be the percentage of patients who respond or remit after 30 to 35 treatments. We will subdivide patients based on the diagnosis of either bipolar I or bipolar II to compare effectiveness between those groups.

The other primary outcome will be the percentage of patients who meet criteria for onset of manic symptoms based on the YMRS. The patients will also be separated based on their diagnostic category.

- Secondary Efficacy Analysis

We will also look at the HAM-D and CGI to see the percentage of patients meeting response criteria.

For the patients meeting remission criteria, we will calculate the number of treatments required to achieve remission. Patients who only meet response criteria will be treated for 30 to 35 sessions.

Responders and remitters will also be followed for six months after the final treatment to see the durability of response. Percentage of patients' meeting relapse criteria will be calculated.

Informed Consent, Institutional Review Board, DSMB, and Regulatory Considerations

- Informed Consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient (legal representatives will not be allowed for this trial). This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

- Institutional Review Board (IRB)

The investigator will obtain documentation of IRB approval of the protocol and the informed consent. The IRB reviewing these documents is the Sheppard Pratt Institutional Review Board

The investigator will supply the IRB with:

1. Informed consent document.
2. Relevant curricula vitae
3. Patient recruitment materials and advertisements.

- Data Safety Monitoring Board

This committee will be composed of three psychiatrists experienced with the study population and qualified to serve in an advisory capacity in order to

evaluate safety and efficacy of the trial. The safety monitoring board will convene every six months or at other times if deemed necessary by the study investigator.

- Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations.

The protocol will be submitted to clinicaltrials.gov

References

Altshuler, L., Suppes, T., Black, D., Nolen, W. A., Keck, P. E., Jr., Frye, M. A., et al. (2003). Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *American Journal of Psychiatry, 160*, 1252-1262.

Connolly KR1, Helmer A, Cristancho MA, Cristancho P, O'Reardon JP (2012), Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *J Clin Psychiatry* Apr;73(4):567-73. .

.

El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, Thommi SB, Goodwin FK, Ghaemi SN (2015) Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial *J Affect Disord*. 184:318-321.

Goldberg JF, Freeman MP Balon R, Citrome L, Thase ME, Kane JM, Fava M. (2015). The American Society of Clinical Psychopharmacology survey of psychopharmacologists' practice patterns for the treatment of mood disorders. *Depress Anxiety.* 2015 Jun 30. doi: 10.1002/da.22378. [Epub ahead of print]

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology, revised 1976.* Rockville, MD: National Institute of Mental Health, Psychopharmacology Research. pp.217-222, 313-331.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56-61.

Montgomery, S. A. & Asberg, M. A. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 382-389.

Nierenberg AA1, McIntyre RS, Sachs GS (2015) Improving outcomes in patients with bipolar depression: a comprehensive review. .*J Clin Psychiatry*, 76(3):e10. doi: 10.4088/JCP.13091ip1.

Noda Y1, Daskalakis ZJ, Ramos C, Blumberger DM (2013) Repetitive transcranial magnetic stimulation to maintain treatment response to electroconvulsive therapy in depression: a case series. *Front Psychiatry* Jul 23;4:73. doi: 10.3389/fpsyt.2013.00073

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ (2011) The

Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 168: 1266-1277.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB (2003) The16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (**QIDS-SR**): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. Sep 1;54(5):573-83. Erratum in: Biol Psychiatry.2003 Sep 1;54(5): 585

Sachs, G.S., Nierenberg, A.A., Calabrese, J.R., et al. (2007), Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression. *New England Journal of Medicine.* 356(17):1711-1722.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* (1998) 59(Suppl 20):22-33.

Thase, M. E. & Sachs, G. S. (2000). Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biological Psychiatry, 48(6)*, 558-572.

Woźniak-Kwaśniewska A, Szekely D, Harquel S, Bougerol T, David O.(2015) Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: A preliminary comparison between unipolar and bipolar depression. *J Affect Disord*. Sep 1;183:15-21.. Epub 2015 Apr 24.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry, 133*, 429-435.

Appendices

Appendix 1: NeuroStar TMS Therapy® System Prescribing Information

Appendix 2: Analysis of Clinical Database on the Routine Clinical Care of Bipolar Depression with TMS

Appendix 3: Montgomery-Asberg Depression Rating Scale (MADRS)

Appendix 4: Mini International Neuropsychiatric Interview (M.I.N.I.) Version 6.0

Appendix 5: Young Mania Rating Scale (YMRS)

Appendix 6: Clinical Global Impression of Severity of Illness (CGI-S)

Appendix 7: Clinical Global Impression of Improvement (CGI-I)

Appendix 8: Columbia Suicide Severity Rating Scale (C-SSRS)

Appendix 9: 16-item Quick Inventory of Depressive Symptomatology – Self Report (IDS-SR 16)

Appendix 10: 17- item Hamilton Rating Scale for Depression (HAM-D17)

List of Tables