NEUROSTAR®
TMS THERAPY

NeuroStar TMS Therapy® System

USER MANUAL SUPPLEMENT

This supplement provides an overview of NeuroStar TMS Therapy and new clinical data, supporting an expanded indication for use as of March 2014. The information contained here supersedes the “Introduction” and “Summary of Clinical Studies” of the NeuroStar TMS Therapy System User Manual dated prior to April 2014.

NEURONETICS

MAY 2014

52-40030-000 Rev A

NOTICE

This *NeuroStar® TMS Therapy System User Manual* is released by Neuronetics®, Inc., as a guide for the operators and administrators of the NeuroStar TMS Therapy System®. It provides information that is necessary for the safe and effective operation of the System. This manual is to be used in conjunction with the *TMS TrakStar User Manual*.

The contents of this manual, which reflect current Neuronetics standards, are subject to revision or change without notice. Hardware or software packages released after the publication of this manual will be documented in addenda or later versions of this user manual.

For additional information, please contact your Neuronetics service representative.

If you have questions or comments regarding this user manual or other Neuronetics technical documents, contact the Neuronetics Technical Publications Department at: customersupport@neuronetics.com.

Preface

This manual provides operating instructions and guidelines for the use of the Neuronetics NeuroStar TMS Therapy System.

NOTE Federal (U.S.A.) law restricts this device to sale to or on the order of a physician.

Operator Requirements and Training

The NeuroStar TMS Therapy System is used by prescription only under the supervision of a physician. The instructions in this manual assume that the operator has been trained in the proper use of the NeuroStar TMS Therapy System and has the required medical education and experience to operate the device safely and effectively. All operators should complete NeuroStar TMS Therapy System training. If additional training is needed, please contact Neuronetics.

Intended Use and Indication

NeuroStar TMS Therapy® is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

Patents

Equipment and software that comprise the NeuroStar TMS Therapy System are covered by the following U.S. patents with other patents pending:

6,255,815	6,086,525	7,104,947 B2	D571,920 S	7,651,459 B2
6,161,757	6,425,852	7,153,256 B2	7,396,326 B2	7,824,324 B2
5,725,471	6,491,620	7,320,664 B2	7,560,058 B2	7,857,726 B2
6,132,361	6,926,660 B2	7,614,996 B2	7,601,115 B2	6,527,695
7,744,523	7,963,903	D646,393	8,088,058	8,118,722

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Certification

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Alternatively, you can send your questions to the following E-mail address: customersupport@neuronetics.com.

The Neuronetics Web site address is http://www.neuronetics.com

To purchase supplies, accessories, or additional NeuroStar TMS Therapy Systems, call Neuronetics at 877-600-7555.

User Manual Symbols

The NeuroStar TMS Therapy System User Manual includes icons that are designed to draw attention to special types of information provided. These icons are explained below:

Warning: Dangerous Voltage

General Warning

Serious injury or death may result if the operator does not follow the associated instructions.

Caution

The following may result if the operator does not follow the associated instructions:

- System damage
- Non-serious injury
- Inadequate treatment

NOTE Important guidance in using the NeuroStar TMS Therapy System is provided.

Introduction

The NeuroStar TMS Therapy® System (see Figure 1) is a computerized electro-mechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex.

FIGURE 1. NeuroStar TMS Therapy System

NeuroStar TMS Therapy® is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. The NeuroStar TMS Therapy System is available upon the prescription of a licensed physician. It can be used in both inpatient and outpatient settings including physicians' offices, clinics, and hospitals.

"Prescription" means that the attending physician has determined that the NeuroStar TMS Therapy System is indicated for use in a particular patient. In addition to patient selection, the attending physician should oversee initial patient motor threshold determinations, treatment parameter definitions and overall TMS treatment course planning for each patient.

"Supervision" means that the attending physician is medically responsible for coordination of the overall clinical care of a patient for whom NeuroStar TMS Therapy has been considered clinically indicated and for the safe and effective use of the NeuroStar TMS Therapy System. If the attending physician is not performing the daily NeuroStar treatment sessions, then the attending physician should assign properly trained personnel who may perform the daily treatment sessions. The attending physician is medically responsible for the routine evaluation of the patient during the course of their TMS Therapy treatment.

The NeuroStar TMS Therapy System is offered in the following configurations:

- Single mobile console configuration: mobile console, treatment coil, head support system, treatment chair, and TMS TrakStar practice data management system.
- Multiple mobile consoles/TMS TrakStar system configurations to address the needs of facilities with large patient populations.

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 neuronal depolarization and changes in brain functional activity that may be associated with various physiologic changes in the brain associated with symptomatic relief of depression in the indicated population.

Indications

NeuroStar TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

Summary of Clinical Trials

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'Reardon, et al., 2007; Janicak, et al., 2008; George, et al., 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, et al, 2012; Janicak, et al, 2013).

In clinical trials, medication adequacy was determined using the Antidepressant Treatment History Form (ATHF), or similar validated method (Study 19-50001), which identified those medications given at or above the minimal effective dose and duration as defined in the product labeling. Failure of benefit was defined as no more than a minimal clinical response to the antidepressant medication as assessed by the clinician. In cases where patients were untreated or insufficiently treated in the current episode, the medication history from the most recent prior episode was utilized to determine medication adequacy.

A major depressive episode as defined in the DSM-5 implies a prominent and relatively persistent (nearly every day for at least two weeks) depressed or dysphoric mood that represents a change from previous functioning, and includes at least five of the following nine symptoms, one of which is either of the first two symptoms:

- Depressed mood
- Markedly diminished interest or pleasure in usual activities
- Significant change in weight and/or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Slowed thinking or impaired concentration
- Recurrent thoughts of death or suicidal ideation or a suicide attempt.

Additional details on study design and outcomes for the NeuroStar TMS Therapy System clinical trials are provided in the “Summary of Clinical Studies” on page 15 in this user manual supplement.

Randomized Controlled Trials

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 1-4 adequate antidepressant medication trials, as defined using the Antidepressant Treatment History Form (ATHF), or who could not tolerate 3 or more antidepressant medications (George, et al, 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 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'Reardon, et al., 2007; Janicak, et al., 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 1-4 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.

Open Label Trials

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, et al, 2012, Janicak, et al., 2013). The 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 evaluated the durability of acute benefit with NeuroStar TMS Therapy during 12 month follow up in patients maintained on antidepressant medication and/or with periodic TMS reintroduction for symptom worsening (Neuronetics data on file). Overall, 36.2% of patients required re-treatment with TMS over 12 months. Amongst remitters, 29.5% of patients experienced relapse through 12 months.

Contraindications

The NeuroStar TMS Therapy System is contraindicated for use in some situations as identified below and further described in Section 7 of the User Manual. All patients must be screened for the following contraindications.

The NeuroStar TMS Therapy System treatment coil produces strong pulsed magnetic fields which can affect certain implanted devices or objects. The magnetic field strength diminishes quickly with increasing distance from the coil. Within 30 cm of the face of the treatment coil, the peak magnetic field can be greater than 5 Gauss, which is the recommended static magnetic field exclusion level for many electronic devices.

Metallic Objects in or near the Head

The NeuroStar TMS Therapy System is ***contraindicated*** for use in patients who have conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death.

NOTE Removable objects that may be affected by the magnetic field should be removed from the patient before treatment to prevent possible injury. (Examples include jewelry and hair barrettes). Once these objects are removed, NeuroStar TMS Therapy is not contraindicated for these patients.

NOTE Examples of metallic objects in or near the head that are ***acceptable*** under certain conditions include standard amalgam dental fillings, single post dental implants, and dental bridge work. The conditions for TMS treatment when these objects are present are clarified in Section 7 of the User Manual.

Implanted Stimulator Devices in or near the Head

The NeuroStar TMS Therapy System is ***contraindicated*** for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death.

Warnings

All operators must consider the following warnings before proceeding to treatment.

NeuroStar TMS Therapy has not been evaluated in patients with psychoses or with psychiatric emergencies where a rapid clinical response is needed, such as marked physical deterioration, catatonia, or immediate suicide risk. Use of NeuroStar TMS Therapy in the treatment of these patients is not recommended since rapid onset of effect in these high-risk populations has not been established.

Following acute treatment with NeuroStar TMS Therapy, patients will need to be monitored and may need to resume antidepressant medications. This device has not been evaluated for durability of antidepressant effect in controlled clinical trials.

Worsening Depression or Suicidality

Patients who have Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are being treated with an antidepressant, and this risk may persist until significant remission of symptoms occurs.

Observe patients undergoing treatment for Major Depressive Disorder closely for worsening symptoms and signs of suicidal behavior and/or unusual behavior. If worsening of symptoms continues, consideration should be given to changing the therapeutic regimen, including discontinuation of treatment with the NeuroStar TMS Therapy System. Families and caregivers should also observe patients and notify the treatment provider if symptoms worsen.

Effects on Medical Devices Containing Electronics or Ferromagnetic Material

The NeuroStar TMS Therapy System should be used only with caution in the situations identified below. All patients must be screened for the conditions noted and appropriate cautionary measures should be taken.

Implants Controlled by Physiologic Signals

The NeuroStar TMS Therapy System should be used with caution in patients who have an implanted device that is activated or controlled in any way by physiologic signals, even if the device is located outside the 30 cm distance. This includes patients with pacemakers and implantable cardioverter defibrillators (ICDs) or patients using wearable cardioverter defibrillators (WCDs) even if the device is removed due to the potentially unstable cardiac condition of such patients. Failure to follow this restriction could result in serious injury or death.

Implants Not Controlled by Physiologic Signals

Patients who have implanted devices or metallic objects located in areas outside the 30 cm distance from the treatment coil may receive NeuroStar TMS Therapy. However, care must be taken by the NeuroStar TMS Therapy System operator to ensure that the treatment coil is never placed within 30 cm of these implants. Otherwise, serious injury could result. (Examples of these devices include staples and implanted insulin pumps.)

Wearable or Removable Devices or Objects

If patients have removable devices or objects that may be affected by the magnetic field, the device(s) should be removed from the patient area before treatment to prevent possible injury to the wearer or damage to the device. (Examples include wearable monitors, bone growth stimulators, earrings, hearing aids, eyeglasses, jewelry, hair barrettes, cell phones, MP3 players, etc.)

Use Near Magnetic Resonance Imaging (MRI) Devices

Keep the NeuroStar TMS Therapy System mobile console outside of MRI-restricted access areas due to possible interaction with the MRI magnetic field.

Metallic Object and Implant Checklist

NOTE

Prior to treatment, each patient should be screened for the presence of metallic objects or implants that could affect the safe use of the NeuroStar TMS Therapy System. A list of items for which all patients should be screened is provided in Section 7 of the User Manual.

This list summarizes compatibility requirements for devices and conductive objects in the vicinity of the NeuroStar TMS Therapy System treatment coil and provides guidance for whether the device is contraindicated for use or may be used if specific precautionary measures are taken.

Clinical Warnings

All operators must consider the following clinical warnings before proceeding with patient treatment.

Risk of Seizure

Generalized seizures have been reported with the use of TMS in the clinical trial literature. No seizures were reported with use of the NeuroStar TMS Therapy System in over 10,000 treatment sessions in trials conducted prior to FDA clearance of the NeuroStar TMS Therapy System. Since the introduction of the NeuroStar TMS Therapy System into clinical practice, seizures have been rarely reported. The estimated risk of seizure under ordinary clinical use is approximately 1 in 30,000 treatments (0.003% of treatments) or 1 in 1000 patients (0.1% of patients). Nevertheless, the NeuroStar TMS Therapy System should be used with caution in patients who have a history of seizures, or a potential for alteration in seizure threshold, as stated below.

In order to reduce the potential risk of seizure, observe the published 1998 National Institute of Neurological Disorders and Stroke (NINDS) Workshop report guidelines (“Summary of Clinical Studies” on page 15 in this user

manual supplement). Treatment with stimulation parameters that lie outside of these guidelines is not recommended.

TMS should be applied to the left dorsolateral prefrontal cortex using the coil placement methods described in the User Manual. Failure to follow these procedures may increase the risk of seizure.

Be alert for signs of an imminent seizure and terminate the treatment session if those signs appear. If a medication that may alter seizure threshold has been taken since the last treatment session, the motor threshold determination should be repeated prior to the next treatment session. Patients at potential increased risk of seizure include those who have:

- History (or family history) of seizure or epilepsy
- History of stroke, head injury, severe headaches, or unexplained seizures
- Presence of other neurological disease that may be associated with an altered seizure threshold (such as CVA, cerebral aneurysm, dementia, increased intracranial pressure, head trauma, or movement disorder)
- Concurrent medication use such as tricyclic antidepressants, neuroleptic medications, or other drugs that are known to lower the seizure threshold
- Secondary conditions that may significantly alter electrolyte balance or lower seizure threshold
- No quantifiable motor threshold such that TMS dosage cannot be accurately determined.

Cautions

All operators must consider the following cautions before proceeding with patient treatment:

- The acute effectiveness of NeuroStar TMS Therapy has not been established beyond a six-week treatment course for MDD.
- NeuroStar TMS Therapy has not been studied as an adjunct to antidepressant treatment in controlled trials; it has been administered safely in the presence of antidepressant medication.

The patient and the operator of the NeuroStar TMS Therapy System must always wear earplugs or similar hearing protection devices with a rating of 30 dB of noise reduction during treatment. When used with appropriate hearing protection, NeuroStar TMS Therapy did not have an effect on auditory threshold.

Longer term effects of exposure to the NeuroStar TMS Therapy System magnetic field are not known. Experimental and observational evidence indicates that exposure to the type of magnetic fields produced by the NeuroStar TMS Therapy System coil does not present any significant risk of acute or long-term adverse effects.

Patients should be monitored for seizures, and seizure management procedures should be available.

Special Populations

The safety and effectiveness of NeuroStar TMS Therapy has not been established in the following patient populations or clinical conditions through a controlled clinical trial.

- Patients who have had no prior antidepressant medication failure.

- Patients who have a suicide plan or have recently attempted suicide.
- Patients with seasonal affective disorder.
- Patients younger than 22 years of age or older than 70 years of age.
- Patients with a history of substance abuse, obsessive compulsive disorder, or post-traumatic stress disorder.
- Patients with a psychotic disorder, including schizoaffective disorder, bipolar disease, or major depression with psychotic features.
- Patients with neurological conditions that include a history of seizures, cerebrovascular disease, dementia, movement disorders, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the CNS.
- Patients with metal in or around the head, including metal plates, aneurysm coils, cochlear implants, ocular implants, deep brain stimulation devices and stents.
- Patients with vagus nerve stimulators or implants controlled by physiologic signals, including pacemakers, and implantable cardioverter defibrillators.
- Patients with major depressive disorder who have failed to receive clinical benefit from ECT* or VNS.
- Patients who are pregnant or nursing.

* *NeuroStar TMS Therapy has not been demonstrated to be equivalent in efficacy to ECT for the treatment of major depressive disorder*

Procedural Warnings and Precautions

This section lists the warnings and cautions associated with the operation of the NeuroStar TMS Therapy System.

Risk of explosion. Do NOT use the NeuroStar TMS Therapy System in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

Risk of electrical shock. Do NOT use the NeuroStar TMS Therapy System in or near water or other liquids, or place liquids on or near the mobile console or any of the cables or the coil.

Risk of electrical shock. Do NOT open the panels of the NeuroStar TMS Therapy System mobile console. There are no operator-serviceable parts in the system. If the system malfunctions, call your local representative for assistance.

Do NOT place the NeuroStar TMS Therapy System near other medical equipment during operation. The effects of the NeuroStar TMS Therapy System on other equipment are unknown and could result in serious injury or death.

Discontinue treatment with the NeuroStar TMS Therapy System in any patient who has a continued significant adverse reaction or discomfort during or immediately after use. (Temporary mild discomfort at the site of stimulation is normal during and/or shortly after treatment.)

If the treatment coil temperature warning message is displayed on the touchscreen, the patient's scalp is in contact with a surface that may exceed 41° C. Clinical judgement should be used to determine whether or not treatment should continue for a patient with impaired ability to sense heat/pain. Patients who may be at increased risk of thermal injury include patients with:

- Diabetes mellitus
- History of stroke
- Under the influence of alcohol
- Current use of any sleep medication.

To avoid injury and equipment or property damage, always install the gantry block in front of the gantry base when the mobile console needs to be moved from one location to another.

Risk of chair tip-over. The NeuroStar treatment chair may tip over if excessive weight is applied to either the back support or the leg support when they are positioned near their horizontal positions. To avoid tip-over, make sure the patient is properly seated against the back support before elevating the leg support. Do not sit or stand on the foot rest.

Risk of pinching. Do NOT place fingers near the mechanisms under the treatment chair when it is being operated; injury could result. Observe the yellow warning triangles located in hazardous areas.

A 10-minute interval between patient treatment sessions is required to guarantee that the coil operates within temperature specifications. Failure to observe the 10-minute interval between treatment sessions could result in an unexpected system shutdown.

Operate the NeuroStar TMS Therapy System only with parts and components provided and/or recommended by Neuronetics, Inc. The performance of the NeuroStar TMS Therapy System cannot be guaranteed if other parts or components are used. Use of other parts may void the warranty.

Do not place computer discs, audio recording tapes, credit cards, hotel room keys, or electronic automotive ignition keys on or near the coil while operating. The NeuroStar TMS Therapy System produces time-varying magnetic fields that may affect the integrity of data stored on these types of magnetic media if placed near an operating coil.

Class 1 Laser Caution – Use of controls or adjustments or performance of procedures other than those specified herein may result in hazardous radiation exposure.

A Class 1 laser is incorporated into the A/P bar to assist in patient positioning. Although the laser meets internationally accepted standards to be "safe to eye and skin under all reasonably foreseeable conditions of operation," it is prudent to avoid prolonged or unnecessary exposure of the eye to the laser.

Operation of the NeuroStar TMS Therapy System requires special precautions regarding electromagnetic compatibility (EMC). The system needs to be installed and put into service according to the following EMC information:

- Portable and mobile radio frequency communications equipment can affect the operation of the NeuroStar TMS Therapy System.
- Use of a power cord other than the one provided may result in increased emissions or decreased EMC immunity of the NeuroStar TMS Therapy System.

Do not use the NeuroStar TMS Therapy System adjacent to or stacked with non-medical equipment. If adjacent or stacked use is necessary, observe the NeuroStar TMS Therapy System to verify that it is operating normally.

For more information on the electromagnetic compatibility of the NeuroStar TMS Therapy System, see “Electromagnetic Compatibility” appendix in the User Manual.

Adverse Events

There were no deaths or seizures reported in the NeuroStar TMS Therapy System controlled clinical trials.

The most common adverse events reported were application site pain and headache. Application site pain was the most frequently reported device-related adverse event with greater frequency in the active TMS treatment group as compared to sham TMS. Headache was reported by about half of patients and nearly equally in both active TMS and sham TMS treatment groups. In general, application site pain and headache were transient and dissipated rapidly with time. These adverse events were graded as mild to moderate in severity for the majority of patients.

For more details, see “Summary of Clinical Studies” on page 15 in this user manual supplement.

Medical Event Reporting

All events should be reported to your local representative:

- Any medical event that the prescribing physician considers to be related to the NeuroStar TMS System.
- Additionally, report any of the following events of special interest, even if unrelated to NeuroStar TMS System:
  - — A patient experiences a seizure
  - — A patient being treated or was recently treated reports a pregnancy
  - — A patient experiences significant worsening of illness resulting in hospitalization during treatment course
  - — A patient with an implantable medical device receives TMS Therapy

Cognitive Function and Auditory Threshold

There was no evidence of cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the NeuroStar TMS Therapy System.

There was no evidence of auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the NeuroStar TMS Therapy System (with use of 30 dB hearing protection during TMS treatment).

Operator Qualifications

The NeuroStar TMS Therapy System is used by prescription only by or under the supervision of a licensed physician trained in the use of the NeuroStar TMS Therapy System.

The physician or operator should provide the patient with the "NeuroStar TMS Therapy Patient Guide for Treating Depression," prior to treatment, to allow each patient sufficient time to review the information about the device and the procedure and discuss this information with his/her physician and family.

It is recommended that the NeuroStar TMS Therapy System operator be a clinical professional who is conducting TMS Therapy under the supervision of a physician. The NeuroStar TMS Therapy System operator should possess, in the opinion of the physician, sufficient clinical expertise to monitor the patient during the conduct of a TMS treatment session.

The operator must be able to observe the patient's physical status for the potential occurrence of adverse events, and make routine adjustments as required and consistent with product labeling, or determine circumstances under which treatment interruption or treatment termination should be considered. The NeuroStar TMS Therapy System operator should be present in the treatment room with the patient at all times.

The operator must be qualified to monitor the patient for seizure activity and to provide seizure management care.

General System Description

The NeuroStar TMS Therapy System consists of the following equipment and software. (See Section 2.2 of the User Manual for complete descriptions.)

- Mobile Console (includes processor module, power module, mast, gantry, halo, and display arm)
- System Software
- TMS TrakStar Practice Data Management System software
- Treatment Coil
- Head Support System (includes laser positioning aid and coil positioning guide)
- Treatment Chair
- Positioning Cushions (to enhance the comfort and positioning of the patient in the required posture for the duration of the treatment session)

Supplies and Disposables Overview

The NeuroStar TMS Therapy System requires the following single-use supplies and disposables for each treatment session. (See Section 2.4 of the User Manual.)

- Head cushion liner
- Head side pad liner
- Head positioning straps
- Side pad
- Earplugs
- SenStar Treatment Link (a single-use medical device)

Connection to Other Equipment

If connection of the NeuroStar TMS Therapy System to any other systems or equipment is planned, be sure to observe the following precaution.

Additional equipment connected to medical electrical equipment must comply with the respective IEC or ISO standards (e.g., IEC 60950 for data processing equipment). Furthermore, all configurations shall comply with these requirements for medical electrical systems (IEC 60601-1-1 or clause 16 of the 3 Ed. of IEC 60601-1, respectively). Anyone who connects additional equipment to existing medical electrical equipment by definition has configured a medical system and is responsible that the system complies with the requirements for medical electrical systems. Local laws may take priority over these requirements. If in doubt, contact your local representative.

Protected Health Information

Patient data is securely stored. Access to the system is controlled by operator name/password combinations. Password entry is unreadable on the display screen. Patient identification information is kept confidential and is accessible only to authorized system users. The system maintains patient records through unique identifiers.

TMS TrakStar operates on a separate personal computer, and the data that is transferred is protected by a wireless encryption program to maintain the confidentiality of patient data.

Access to the NeuroStar TMS Therapy System and to the TMS TrakStar program requires a unique operator ID/password combination.

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Summary of Clinical Studies

Study Results

The NeuroStar TMS System is indicated for the treatment of major depressive disorder (MDD) in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

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 antidepressant medication was established in two randomized controlled trials (George, et al, 2010; O'Reardon, et al., 2007; Janicak, et al., 2008).

Post-market Study 19-50001 evaluated the efficacy of NeuroStar TMS Therapy in adult patients with major depression (N=307) in a naturalistic, observational multisite trial in 42 US centers (Carpenter, et al, 2012; Janicak, et al, 2013) under conditions of general use.

Study Results: Evidence of Efficacy in the Treatment of Major Depressive Disorder [NIMH-funded Independent Study]

A company-independent, NIMH-funded randomized controlled trial utilized a clinical trial version of the NeuroStar TMS Therapy System to evaluate the safety and efficacy of TMS in adult patients (N=197) with moderate to severe major depressive disorder and who failed to benefit from 1-4 adequate antidepressant medication trials as defined using the Antidepressant Treatment History Form (ATHF). The ATHF is an instrument designed to assess adequacy of medication trials for major depression.

After determination of protocol eligibility and medication washout, patients participated in a multi-site, parallel group, double-blind, sham-controlled, randomized comparison of active TMS and sham treatment for a fixed trial period of 3 weeks. At the end of this period, patients who showed a criterion level of improvement were eligible to continue with their blinded randomized assignment for up to 3 additional weeks in a duration adaptive manner based on twice weekly determinations of clinical progress.

Treatment was according to the standard treatment protocol used for the NeuroStar TMS Therapy System for major depression standardized at 120% magnetic field intensity relative to the patient's resting Motor Threshold (MT), at 10 pulses per second for 4 seconds on time, with an off time of 26 seconds. During the first week of the acute phase only, treatment intensity could be reduced to 110% for tolerability but then had to return to 120% from week 2 onward. Treatment sessions lasted for 37.5 minutes (75 trains) for a total of 3000 pulses each session. During the 3-week fixed-treatment phase and in the 3-week blinded duration adaptive phase, TMS sessions were scheduled daily in a 5-day sequence, typically Monday through Friday, for a total of 15-30 sessions. MT was determined weekly using electromyographic measurement or visual monitoring of the resting right thumb (abductor pollicis brevis [APB]). The scalp spatial coordinates of the MT and treatment positions were recorded using the device's mechanical coil positioning system, allowing reliable repositioning.

Demographic and clinical features of the enrolled population were not statistically significantly different between the active TMS and sham TMS treatment groups. Roughly half of the population was female and the average age was 47 years. Patients had moderate to severe major depression by symptom measures. Current episode treatment resistance averaged 1.6 failed research-quality adequate treatment trials (verified by ATHF criteria), which translates approximately to 3 to 6 clinical antidepressant medication attempts in the current episode. During their lifetime, patients had failed 3.3 research-adequate treatment trials (approximately 9 clinical attempts) (Table 1).

TABLE 1. RCT: Demographic and Clinical Characteristics at Study Enrollment (N=197, ITT)

Demographic variables	Sham (N=100)	TMS (N=97)	P-value	Total (N=197)
Females (N (%))	52 (52.0)	61 (62.9)	0.1224	113 (57.4)
Age (years, mean ± SD)	46.5 (12.2)	47.0 (10.9)	0.7399	46.7 (11.6)
Age range (years)	23-69	21-69	—	21-69
Current episode duration (weeks, mean ± SD)	80.9 (65.3)	72.9 (64.0)	0.3839	77.0 (64.6)
Range (weeks)	3-260	8-280	—	3-280
Antidepressant treatment history				
Number of antidepressant treatment failures in current illness episode by ATHF (mean ± SD)	1.4 (1.0)	1.6 (1.4)	0.2143	1.5 (1.2)
Range	0-4	0-6	—	0-6
Lifetime number of antidepressant treatment failures by ATHF (mean ± SD)	3.3 (2.1)	3.4 (2.7)	0.9205	3.3 (2.4)
Range	0-9	0-14	—	0-14
Low antidepressant resistance by ATHF (N (%))	70 (70.0)	57 (58.8)	0.0995	127 (64.5)
High antidepressant resistance by ATHF (N (%))	30 (30.0)	40 (41.2)	—	70 (35.5)
Baseline symptoms scores				
HAMD24 (mean ± SD)	26.6 (4.9)	26.4 (4.9)	0.7425	26.5 (4.9)
Range	20-42	20-43	—	20-43
MADRS (mean ± SD)	29.9 (6.4)	29.6 (6.8)	0.7266	29.8 (6.6)
Range	12-44	12-44	—	12-44
IDS-SR (mean ± SD)	40.5 (10.1)	41.1 (9.1)	0.6713	40.7 (9.6)
Range	18-65	24-63	—	18-65
CGI-S (mean ± SD)	4.6 (0.7)	4.6 (0.7)	0.9319	4.6 (0.7)
Range	3-7	3-6	—	3-7

The primary outcome measure was the clinically significant categorical outcome of *remission*, defined as HAMD24 ≤ 3 or 2 consecutive HAMD24<10 through 6 weeks of treatment according to a pre-specified duration adaptive design. There was a statistically significant effect of active TMS on remission rate as compared to sham control (P=0.0173) in the ITT sample (N=197). There were 13.4% remitters in the TMS arm and 5.0% in the sham arm; the adjusted odds ratio was 4.05 (95% confidence interval (CI), 1.28-12.83) (Table 2). Remission occurred as early as week 3, with most patients achieving remission across weeks 4-5 (George, et al, 2010).

TABLE 2. RCT: Primary Outcome (N=197, ITT)

Measure HAMD24	Active TMS N=97	Sham TMS N=100	P-Value (Favoring Active TMS)	Adjusted odds ratio (95% CI)[1]
Remission	13.4%	5.0%	0.0173	4.05 (1.28-12.83)

[1] Odds ratios were adjusted for site (categorical), age (continuous), duration of current depressive episode, and medication resistance (low vs. high).

A pre-specified analysis of treatment resistance as a covariate with outcome was not statistically significant in the primary analysis logistic regression model thereby establishing efficacy across the ATHF 1-4 study population.

The baseline to endpoint change score outcome using the HAMD24 favored active TMS to sham treatment (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).

The results for these continuous outcome measures are shown in Table 3 with 95% confidence intervals for the treatment difference, and estimates of the standardized effect size. Standard effect sizes range from 0.43 to 0.67 indicating a moderate to large treatment effect for TMS in this study.

TABLE 3. RCT: Continuous Outcomes Measures (N=197, ITT)

Outcome Measure	Treatment Group	Baseline		End of Acute Phase		Treatment Effect (95% CI)	Standardized Effect Size	P-Value
		Mean (SD)	N	Mean (SD)	N			
HAMD24	Active	26.4 (4.9)	97	21.8 (9.2)	85	–2.11 (–4.30, 0.08)	–0.43	0.0588
HAMD24	Sham	26.4 (4.9)	100	23.5 (7.4)	93			
MADRS	Active	29.6 (6.9)	97	24.8 (11.5)	85	–3.41 (–6.12, –0.71)	–0.51	0.0136
MADRS	Sham	29.9 (6.5)	100	27.9 (9.0)	93			

Outcome Measure	Treatment Group	Baseline		End of Acute Phase		Treatment Effect (95% CI)	Standard-ized Effect Size	P-Value
		Mean (SD)	N	Mean (SD)	N			
CGI-S	Active	4.6 (0.7)	95	4.0 (1.2)	84	–0.36 (–0.65, –0.06)	–0.52	0.0181
CGI-S	Sham	4.6 (0.7)	100	4.3 (0.9)	92			
IDS-SR	Active	41.1 (9.1)	91	32.7 (15.3)	80	–6.46 (–10.19, –2.74)	–0.67	0.0008
IDS-SR	Sham	40.5 (10.1)	96	37.1 (14.0)	90			

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). The results for these categorical outcome measures are shown in Table 4.

TABLE 4. RCT: Categorical Secondary Outcome Measures (N=197, ITT)

Outcome Measure	Sham (N=100)	NeuroStar TMS (N=97)	Between-groups differences (P-Value)	Odds Ratio (95% CI)[1]
MADRS Remission	5.0%	12.4%	0.0170	4.19 (1.29, 13.60)
IDS-SR Remission	7.0%	12.4%	0.1199	2.23 (0.81, 6.10)
HAMD24 Response	5.0%	14.4%	0.0104	4.44 (1.42, 13.90)
MADRS Response	6.0%	15.5%	0.0063	4.48 (1.53, 13.14)
IDS-SR Response	8.0%	16.5%	0.0145	3.40 (1.28, 9.05)

[1] Odds ratios were adjusted for site (categorical), age (continuous), duration of current depressive episode, and medication resistance (low vs. high).

Study Results: Evidence of Efficacy in the Treatment of Major Depressive Disorder [Study 101]

Study 101 was a randomized sham-controlled clinical trial (RCT) designed to evaluate the safety and efficacy of the NeuroStar TMS Therapy System for the treatment of patients with MDD (N=301) who have failed to receive benefit from 1 to 4 prior antidepressant medications verified by the ATHF. Patients meeting ATHF 1 criteria comprised the majority of the overall study population (N=164, 54.5% of the total study population).

The primary efficacy measure, the Montgomery Asberg Depression Rating Scale (MADRS) at 4 weeks, favored the NeuroStar TMS Therapy System over sham treatment in the overall patient population (ATHF 1-4, MADRS, P = 0.057). A subgroup analysis of the original dataset according to the number of antidepressant medications to

which the patient had failed to respond, indicated that the device was safe and effective and showed a statistically significant benefit for NeuroStar TMS Therapy over sham treatment for the ATHF 1 subgroup (MADRS, P = 0.0006, Table 5). As shown, for the primary outcome measure, treatment with active NeuroStar TMS Therapy resulted in a greater than three-fold improvement in symptoms as compared to sham treatment.

TABLE 5. Study 101 RCT: Primary Outcome Measure (mITT, ATHF 1 Population, N=164)

Primary Outcome Measure	Week 4 Change from Baseline[1,2] (±SEM)		Mean Difference (±SEM) Between Treatment Groups
	NeuroStar TMS (N=88)	Sham TMS (N=76)	
Montgomery-Asberg Depression Rating Scale (MADRS) Total Score	–7.1 (1.0)	–2.1 (1.2)	–5.0 (1.4)

1. The average baseline score was active TMS = 32 points and sham (placebo) treatment = 33 points.
2. LS means for the change from baseline (SEM) and the differences of LS means (SEM) are derived using the following ANCOVA model: Change from baseline = Baseline score, center, and treatment.

Secondary efficacy outcome evaluations pre-specified in Study 101 for the overall patient population were further evaluated for the ATHF 1 population. These included clinician and patient-rated efficacy outcomes utilizing depression rating scales, global wellness scales, and quality of life assessments. Table 6 summarizes the categorical outcomes by proportion of patients who met criteria for response (i.e., percentage of patients achieving a 50% or greater reduction in total score from baseline) or remission (i.e., full resolution of depressive symptoms, MADRS total score < 10, HAMD24 score < 11 or HAMD17 < 8, respectively).

TABLE 6. Study 101 Secondary Outcome Measures (Categorical Variables) for ATHF 1 Population: Response and Remission Rates for NeuroStar TMS Therapy and Sham Treatment at Week 4 and Week 6[1]

Secondary Outcome Measures (Categorical Variables)	NeuroStar TMS (N=88)		Sham TMS (N=76)	
	Week 4	Week 6	Week 4	Week 6
Response Rates (%)				
- MADRS	20.5%	25.0%	9.2%	9.2%
- HAMD24	21.6%	25.0%	9.2%	13.2%
- HAMD17	25.0%	27.3%	10.5%	10.5%
Remission Rates (%)				
- MADRS	8.0%	15.9%	5.3%	5.3%
- HAMD24	10.2%	17.0%	6.6%	6.6%
- HAMD17	9.1%	14.8%	5.3%	7.9%

1. Percentage response or remission at the week 4 and week 6 time points is presented in a last observation carried forward (LOCF) analysis and shows the number of patients meeting the stated categorical outcome criterion at that time point as a percentage of the total enrolled sample for each treatment group (N=88 active TMS, N=76 sham TMS)

NOTES:

MADRS = Montgomery-Asberg Depression Rating Scale; HAMD = Hamilton Depression Rating Scale

Response = ≥ 50% improvement at endpoint compared to baseline score.

Remission = MADRS total score of < 10, a HAMD24 total score of < 11, or a HAMD17 total score of < 8 at endpoint

Study Results: Evidence of Post-Market Efficacy in the Treatment of Major Depressive Disorder [Study 19-50001]

Study 19-50001 evaluated 307 patients with a primary clinical diagnosis of unipolar, non-psychotic MDD who were determined by their physician to be an appropriate candidate for NeuroStar TMS Therapy.

The enrolled patient population was similar in demographic and clinical characteristics to those studied in the OPT-TMS and Study 101 randomized controlled trials. The mean number of antidepressant medication exposures of adequate dose and duration (verified by the Antidepressant Treatment Record [ATR]) in the current episode was 2.5 (SD = ± 2.4) with a range of 0-14.

There was a statistically significant improvement from baseline in CGI-S total score (CGI-S, −1.9 ± 1.4, $P < 0.0001$, 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 evaluated the durability of acute benefit with NeuroStar TMS Therapy during 12 month follow-up in patients maintained on antidepressant medication and/or with periodic TMS reintroduction for symptom worsening (Neuronetics, data on file). Compared with baseline scores obtained prior to acute treatment, there was a statistically significant reduction in mean [SD] CGI-S, PHQ-9 and IDS-SR total scores at the end of acute treatment (Baseline vs. End of Acute Treatment: 5.0 [0.9] vs. 3.0 [1.4], 18.0 [5.3] vs. 8.8 [6.7], and 44.9 [11.1] vs. 25.7 [15.5] respectively, all $P < 0.0001$), which was sustained throughout the one year follow-up (End of 12 Months Follow-Up: 2.8 [1.5], 8.6 [6.9], and 25.6 [15.8] respectively, all $P < 0.0001$). The proportion of patients who achieved remission at the conclusion of acute treatment remained similar to that observed following the conclusion of the long-term follow-up phase: CGI-S (total score 1 or 2), 41.2% (end of acute) and 45.1% (end of long-term); PHQ-9 (total score < 5), 31.1% (end of acute) and 37.0% (end of long-term); IDS-SR (total score < 15), 29.7% (end of acute) and 29.3% (end of long-term).

A total of 120 (46.5%) patients met IDS-SR responder or remitter criteria at entry into long-term follow-up, and among these, 75 (62.5%) met criteria for sustained response by IDS-SR criteria at every time point throughout the 12 month follow-up period. In a separate analysis, the proportion of patients who achieved remission (QIDS-SR < 6) and subsequently experienced illness relapse (QIDS-SR score > 11) at any point during long term follow-up was 29.5% (N=23 patients). Following completion of tapering of acute treatment with NeuroStar TMS Therapy, 93 of the 257 patients in long term follow-up (36.2% of all patients) subsequently received reintroduction of TMS based on clinician decision for clinical worsening. In this group, the mean [SD] number of TMS treatment days was 16.2 [21.1] over the period of long term follow-up.

Clinical Studies – Summary of Safety

Safety data obtained from Study 101 during acute treatment through 6 months of follow-up forms the basis of evidence for the safety of the NeuroStar TMS System in the acute treatment of patients with MDD (Janicak, et al., 2008). This includes safety data from Study 102 (Avery, et al., 2009), an open-label acute efficacy study for Study 101 non-responders and Study 103 (Janicak, et al., 2010), a 6-month maintenance of effect study for responders in Study 101 and Study 102. In Study 101, 323 patients were randomized to a treatment condition and received at least one of their assigned treatment sessions and therefore comprised the overall human safety exposure population. Safety data from Studies 102 and 103 and the independent NIMH-funded RCT (George, et al., 2010) were consistent with the results obtained in Study 101 in all safety outcomes.

Active TMS Treatment Session Exposures

10,096 active TMS treatment sessions were conducted in the overall safety exposure study population. The average (SD) number of sessions for patients in Study 101 acute treatment (to week 6) was 26.3 (13.0) sessions. In Study 102, the open-label study for Study 101 non-responders, TMS treatment was provided for an additional 6 weeks, with the average (SD) number of sessions being 54.4 (10.8) for patients who received active TMS exposure across Studies 101 and 102.

Serious Adverse Events (All Studies)

A listing of serious adverse events observed in the overall safety exposure study population across all studies is shown in Table 7. As is seen in Table 7, in Study 102, the type and incidence of serious adverse events was consistent with those reported for Study 101 with the exception of a single serious adverse event of facial numbness that occurred during open-label TMS treatment and fully resolved following discontinuation of treatment. Serious adverse events in Study 103 were also consistent with the two prior studies. Note that serious adverse events in Study 103 also reflect the concurrent exposure of all patients in the study to antidepressant pharmacologic monotherapy according to protocol criteria.

TABLE 7. Serious Adverse Events Across All NeuroStar TMS Therapy System Clinical Studies (Studies 101, 102 and 103)

Serious Adverse Event	Study 101			Study 102	Study 103	Relationship of Adverse Event to TMS Device
	Prior to Randomization (Lead-In Phase)	Sham TMS	Active TMS	Open-Label Active TMS	Open-Label Adjunctive Active TMS	
Worsening depression only	3	2	0	1	0	Not related
Suicidal ideation only	1	2	2	1	0	Not related
Worsening depression and suicidal ideation	1	0	0	2	1	Not related
Operator error (exceeded maximum specified treatment duration)	0	0	5	4	1	Not related
Device malfunction/first degree burn	0	0	2	0	0	Probably related
Suicide attempt	0	1	0	0	0	Not related
Device malfunction/severe pain at treatment site	0	0	1	0	0	Probably related
Lower lobe pneumonia	0	1	0	0	0	Not related
Bowel obstruction	0	1	0	0	0	Not related
Shortness of breath and increased heart rate	1	0	0	0	0	Not related
Left-sided facial numbness	0	0	0	1	0	Probably related
Tinnitus	0	0	0	1	0	Probably not related
Atrial fibrillation	0	0	0	2	1	Not related
Coronary artery disease (catheterization and stent placement)	0	0	0	0	1	Not related
Bladder tumor (surgical removal)	0	0	0	0	1	Not related
Hip pain	0	0	0	0	1	Not related

Common Adverse Events and Study Discontinuations

Common Adverse Events [Study 101 Controlled Trial Data]

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 Study 101 are shown in Table 8, 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.

TABLE 8. Adverse Events with an Incidence in Active TMS at a Rate of > 5% and at Least 2x Sham in the Safety Exposure Study Population in Study 101

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)

All-Cause Discontinuation and Discontinuation Due to Adverse Events [Study 101]

Adherence to the study protocol in Study 101 through the primary efficacy time point (Week 4) was excellent. The all-cause discontinuation rate was low and was similar in the active TMS (7.7%) and sham TMS (8.2%) treatment groups. Discontinuation due to adverse events was also uncommon and similar across treatment conditions (4.5% in active TMS vs. 3.4% in sham TMS patients).

Time Course of Common Adverse Events During Acute Treatment

The most common adverse events reported in the study population were headache and application site pain. Headache was reported at nearly equal frequencies in both active TMS and sham TMS treatment groups, 58.2% and 55.1%, respectively. Application site pain was reported with greater frequency in the active TMS treatment group compared to sham TMS, 35.8% and 3.8%, respectively. Unblinding due to treatment related adverse events, such as application site pain, was a concern in this study. Sensitivity analyses for this concern were not conclusive.

In general, these adverse events were transient and dissipated rapidly with time (see Figure 2 and Figure 3 for a summary of the time course of these events in Study 101). Investigator clinical assessment of these adverse events was graded as mild to moderate in severity for the majority of patients.

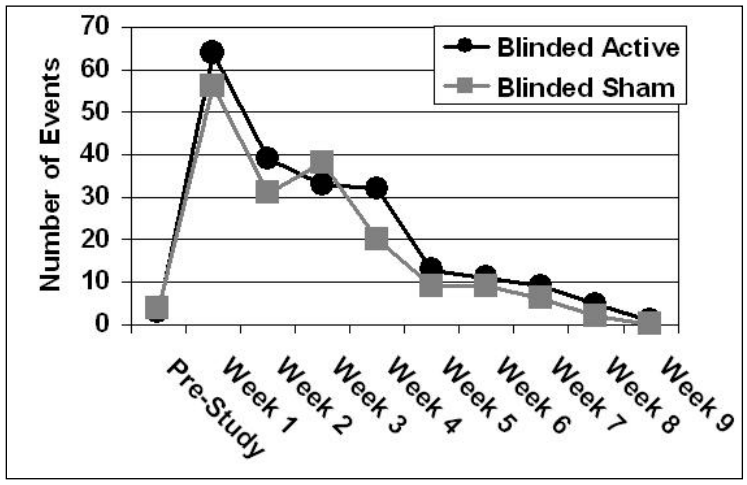

FIGURE 2. Time Course of Headache [Study 101]

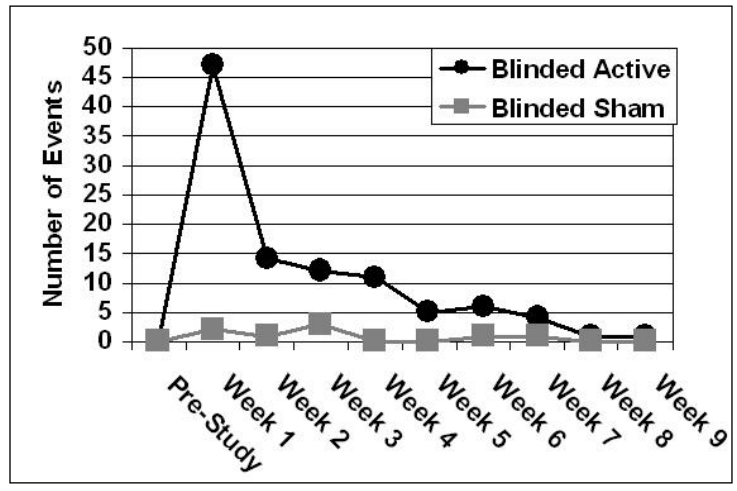

FIGURE 3. Time Course of Application Site Pain [Study 101]

Concomitant Medication Use [Study 101 Taper Phase and Study 103]

In Study 101, patients were entered into a TMS taper phase at the end of 6 weeks. During this taper phase study period, patients were transitioned onto a monotherapy antidepressant medication as they were simultaneously tapered from NeuroStar TMS treatment (3 treatments during week 7, 2 treatments during week 8, 1 treatment during week 9). In addition, thirty-five patients in the ATHF 1 study population from Study 101 were enrolled into Study 103, an open-label study, during which they were continued on open-label medication antidepressant that was received during the Study 101 taper phase. Patients were followed for up to 24 weeks. There were no unanticipated adverse events.

Cognitive Function Testing

Cognitive function was assessed by standardized testing at baseline, Week 4 and Week 6 of the acute treatment phase for the blinded and open-label studies and at the end of treatment for the maintenance of effect study. These assessments surveyed general cognitive function (Mini Mental Status Exam), short term and delayed recall (Buschke Selective Reminding Test) and long-term retrieval (Autobiographical Memory Interview). No adverse effects on cognitive function were observed.

Audiometry Testing

No differences in air conduction thresholds were detected between treatment groups or within treatment groups, evaluated using the Earscan™ device (Micro Audiometrics, Inc., Murphy, NC) at baseline, Week 4, and Week 6 of the acute treatment phase for the blinded and open-label studies and at the end of treatment for the maintenance of effect study.

All patients used earplugs during treatments with a 30 dB ear protection rating. Treaters were also instructed to use ear protection during treatments.

Additional Safety Analyses [Study 101]

Manic Reaction

There were no reports of mania or hypomania with the NeuroStar TMS Therapy System.

Worsening of Depressive Symptoms and Emergent Suicidal Ideation

Because a risk of disease worsening is inherent in the treatment of major depression, specific safety analyses were performed to define further the incidence of disease worsening or the risk of emergent suicidal ideation in the study

population. These analyses were conducted for the randomized controlled Study 101, where a direct comparison to the background sham treatment condition could be performed.

During Study 101, six patients experienced serious adverse events with worsening of their depression and resulting in hospitalization. None of the six patients had been allocated to active TMS treatment; four patients were in the pre-randomization phase of the study and two had been randomized to sham treatment.

In Study 101, there were seven patients who were hospitalized following the development of suicidal ideation or a suicide attempt. Two patients were in the pre-randomization phase, two were on active TMS treatment, and three patients were assigned to sham treatment. The one patient who experienced a suicide attempt and was hospitalized was among the sham treated patients.