

20. PERFORMANCE TESTING CLINICAL

This section provides a *summary of clinical studies* conducted using the Neuronetics TMS System. Full details of these studies are provided in the study reports that are cited in this section.

20.1. Investigator-Sponsored Clinical Studies Using the Neuronetics TMS Device

Three investigator-sponsored studies were conducted to evaluate safety and efficacy of the Neuronetics (previously Neotonus) Model 2100 TMS System. These studies used an earlier version of the Neuronetics Model 2100 TMS System under investigator-sponsored IDEs. The system used the same console and therapy coil but did not use the sham coil, interlock, coil positioner, or the newly designed E-Shield.

The progenitor Model 2100 TMS System was also tested in a clinical trial at a single site in Canada under Neuronetics' Investigational Testing Application No. 67734 to test the safety and performance of various E-Shield models that were tested in conjunction with the Model 2100 TMS System.

These studies are summarized in Table 20.1. More details of the safety and efficacy studies are provided in original [redacted] dated 11 September [redacted] pages 39-41. Study No. PD-001 is described in more detail in [redacted], Ser. No. 014, dated 30 September 2004, Vol. 1, pages 11-12. A summary of each study is provided in Table 20.1.

Table 20.1. Clinical Studies Conducted using the Neuronetics (Neotonus) Model 2100 TMS System

Reference	Study Description
Epstein, et al (1998)	Statistically significant improvement ($p < 0.0001$) in HRSD scores in 16 of 28 medication-free treatment-resistant patients. Response was defined as a 60% reduction in HRSD scores compared to baseline. Stimulation was delivered at 110% MT, 10Hz, in 10, 5 second trains with each treatment repeated daily for five days. Adverse events were transient headache (10 patients), pain at the site of stimulation (2 patients), transient motor tics (1 patient), transient arm, leg and lower face paresthesias (1 patient), and focal motor pseudo seizures occurring 2 weeks after treatment in a patient with unreported pre-existing epilepsy (1 patient).
Greene, et al. (1999)	A 2-week, open trial in 32 treatment-resistant patients who were antidepressant free for 1 week prior to the study. TMS dosing was 10 daily treatments over the left prefrontal cortex at 110% MT, 10 Hz (5 second trains). Twenty-five patients completed the study. Treatment response was defined as a $\geq 50\%$ reduction in HRSD scores. A treatment response was noted in 12%, 40%, 44% and 32% of patients at weeks 1 and 2, and at 2 week and 4 week follow-up, respectively. Remission ($HRSD \leq 7$) occurred in 24% of subjects after 2 weeks of treatment, and 28% and 16% at the 2 week and 4 week follow-ups, respectively. Thirty patients (94%) experienced pain at the site of stimulation (2 with severe pain), 2 patients (6%) experienced headache that responded to acetaminophen or aspirin. A series of cognitive function tests were performed at baseline and at end of treatment (2 weeks). There were no statistically significant differences in cognitive measures.
Epstein at al, (2000)	Investigator-sponsored IDE (G960203): A 2-week, multi-center, randomized, double-blind, sham-controlled trial of left prefrontal TMS in medication-free, treatment-resistant patients with severe depression. Five clinical sites enrolled 113 patients; 71 completed treatment. Patients received 10 daily treatments at 110% MT, 10 Hz (10, 5 second trains). 30% (13/44) of the treatment group and 19% (5/27) of the sham group had a $\geq 50\%$ reduction in HRSD scores. TMS was not significantly more effective than sham. Four percent (4%) of subjects experienced mild-to-moderate discomfort at the site of stimulation and 27% had a post-treatment headache. One patient experienced a vitreous detachment 4 months after treatment that was considered unlikely to be related to TMS treatment. Performance on neuropsychological measures taken immediately prior to treatment and one hour after the 2-week treatment period were found to be statistically equal at the 95% confidence level.
Dr. G. Hasey (Neuronetics ITA 67734; approved 28 Nov 2003)	<p>Study Title: Evaluation of E-Shield Prototype Designs in Reducing Scalp Sensation During Repetitive Transcranial Magnetic Stimulation (rTMS) in Healthy Human Volunteers.</p> <p>The objective of the study was to determine the optimal configuration of the Neuronetics E-Shield by testing a variety of configurations under the same experimental conditions during TMS. Outcome measures included visual analog assessment of pain sensation experienced during test conditions, global mood state, and adverse events. A secondary outcome was passive measurement of brain electrical activity using quantitative EEG before and after the test condition. Eleven healthy volunteers were exposed to a maximum of 1000 pulses of TMS over the left prefrontal cortex under the various E-Shield test conditions. Stimulation parameters were 10 Hz, 120% MT, 4 second train, and at least 26 second inter-train interval. Trains were provided in groups of 3 under each different E-Shield configuration. Spontaneous adverse events reported were diffuse cutaneous sensation under the coil during the stimulation train, and in some instances, more focal irritation of cranial nerves located in the immediate vicinity of the coil during stimulation.</p>

20.2. Neuronetics-sponsored Clinical Studies using the Neuronetics Model 2100 TMS System

20.2.1. Neuronetics Investigational Plan for the Neuronetics TMS System for Major Depressive Disorder

The clinical development program for the Neuronetics TMS System in major depressive disorder consisted of three integrated clinical protocols as displayed in [redacted] these studies were conducted under Neuronetics' [redacted] that was initially approved by the FDA on 10 October 2003, with final approval being granted on 24 May 2004.

In brief, the efficacy of the Neuronetics TMS System was established in adult outpatients with major depressive disorder in a 9-week, randomized, placebo-controlled clinical trial, Study 44-01101.

Patients with major depressive disorder who failed to receive benefit from their randomized assignment in Study 44-01101 were eligible to enter a 9-week, open-label cross-over study with the Neuronetics TMS System in Study 44-01102.

The maintenance of an acute clinical response to the Neuronetics TMS System in either Study 44-01101 or Study 44-01102 was established in a 24 week, open-label continuation clinical trial, Study 44-01103.

The design, objectives and summary results obtained for studies 44-01101, 44-01102 and 44-01103 are summarized in Table 20.2.

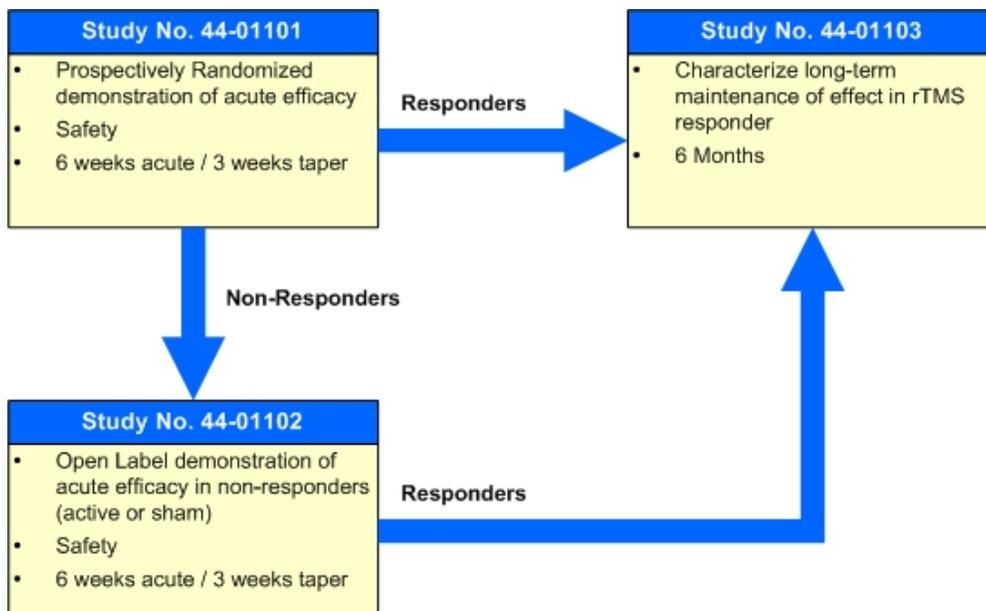


Figure 20.1. Neuronetics' Clinical Studies and Patient Allocation

Table 20.2. Summary of Neuronetics Clinical Studies 44-01101, 44-01102 and 44-01103

Study No.	Study Summary	Study Objective
44-01101	<p>A randomized, parallel-group, sham-controlled clinical trial designed to test the efficacy of TMS treatment for patients diagnosed with DSM-IV defined major depression who have not benefited from prior adequate treatment with oral antidepressants.</p> <p>The study design was comprised of three phases: a one week, no-treatment screening phase, a six week acute treatment phase, and a 3 week rTMS taper phase.</p> <p>During the taper phase, as TMS was tapered, monotherapy with oral antidepressant medications was initiated.</p> <p>At the conclusion of Study 44-01101, or at any time after 4 weeks of participation in the acute phase of that study, patients were considered for enrollment in either of the two open-label, uncontrolled extension studies.</p>	<p>The primary objective was to evaluate the antidepressant effect [using the last post-treatment total symptom score on the MADRS] of a specified treatment course of TMS when compared to sham treatment given under the same experimental conditions in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode. Only patients meeting diagnostic criteria for Major Depression were included in this study.</p> <p>Personnel at the study sites were blind to the choice of primary efficacy measure and to the point of declaration of the efficacy outcome.</p> <p>Secondary outcome measures were HAMD17 and 24 item total symptom score, and response and remission rates for MADRS, HAMD17 and 24. Additional physician and patient rates scale were administered and evaluated as secondary outcome measures.</p> <p>Safety was assessed by adverse event reports, and by targeted safety evaluation of air-conduction auditory threshold. Cognitive function was assessed with the Mini Mental Status Examination, the Buschke Selective Reminding Test, and the Autobiographical Memory Inventory-Short Form.</p>
44-01102	<p>An open-label, uncontrolled clinical trial for patients who did not meet pre-defined criteria for response in Study 44-01101. This protocol was otherwise identical in design and treatment sequence to Study 44-01101.</p>	<p>The primary objective was to describe the symptom changes [using the last post-treatment total symptom score on the MADRS] observed with up to 6 weeks of open-label TMS treatment in patients in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode, who had not shown an acute clinical response to daily dose active of sham rTMS administered for up to 6 weeks.</p> <p>Personnel at the study sites were blind to the choice of primary efficacy measure and to the point of declaration of the efficacy outcome.</p>

Study No.	Study Summary	Study Objective
44-01103	<p>An open-label, uncontrolled clinical trial providing six months of oral antidepressant monotherapy to patients who met pre-defined criteria for response upon exit from Study 44-01101.</p> <p>Study 44-01103 also permitted open-label access, on a defined treatment schedule, to TMS treatment in the event of symptom recurrence despite adequate oral antidepressant treatment.</p>	<p>The primary objective was to evaluate the efficacy of maintenance pharmacotherapy in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode, who showed an adequate clinical response to daily dose TMS administered for up to 6 weeks by examining the time to first symptom recurrence.</p> <p>To minimize study bias, the Investigator was blinded to the definition of response.</p>

The section describes the primary and secondary efficacy outcome measures and safety outcomes collected in Studies 44-01101, 44-01102 and 44-01103 and describes the instruments used for their collection and assessment.

The sections that follow provide for each of the studies, 44-01101, 44-01102 and 44-01103, a summary of the study design, data collection methods and statistical analysis and the efficacy and safety results of each study. The final study reports for studies 44-01101 and 44-01102 are located in Appendices 19 and 20, respectively. An interim study report for the ongoing study 44-01103 is provided in Appendix 21.

The study reports fully describe all aspects of study design, data collection, statistical analysis and study results. They also contain the following study documentation in appendices to the study reports as follows:

- List of Investigators Participating in Studies 44-01101, 44-01101 and 44-01103
- Study Protocol and Informed Consent Document
- Referenced Data Tables
- Serious Adverse Event (SAE) vignettes and Case Report Forms for Patients Experiencing SAEs
- Appendix 5: Annotated Case Report Form (for final study reports)

20.2.2. Primary and Secondary Efficacy Outcome Measures

The primary and secondary outcome measures collected and analyzed in Neuronetics studies 44-01101 and 44-01102 are shown below in Table 20.3. Study 44-01102 was an open-label study that, in all other ways, was of the same design as Study 44-01101. Study 44-01103 used the same primary and secondary outcome measures as those cited for Studies 44-01101 and 44-01102, however, they were collected in accordance with the

schedule of events for this 24-week open-label maintenance study, as given in the interim study report for Study 44-01103, Appendix 21, Section 17.

Table 20.3. Primary Outcome Measure and Secondary Outcome Measures in Protocol 44-01101 and Their Sequential Order of Importance in Testing

Measure	Discussion
Primary Outcome Measure	Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the last post-treatment <u>total symptom score on the Montgomery-Asberg Depression Rating Scale (MADRS) through week 4 of the acute treatment phase</u> of a specified course of active treatment when compared to sham treatment given under the same experimental conditions in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode. The specified data set for this analysis is the intent-to-treat population.
Secondary Outcome Measures	<ol style="list-style-type: none"> 1) Evaluate the antidepressant effect of TMS treatment with the Neuronetics TMS System, using the last post-treatment total symptom score on the 24- Item Hamilton Depression Rating Scale (HAMD24) through week 4 and week 6 of the acute treatment phase, of a specified course of active treatment when compared to sham treatment 2) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the last post-treatment total symptom score on the 17- Item Hamilton Depression Rating Scale (HAMD17) through week 4 and week 6 of the acute treatment phase, of a specified course of active treatment when compared to sham treatment 3) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the total symptom score on the MADRS for the last post-treatment value observed through week 6 of the acute treatment phase, of a specified course of active treatment when compared to sham treatment 4) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using categorical outcomes of response (percent of patients achieving 50% reduction on each of the MADRS, HAMD24, and HAMD17 total symptom scores at the last post-treatment visit through week 4 and week 6 of the acute phase), of a specified course of active treatment when compared to sham treatment 5) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using health outcomes scores from the Medical Outcomes Study Short Form 36-Item Questionnaire (SF-36, v1) and the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) at the last post-treatment visit through week 4 and week 6, of a specified course of active treatment when compared to sham treatment 6) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using categorical outcome of remission/recovery (percent of patients achieving HAMD17 total symptom score < 8, HAMD24 total symptom score < 11, and MADRS total symptom score < 10 at the last post-treatment visit through week 4 and week 6, of a specified course of active treatment when compared to sham treatment 7) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using factor scores derived from the HAMD17 including: Anxiety/Somatization (sum of items 10, 11, 12, 13, 15, 17), Core Factor (sum of items 1, 2, 3, 7, 8), Maier (sum of items 1, 2, 7, 8, 9, 10), Gibbons (sum of items 1, 2, 3, 7, 9, 10, 11, 14), Retardation (sum of items 1, 7, 8, 14), and Sleep (sum of items 4, 5, 6) using the last post-treatment value through week 4 and week 6,

Measure	Discussion
	<p>of a specified course of active treatment when compared to sham treatment</p> <p>8) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the total score on the Inventory of Depressive Symptoms – Self Report version (IDS-SR), using the last post-treatment value through week 4 and week 6, of a specified course of active treatment when compared to sham treatment</p> <p>9) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the Clinical Global Impressions – Severity (CGI-S) score, using last post-treatment value through week 4 and week 6, of a specified course of active treatment when compared to sham treatment</p> <p>10) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using the Patient Global Impressions – Improvement (PGI-I) score, using last post-treatment value through week 4 and week 6, of a specified course of active treatment when compared to sham treatment</p>

A comprehensive set of efficacy instruments was used in the Neuronetics studies to confirm the diagnosis and illness severity of the patient population, and to define the symptomatic and functional response to acute treatment with the Neuronetics TMS System. All instruments used are well-accepted and psychometrically valid psychiatric assessments, and are summarized in Table 20.4, and include both clinician-rated and patient-reported outcome measures.

Table 20.4. Diagnostic, Symptom Assessment, Functional Status and Quality of Life Instruments Used in Protocols 44-01101, 44-01102 and 44-01103

Assessment Tool	Description
<p><u>Psychiatric Diagnostic Interview</u></p> <ul style="list-style-type: none"> - Structured Clinical Interview for the DSM-IV (SCID-IV) 	<ul style="list-style-type: none"> - The SCID-IV is a semi-structured diagnostic interview used to confirm the clinical diagnosis according to diagnostic criteria for Major Depressive Disorder consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition
<p><u>Treatment History</u></p> <ul style="list-style-type: none"> - Antidepressant Treatment History Form (ATHF) 	<ul style="list-style-type: none"> - The ATHF is a semi-structured inventory used to rigorously characterize antidepressant treatment in terms of dosing adequacy, treatment duration, patient compliance and outcome. It has been shown to demonstrate predictive validity for the outcome of somatic treatments for depression, and hence is a valid alternative to a prospective treatment trial to establish antidepressant treatment resistance.

Assessment Tool	Description
<p><u>Clinician-Rated Symptom Assessments</u></p> <ul style="list-style-type: none"> - Montgomery-Asberg Depression Rating Scale (MADRS) - Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions - Clinician Global Impressions – Severity of Illness (CGI-S) 	<ul style="list-style-type: none"> - The MADRS is a well-recognized, observer-administered disease-specific rating scale that measures core symptoms of major depression on 10 items, with an emphasis on vegetative signs. Each item is scored on an integer scale from 0 to 6. - The HAMD is a standardized, observer-administered disease-specific rating scale that assesses up to 24 items characteristically associated with major depression. Each item is variably anchored with up to 5 integer scores, and item-specific anchor verbatim descriptions. It is reported as the first 17-items (HAMD17) or the full 24-items (HAMD24). - The CGI-S is an accepted, observer-administered, global illness rating scale that measures disease severity on a 7-point Likert scale.
<p><u>Patient-Reported Symptom, Quality of Life, and Functional Status Assessments</u></p> <ul style="list-style-type: none"> - Inventory of Depressive Symptoms – Self Report version (IDS-SR) - Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q) - Medical Outcomes Study Short Form – 36 Item Questionnaire, version 1 (MOS SF-36) - Patient Global Impressions – Improvement of Illness Scale (PGI-I) 	<ul style="list-style-type: none"> - The IDS-SR is a self-administered, 30-item rating scale that asks patients to identify symptoms characteristically associated with major depression, and rate the severity of each of these symptoms on a 4-point scale. - The Q-LES-Q short form is a self-administered quality of life instrument that asks patients to identify their overall level of satisfaction in 14 different areas of life function and 2 questions about global life satisfaction on a 5-point scale with 1 = Very Poor and 5 = Very Good. - The MOS SF-36 is a well-validated, self-administered questionnaire that measures a patient’s functional health status. It has eight subscales that measure physical, social and role functioning, mental health, pain, and general health perceptions. This scale is a criterion standard for health-related quality of life. - The PGI-I is a well-recognized, self-administered, global rating scale that measures disease improvement on a 7-point Likert scale.
<p><u>Patient-Reported Health Care Resource Utilization and Work Productivity Assessment</u></p> <ul style="list-style-type: none"> - Health Resource Utilization Questionnaire (HRQ) 	<ul style="list-style-type: none"> - The HRQ is a multi-item self-reported questionnaire which assesses health care utilization, work status and productivity, and caregiver burden.

20.2.3. Safety Outcome Measures

In all Neuronetics studies, safety was assessed at each study visit by review of spontaneously reported adverse events, and separate reporting of all serious adverse events. All adverse events were initially coded by [redacted] contracted vendor for electronic data capture (EDC) [redacted] using the current version of the Medical Dictionary for Activities (MedDRA). All coding runs were reviewed and verified by Neuronetics clinical staff prior to final approval. Independent of coding, all adverse events were categorized by the investigative site staff that recorded the event, by severity and by relatedness to the device, i.e., the Neuronetics TMS System.

Additional targeted safety assessments included assessment of cognitive function and auditory threshold. Auditory threshold was examined since animal and human studies have suggested that prolonged exposure to the sound of the magnetic pulses during a TMS treatment course may be associated with short-term changes in auditory threshold. Cognitive function was a specific area of interest because of the known propensity for the relevant predicate device, namely electroconvulsive therapy (ECT) devices, to disrupt critical areas of general cognitive function and memory. The specific cognitive instruments were selected because they were similar or identical to instruments used in studies of cognitive function in patients receiving ECT treatment. These specific measures are shown in Table 20.5. As commonly done in studies assessing cognitive effects, multiple versions of the MMSE and BSRT were used to allow repeat administrations and to deter potential learning effects.

Table 20.5 Cognitive Function Testing Instruments for Neuronetics Studies 44-01101, 44-01102, 44-01103

Assessment Tool	Description
Modified Mini Mental Status Examination (MMSE)	This instrument assesses global cognitive function in several major neuropsychological domains
Buschke Selective Reminding Test (BSRT)	This test evaluates short-term memory using immediate and delayed recall of common word lists
Autobiographical Memory Inventory-Short Form (AMI-SF)	This interview assesses the integrity of long-term memory functions by examining the ability to recall basic autobiographical information at post-treatment timepoints that were obtained prior to the start of treatment

20.2.4. Protocol 44-01101: “A Randomized, Parallel-Group, Sham-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of the Neuronetics Model 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) System in Patients with Major Depression”

20.2.4.1. Objectives

Primary Study Objective:

- Evaluate the antidepressant effect of a specified course of treatment using the Neuronetics TMS System compared to sham treatment given under the same experimental conditions

Secondary Study Objectives:

- Determine the safety and tolerability of treatment with the Neuronetics TMS System as assessed by both spontaneous adverse events and formal assessment of cognitive function
- Assess the change in depressive symptomatology and functional capacities across the duration of acute treatment and its clinical impact through use of additional observer and self-administered efficacy measures and measures of work status and functional capacity
- Assess the short-term durability of efficacy obtained using the Neuronetics TMS System during a 3-week taper phase (at which time patients were transitioned to maintenance, open-label antidepressant pharmacotherapy)

20.2.4.2. Experimental Design

Protocol 44-01101 was a randomized, parallel-group, sham-controlled clinical trial designed to test the efficacy and safety of the Neuronetics TMS System in the treatment of patients diagnosed with DSM-IV defined major depressive disorder, who have not benefited from prior adequate treatment with antidepressant pharmacotherapy. The design for this study was organized into three experimental phases: a one-week, no treatment screening phase, a six week acute treatment phase, and a 3-week taper phase. During the acute treatment phase, TMS treatments using the Neuronetics TMS System were scheduled in five-day contiguous treatment blocks, generally scheduled on Monday through Friday, for a maximum possible number of 30 treatment sessions. During the taper phase, all patients were simultaneously tapered from treatment with the Neuronetics TMS System in a schedule of gradually less frequent treatment sessions (3 times per week, twice per week and then once per week), and simultaneously tapered onto open-label antidepressant pharmacotherapy.

All site personnel were blinded to which efficacy measure was declared as the primary outcome and the time point at which this outcome was defined in order to improve the study's signal detection ability. Declaration of the primary outcome measure was documented in the study master file prior to interim data lock.

The design of protocol 44-01101 was specifically structured in a manner to address two questions:

- 1) *Is treatment with the Neuronetics TMS System an effective acute antidepressant when administered as monotherapy?***
- 2) *Can the acute effect of treatment with the Neuronetics TMS System be shown to be sustained in a clinically meaningful manner for a clinically appropriate duration subsequent to completion of an acute treatment course?***

The answer to the first question is derived from the information obtained from patients observed through the fourth week of the acute treatment phase. This time point was stipulated *a priori* as the declared primary endpoint for inferential statistical analysis to determine the efficacy of treatment using the Neuronetics TMS System. Supportive data in answer to the first question is provided by the additional clinician-rated and patient-rated outcome measures obtained at both the four and six week time points of the acute treatment phase. The primary and secondary outcome measures used in these analyses, and the order of their sequential testing is listed in Table 20.3 above, and is also described in the original protocol provided in Appendix 2 of the study report for study 44-01101 (Appendix 19).

In all analyses, the primary study population of interest was declared as the intent-to-treat population, defined as including all subjects who signed an informed consent, were randomized to a treatment condition and received at least one treatment (whether partial or complete), and for whom at least one completed post-randomization observation was available for analysis.

As noted above, the second question to be addressed by the data obtained in this protocol concerns the clinical durability of the acute response to treatment with the Neuronetics TMS System. The answer to this question is derived from descriptive observations of the pattern and time course of response during the final phase of protocol 44-01101, namely the taper phase. Although the treatment assignment to either active or sham TMS remained masked as patients entered this continuation phase of the study, antidepressant pharmacotherapy of clinician and patient choice was administered in an open-label manner throughout this taper phase. In addition, because all patients who were not receiving benefit from study participation at or after week 4 of the acute phase were

permitted access to enter Protocol 44-01102, the population subgroups entering the taper phase cannot be considered to represent a fully randomized sample as was the case at entry to the acute treatment phase. Therefore, data obtained in the taper phase of the study does not permit inferential statistical comparisons across population subgroups, and all data is provided in a descriptive statistical manner only. Conclusions obtained from the taper phase of protocol 44-01101 are discussed in terms of their clinical relevance in addressing the question of clinically meaningful sustained effect of the acute response to TMS monotherapy as delivered by the Neuronetics TMS System.

All patients who discontinued from Study 44-01101 at any time after the primary outcome endpoint was assessed, namely at or after week 4 of the acute treatment phase, were eligible for consideration to enter into the open-label acute treatment study, Study 44-01102, if appropriate eligibility criteria for non-response to treatment were met (see Section 20.2.5 for further details of this protocol). If a patient completed participation in Study 44-01101 through the taper phase, they were eligible for consideration to enter into the open-label maintenance of effect study 44-01103 if they met the criteria for response to treatment (see Section 20.2.6 for further details of this protocol).

20.2.4.3. Data Collection and Analysis

The study protocol and procedures are included in the original protocol for Study 44-01101 that is contained in Appendix 2 of the final study report for Study 44-01101(Appendix 19). A schedule of events for Study 44-01101 is also provided in Section 3.2 of the final study report. The primary and secondary efficacy outcome measures and safety measures collected in Protocol 44-01101 are summarized in Section 20.2.2 and 20.2.3 above.

The study procedures and foreseeable risks of the protocol and use of the study device were explained to all patients and informed consent was obtained prior to any study procedures.

20.2.4.4. Inclusion and Exclusion Criteria

Patients were eligible to participate in this study if they were outpatients ages 18 to 70, who met DSM-IV criteria for Major Depressive Disorder (MDD), single episode or recurrent, with a current illness duration of 3 years or less. The clinical diagnosis was confirmed by structured psychiatric interview using the SCID-IV. Any patient currently receiving treatment with psychotropic medication was required to complete a washout from these medications prior to completing the final screening process.

At initial screening, patients were required to have a CGI-S score of at least 4, and a minimum symptom severity as reflected by a total score of at least 20 on the HAM-D17, with an Item 1 (Depressed Mood) score of at least 2 on that instrument. In addition, all patients had to demonstrate sustained symptom severity after the one week no-treatment lead-in period, as reflected by a HAM-D17 total score of at least 18, and $\leq 25\%$ decrease in score from that observed at the screening assessment.

Treatment history in all patients was evaluated using the ATHF. To be eligible for study entry, patients must have failed to receive benefit from at least 1 but no more than 4 adequate trials of an antidepressant in their current episode. Adequacy of treatment was defined as an ATHF antidepressant resistance rating of at least Level 3 for the specific antidepressant. If the patient had not received treatment in the current episode, the next most recent episode was explored for qualifying status on the ATHF.

Exclusionary criteria for study entry included a history of psychosis, bipolar disorder, or obsessive compulsive disorder. Post-traumatic stress disorder and eating disorders were excluded only if active in the past year. Patients who had failed to receive benefit from an adequate trial of electroconvulsive therapy at any point in their lifetime were excluded. Patients who had been previously treated with experimental TMS or had received a vagus nerve stimulator implant were excluded from the study. Patients who had recently entered psychotherapy or for whom the psychotherapy treatment plan was expected to change during the course of the study were excluded. Pregnancy, or women of reproductive age who were not using a medically accepted form of contraception during intercourse, were not permitted to enroll. A history of seizure disorder or any neurologic disease or medication therapy known to alter seizure threshold was not permitted. Due to the use of magnetic stimulation, patients were excluded for the presence of ferromagnetic material anywhere in or in close proximity to the head, or for the presence of intracardiac lines. Laboratory studies, including a urine toxicology screen and electrocardiogram were performed at study entry.

20.2.4.5. Site Selection Procedures, Training Methods and Follow-Up Procedures for Study Device Operation and Clinician-Rates Assessments

All study sites were assessed with an on site visit and interview of potential staff, using established standard operating procedures at Neuronetics. Qualified study sites were provided an extensive training sequence prior to being permitted to utilize the Neuronetics TMS system in the study protocol. The process for site qualification, training and site initiation are described further in the study report for Study 44-01101 in Appendix 19, Section 3.2.

The HAMD and MADRS were assessed by clinical raters using a semi-structured interview developed for this study by Drs. Harold Sackeim, Judith Kiersky and Mark Demitrack, and modeled after the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) developed by Dr. Janet Williams at Columbia University (1988). This interview guide provides a verbatim leading question and a series of follow up questions designed to sequentially probe the symptom domains covered in the HAMD and MADRS interview, and permitted simultaneous scoring of the relevant items from both scales. Rater quality and reliability on the use of this interview was assessed as described further in Section 3.4 of the study report for Study 44-01101 (Appendix 19). The results of rater reliability assessment are provided in Section 20.3 of the study report.

20.2.4.6. Case Report Forms and Methods of Data Management

Data was entered from source data records into a web-based electronic case report form database, or electronic data capture (EDC) system, at all participating clinical sites. Only site staff trained in data entry using this EDC system were authorized to enter the data.

Neuronetics clinical study monitors verified entered data against source data records and queried all investigative site staff when needed for logical clarification of data or for missing data. The complete dataset for Study 44-01101 was locked on 31 January 2006, and final data was

transferred from [redacted] to [redacted] research organization [redacted] N

[redacted] n [redacted] in 06 February 2006.

20.2.4.7. Statistical Analysis Plan

The statistical analysis plan, sample size justification and power analysis, and statistical methods for Study 44-01101 are described in the final study report for Study 44-01101 in section 5.2 (see Appendix 19).

In brief, the sample size was arrived at by requiring 90% power and a two-sided 5% test, and is based on the standard t-test method. The targeted standardized effect size (difference in LV means divided by the standard deviation of the score) was $d=0.4$. As stated in Protocol 44-01101, an interim analysis for futility was to be conducted *a priori* when a total sample of approximately N=100 patients were enrolled. Stopping for futility at a conditional power of 20% increases the nominal type II error rate by less than a factor of $10/8 = 1.25$. To guarantee a final 10% type II error rate (90% power), a nominal type II error rate was set at 8% (power = 92%) for a total N=286 (143 per treatment group). This sample size included evaluable patients only, since the specific number of potential non-evaluable patients in the sample could only be observed as the study was underway.

Study 44-01101, a randomized, parallel-group comparison of treatment with the Neuronetics TMS System with a matched Neuronetics TMS System sham control at 23 clinical sites, used a permuted block design (block size = 6) to improve balance within sites. As stated above, the primary hypothesis to be tested in this study compared the active treatment with the Neuronetics TMS System and sham treatment groups on the last post-treatment symptom score (LV) measured using the primary efficacy outcome measure (MADRS total symptom score at 4 weeks of acute phase treatment) for each patient. The primary efficacy analysis was performed on the intent-to-treat sample of all evaluable patients, meaning those patients with a baseline and at least one post-baseline observation available for analysis.

In the Protocol 44-01101, an *a priori* consideration was made which stipulated that poorly recruiting sites, defined as those with fewer than 2 randomization blocks (randomization schedule block size = 6), would be pooled into one or more pseudo-sites for purposes of analysis. Prior to breaking of the study blind, review of patient recruitment across sites revealed that the most logical pooling of low enrolling study sites would be accomplished by establishing a single pseudosite of all sites that enrolled less than one complete block size, i.e., less than 6 patients. This produced a single pseudosite of N=11 patients, and was employed as such in the statistical analysis.

For the primary efficacy outcome measure (i.e., MADRS total symptom score observed at 4 weeks of treatment during the acute treatment phase), the null hypothesis was tested in an analysis of covariance of the LV,

using baseline score, and ATHF medication resistance level as fixed effect covariates, adjusting for site differences using a random effect. The ATHF medication resistance levels were grouped into two categories in the statistical model, 2 or less in the reference episode (current or past) or 3-4 in the reference episode (current or past). All tests were two-sided, with a conventional level of statistical significance set at the 5% level.

Key secondary efficacy outcomes were tested as supportive indices of clinical efficacy of the Neuronetics TMS System and included other continuous measures, and within-patient dichotomous variables. For these secondary analyses, the treatment effect null hypothesis was tested by logistic regression of treatment group assignment with adjustment for site and ATHF medication resistance level. In addition, the longitudinal symptom scores were analyzed with a repeated measures general linear model, adjusting for baseline scores and ATHF medication resistance level (using Proc Mixed in SAS Version 8.2 or higher). The model included the covariates of baseline score and ATHF medication resistance level as fixed effect covariates, treatment effect, and site differences using a random effect. Time was included in the model as a repeated measure. Additionally, the treatment by time interaction was included in the model. The inclusion of this interaction term allowed for an assessment of the treatment effect at each time point. An unstructured covariance matrix was used in the analysis.

20.2.4.8. Results

20.2.4.8.1. Efficacy

A summary of efficacy results for study 44-01101 are shown in Tables 20.6 and 20.7 for physician-rated outcomes and in Table 20.8 for patient-rated outcomes.

Levels of statistical significance are summarized below for the *a priori* declared contrasts between active and sham treatment with the Neuronetics TMS System in Study 44-01101. The order of presentation reflects the priority order stated in the protocol text. The listing specifically highlights those outcomes that are considered clinically significant and exceeded statistical significance at levels of either $p < 0.10$ [considered a strong statistical trend] or $p < 0.05$ [considered the conventional threshold level of statistical significance per protocol]. All other contrasts were less than these statistical limits and are considered statistically and clinically non-significant.

The results indicate that the Neuronetics TMS System is effective in treatment of major depressive disorder as compared to sham treatment for all clinically relevant outcome measures as would be expected to occur with an antidepressant effect as rated by clinician and patient-rated measures.

The outlier data to this analysis was MADRS total score (p=0.057 @ 4 weeks) which was noted to be due to a baseline imbalance for MADRS scores and not HAMD 17 and 24 item measures as a result of a study design requirement for a minimum baseline for HAMD scores and not MADRS scores. Reanalysis of the full data set setting a MADRS baseline results in a statistical superiority of the MADRS total score p=0.038 over sham without a significant change in the results for other outcome measures.

Table 20.6. Clinician-Rated Efficacy Outcomes: P Values for LOCF contrasts between active TMS vs sham TMS

Variable Name	Week 2	Week 4	Week 6
MADRS Total Score	--	.057	.058
MADRS (baseline adjustment) ¹		.038	.051
HAMD24 Total Score	.051	.012	.015
HAMD17 Total Score	.098	.006	.005
<u>Response Rate (>50% reduction from baseline)</u>			
• MADRS	--	.045	.007
• HAMD24	--	.030	.042
• HAMD17	--	.018	.015
<u>Remission Rate</u>			
• MADRS (Total score <10)	--	--	.011
• HAMD24 (Total score <11)	--	--	.012
• HAMD17 (Total score <8)	--	--	.065
CGI-S Total Score	.047	.009	.012

-- = p>.10

1. A baseline imbalance between active and sham TMS arms was observed for MADRS ((LS mean for active TMS = 32.4 [SD 5.99], LS mean for sham TMS = 33.7 [SD 5.69], p = .036). Reanalysis was conducted using a MADRS baseline cut-off of >20.

Table 20.7. Clinician-Rated Efficacy Outcomes: P Values for LOCF contrasts between active TMS vs sham TMS

Variable Name	Week 2	Week 4	Week 6
<u>HAMD Factor Scores</u>			
• Anxiety/Somatization Factor	--	.025	.023
• Core Depression Factor	--	.012	.008
• Maier Factor	--	.003	.003
• Gibbons Factor	--	.007	.006
• Retardation Factor	.057	.007	.003
• Sleep Factor	--	--	--

-- = p>.10

Table 20.8. Patient-Rated Efficacy Outcomes: P Values for LOCF contrasts between active TMS vs sham TMS

Variable Name	Week 2	Week 4	Week 6
<u>MOS Short Form 36-Item</u>			
Physical Functioning	N/A	--	--
Role-Physical	N/A	--	--
Bodily Pain	N/A	--	--
General Health	N/A	.049	.047
Vitality	N/A	--	.081
Social Functioning	N/A	--	--
Role Emotional	N/A	--	.044
Mental Health	N/A	.006	.015
Q-LES-Q	N/A	--	.035
IDS-Self Report	--	.058	.053
PGI-Improvement Total Score	--	--	--

-- = p>.10; N/A = scale not obtained at that time point

PRIMARY OUTCOME MEASURE:

MADRS Total Score

- *After 4 weeks*, active treatment using the Neuronetics TMS System showed a strong statistical trend for superiority compared to sham treatment on the MADRS total score (p=.057)
- A statistically significant baseline imbalance was observed in the total score on the MADRS between the active TMS and sham TMS treatment groups (LS mean for active TMS = 32.4

[SD 5.99], LS mean for sham TMS = 33.7 [SD 5.69], $p = .036$). This unexpected outcome arose because of the nature of the study design itself, whereby the baseline screening measure used (i.e., the HAMD17) had a minimum numerical threshold for entry, while the primary outcome measure (i.e., the MADRS) did not. In order to characterize the specific influence of the baseline imbalance observed on MADRS scores, a supplementary analysis was conducted of the overall intent-to-treat evaluable study population with this small subset of patients removed from the analysis using a MADRS cut-off of >20 . This analysis also resulted in a statistically significant outcome for MADRS total score ($p=0.038$), which is consistent with the other two major efficacy outcome measures, namely the HAMD24 and the HAMD17.

SECONDARY OUTCOME MEASURES:

HAMD24, HAMD17 (Weeks 4 and 6) and MADRS Total Score (Week 6)

- *After 2 weeks*, active treatment with the Neuronetics TMS Systems showed a strong statistical trend for superiority compared to sham treatment on the HAMD24 total score ($p=.051$) and the HAMD17 total score ($p=.098$)
- *After 4 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by the total score on the HAMD24 ($p=.012$) and HAMD17 ($p=.006$)
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by the total score on the HAMD24 ($p=.015$) and HAMD17 ($p=.005$) and continued to show a strong statistical trend for superiority compared to sham treatment on the MADRS total score ($p=.058$)

HAMD24, HAMD17, and MADRS Response Rate (Weeks 4 and 6)

- *After 4 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by categorical response rate ($\geq 50\%$ reduction in score from baseline) on all measures, the MADRS, ($p=.045$), the HAMD24 ($p=.030$), the HAMD17 ($p=.017$)
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by categorical response rate on all measures, the

MADRS ($p=.007$), the HAMD24 ($p=.042$), and the HAMD17 ($p=.015$)

Functional Status Outcome (MOS SF-36 and Q-LES-Q) (Weeks 4 and 6)

- *After 4 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by the SF-36 General Health ($p=.049$), and Mental Health ($p=.006$) subscales
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by the SF-36 General Health ($p=.047$), Role-Emotional ($p=.044$) and Mental Health ($p=.015$) subscales, and showed a strong statistical trend for superiority compared to sham treatment on the Vitality ($p=.081$) subscale
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire ($p=.035$)

HAMD24, HAMD17, and MADRS Remission Rate (Weeks 4 and 6)

- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham as measured by categorical remission rate on the MADRS ($p=.011$), and the HAMD24 ($p=.012$), and showed a strong statistical trend for superiority on the HAMD17 ($p=.065$)

HAMD Factor Scores (Weeks 4 and 6)

- *After 2 weeks*, active treatment with the Neuronetics TMS System showed a strong statistical trend for superiority compared to sham treatment as measured by the HAMD Retardation Factor ($p=.057$)
- *After 4 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by all but one of the HAMD Factor Scores, including the Anxiety/Somatization Factor ($p=.025$), Core Depression Factor ($p=.012$), Maier Factor ($p=.003$), Gibbons Factor ($p=.007$), and Retardation Factor ($p=.007$)
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by all but one of the HAMD Factor Scores, including the Anxiety/Somatization Factor ($p=.023$), Core

Depression Factor ($p=.008$), Maier Factor ($p=.003$), Gibbons Factor ($p=.006$), and Retardation Factor ($p=.003$)

Other Efficacy Measures (IDS-SR, CGI-Severity, PGI-Improvement) (Weeks 4 and 6)

- *After 2 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by all the CGI-Severity score ($p=.047$)
- *After 4 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by all the CGI-Severity score ($p=.009$) and showed a strong statistical trend for superiority compared to sham treatment as measured by the IDS-SR Total Score ($p=.058$)
- *After 6 weeks*, active treatment with the Neuronetics TMS System was statistically significantly superior to sham treatment as measured by all the CGI-Severity score ($p=.012$) and showed a strong statistical trend for superiority compared to sham treatment as measured by the IDS-SR Total Score ($p=.053$)

20.2.4.8.2. Durability of Effect

At the conclusion of the acute treatment phase, all remaining patients were entered into a continuation phase referred to as the *post-treatment taper phase*. During this portion of the study, all patients began a scheduled taper of their blinded treatment assignment across a 3-week schedule. At the same time, *all patients were initiated on open-label pharmacotherapy with a single antidepressant medication* selected from a protocol-defined list.

Categorical responder and remission rates for the primary disease-specific efficacy outcome measures (the MADRS, the HAMD24 and the HAMD17) were determined for all patients continuing into the post-treatment taper phase. This data is described in detail in Section 16 of the Study Report for Study 44-01101 (Appendix 19) and showed that:

- The clinical effect of active TMS is sustained during transition to single-drug antidepressant monotherapy. (MADRS, HAMD 17 and HAMD mean total score at 6 weeks was maintained through week 3 of taper). This indicates that patients may be appropriately transitioned to clinically relevant continuation treatment without loss of clinical benefit achieved in the acute treatment phase.

- Patients allocated to active TMS showed a greater clinical benefit during this continuation period compared to those patients allocated to sham TMS.
- The remission rate at the end of the 3 week taper phase for active TMS patients was greater than the responder rate seen in the sham TMS group at the same time point.

20.2.4.8.3. Safety

The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and emergent suicidal ideation. A summary of MedDRA preferred term adverse events occurring with an incidence on active TMS of $\geq 2\%$ and greater than the incidence on sham TMS in study 44-01101 is provided in Table 20.9.

Serious Adverse Events

- There were no deaths or seizures reported in this study

Spontaneous Adverse Events During the Acute Treatment Phase

- The adverse event profile associated with acute treatment with the Neuronetics TMS System was similar to the expected profile reported in the scientific literature.
- The most frequently reported events were application site pain (35.8% of active TMS treated patients vs. 3.8% of sham treatment) and headache (58.2% of active TMS treated patients vs. 55.1% of sham treatment).

Cognitive Function Testing During the Acute Treatment Phase

- There was no evidence of clinically significant cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System

Auditory Threshold Testing During the Acute Treatment Phase

- There was no evidence of clinically significant auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System

Emergent Suicidal Ideation

- There was an excess of cases of worsening suicidal ideation in the patients allocated to the sham TMS treatment group.
- There was no evidence that active TMS treatment was associated with worsening of suicidal ideation or emergent suicidal ideation during the acute treatment phase.

Table 20.9. Summary of MedDRA Preferred Term Adverse Events Occurring with an Incidence on Active TMS of $\geq 2\%$ and Greater Than the Incidence on Sham TMS in Study 44-01101

Body System (-) Preferred Term	Sham (N=158) N (%)	Active (N=165) N (%)
Ear and labyrinth disorders		
- Ear pain	1 (0.6)	4 (2.4)
- Tinnitus	2 (1.3)	7 (4.2)
Eye disorders		
- Eye pain	3 (1.9)	10 (6.1)
- Lacrimation increased	1 (0.6)	7 (4.2)
- Visual disturbance	2 (1.3)	4 (2.4)
Gastrointestinal disorders		
- Diarrhoea	6 (3.8)	8 (4.8)
- Nausea	10 (6.3)	17 (10.3)
- Toothache	1 (0.6)	12 (7.3)
- Vomiting	3 (1.9)	7 (4.2)
General disorders and site administration conditions		
- Application site discomfort	2 (1.3)	18 (10.9)
- Application site pain	6 (3.8)	59 (35.8)
- Facial pain	5 (3.2)	11 (6.7)
- Pain	3 (1.9)	7 (4.2)
- Pyrexia	1 (0.6)	4 (2.4)
Injury, poisoning and procedural complications		
- Overdose*	0	4 (2.4)
Musculoskeletal and connective tissue disorders		
- Arthralgia	5 (3.2)	10 (6.1)
- Muscle twitching	5 (3.2)	34 (20.6)
- Musculoskeletal stiffness	4 (2.5)	5 (3.0)
- Neck pain	4 (2.5)	8 (4.8)
Nervous system disorders		
- Dyskinesia	2 (1.3)	5 (3.0)
- Headache	87 (55.1)	96 (58.2)
- Hypoaesthesia	2 (1.3)	5 (3.0)
- Paraesthesia	4 (2.5)	6 (3.6)
- Tension headache	2 (1.3)	4 (2.4)
Psychiatric disorders		
- Agitation	3 (1.9)	4 (2.4)
- Anxiety	18 (11.4)	19 (11.5)
Reproductive system and breast disorders		
- Dysmenorrhoea	2 (1.3)	5 (3.0)
Respiratory, thoracic and mediastinal disorders		
- Cough	2 (1.3)	4 (2.4)
- Dyspnoea	1 (0.6)	6 (3.6)
Skin and subcutaneous tissue disorders		
- Pain of skin	1 (0.6)	14 (8.5)

Notes: * Overdose refers to events associated with inadvertent smart card operator error resulting in > 75 trains of active or sham TMS delivered to the patient on a single calendar day. Per protocol procedure, all of these events were considered as adverse events to be reported in the time frame and manner of serious adverse events.

20.2.4.8.4. Overall Safety and Efficacy Conclusions

Data collected in study 44-01101 indicates that TMS therapy delivered by the Neuronetics TMS System is safe and effective in the treatment of major depressive disorder. The key conclusions drawn from the results of Study 44-01101 in answer to the above questions were:

- TMS treatment using the Neuronetics TMS System was shown to be a clinically and statistically effective antidepressant monotherapy for the treatment of patients with Major Depressive Disorder, with single or recurrent episode, who had not previously been shown to receive adequate benefit from at least one but no more than four antidepressant medications during the qualifying episode.
- The acute clinical response to TMS treatment using the Neuronetics TMS System was successfully maintained over the course of a three week transition to maintenance of effect antidepressant pharmacotherapy.
- TMS treatment using the Neuronetics TMS System was demonstrated to have an adverse event profile consistent with previous exploratory studies and clinical case reports, and was notably absent of suicides, seizures, or of any effect on cognitive function or auditory threshold (with earplug use during TMS treatment) during the course of six weeks of acute treatment.
- TMS treatment using the Neuronetics TMS System was well tolerated by patients as evidenced by a low discontinuation rate during the acute treatment phase.

20.2.5. Protocol 44-01102: “A 9-Week, Uncontrolled, Open-Label, Multicenter Study To Evaluate the Efficacy and Safety of the Neuronetics Model 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) System in the Treatment of Patients with Major Depression Previously Non-Responsive to Active or sham rTMS Treatment”

20.2.5.1. Objectives

Primary Study Objective:

- Describe the symptom changes observed during open-label treatment with the Neuronetics TMS System for up to 6 weeks in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode, who have not shown an acute clinical response to daily dose administration of active or sham TMS administered by the

Neuronetics TMS System for at least 4 weeks of masked treatment in Protocol 44-01101

Secondary Study Objectives:

- Determine the safety and tolerability of treatment using the Neuronetics TSM System as assessed by both spontaneous adverse event report and formal assessment of cognitive function
- Assess the change in depressive symptomatology and functional capacities across the duration of acute treatment and its clinical impact through use of additional observer and self-administered efficacy measures and measures of work status and functional capacity
- Assess the short-term durability of efficacy obtained using the Neuronetics TMS System during a 3-week taper phase (at which time patients will be transitioned to maintenance, open-label antidepressant pharmacotherapy)

20.2.5.2. Experimental Design

Protocol 44-01102 was an uncontrolled, open-label, multicenter clinical trial designed to provide confirmatory evidence of efficacy in outpatients who participated in Protocol 44-01101 and who did not respond to active or sham treatment using the Neuronetics TMS System in that study. Patients were permitted to enter Protocol 44-01102 at any time at or after week 4 of the acute treatment phase of Protocol 44-01101. Clinical consideration for entry into Protocol 44-01102 was based on either patient request to exit Protocol 44-01101 or clinician assessment that further participation in Protocol 44-01101 was not in the best clinical interest of the patient. In order to assess the patient's eligibility for enrollment in Protocol 44-01102, without unmasking of treatment assignment, the clinical study site staff contacted Neuronetics clinical staff and provided the following information:

- Baseline total scores for MADRS, HAMD24, HAMD17 and CGI-S
- Point of exit total scores for MADRS, HAMD24, HAMD17 and CGI-S
- Patient identification code

Criteria for insufficient response to treatment were defined prior to the start of Study 44-01101 and were documented in a note to file dated 09 Dec 2003 and included in the study master files. These criteria were concealed from the study sites in order to minimize bias in clinical ratings. The specific criteria used to determine eligibility based on clinical response was declared *a priori* and stated as follows:

“Response is defined as a reduction in baseline total HAM-D17 score that is greater than or equal to 25%. This calculation is performed by comparing the total score at the study exit visit against the total score obtained at the baseline visit (the visit at which patients are randomized to treatment condition). In other words, if the exit score is 25% or more lower than the score seen at the baseline visit, then the patient is considered to have met criteria for response.”

If the patient fell below this criterion, the remaining inclusion and exclusion criteria for the study was reviewed by the site, and if the patient remained eligible for enrollment, then the study was discussed with the patient and informed consent obtained, otherwise, the patient was discontinued from further study and referred for clinical treatment as appropriate.

The study design for Protocol 44-01102 was in other respects identical in formal structure to Protocol 44-01101. Full details of protocol 44-01102 are provided in Appendix 2 of the final study report for Study 44-01102 (Appendix 20). Similar to Protocol 44-01101, if a patient completed participation in Protocol 44-01102 through the taper phase, they were eligible for consideration to enter into the open-label maintenance of effect study Protocol 44-01103 (Appendix 21, interim report for Study 44-01103).

Protocol 44-01102 is an uncontrolled, open-label study design, and therefore is limited in its ability to provide inferential statistical comparisons, however, the descriptive statistical reports provide circumstantially supportive data that confirms the efficacy of treatment using the Neuronetics TMS System that was provided in the randomized controlled study contained in Protocol 44-01101.

There are two potential routes of entry into Study 44-01102, and they represent two separate Groups contained within the evaluable study population for purposes of study analysis and reporting. Unless otherwise stipulated, data will always be reported for the two Groups separately. The two Groups are:

Group A: Patients who were randomized to active TMS in Study 44-01101, did not respond, and who agreed to enter Study 44-01102

Group B: Patients who were randomized to sham TMS in Study 44-01101, did not respond, agreed to enter Study 44-01102

Patients and study site personnel remained masked to the patient's treatment assignment and therefore their specific group stratification in Protocol 44-01102. To the extent that the pattern and phenomenology of the clinical response in the acute treatment phase and the taper phase of

this study replicate the results of Protocol 44-01101, they can be considered as important confirmatory observations. In addition, Protocol 44-01102 also provides important information on late responders to treatment with the Neuronetics TMS System, since the subjects in Group A may have received up to 60 TMS treatment sessions across the combined acute treatment phases in both protocols.

In summary, the design of Protocol 44-01102 was specifically structured in a manner to address the following questions:

- 1) *What is the likelihood of clinical response to open-label treatment with TMS after failure to receive benefit from sham TMS assignment in Protocol 44-01101?*
- 2) *What is the likelihood of experiencing benefit from extended acute treatment with TMS after failure to receive sufficient clinical response from active TMS assignment in Protocol 44-01101?*
- 3) *Is the adverse event profile with TMS after extended exposure to acute treatment for up to 12 weeks similar compared to that observed after 6 weeks of treatment in Protocol 44-01101?*

The primary and secondary outcome measures for Protocol 44-01102 and the order of their sequential testing is identical to the sequence for Protocol 44-01101, and therefore remains as outlined in Table 20.3.

20.2.5.3. Data Collection and Analysis

The study protocol and procedures are included in the original protocol for Study 44-01102 that is contained in Appendix 2 of the final study report for Study 44-01102 (Appendix 20). A schedule of events for Study 44-01102 is provided in the final study report in Section 3.2. The primary and secondary efficacy outcome measures and safety measures collected in Protocol 44-01102 are summarized in Section 20.2.2 and 20.2.3 above.

The study procedures and foreseeable risks of the protocol and use of the study device were explained to all patients and informed consent was obtained prior to any study procedures.

20.2.5.4. Inclusion and Exclusion Criteria

Only patients who had been previously enrolled in Study 44-01101 and who had failed to receive benefit from their randomized treatment assignment in that study were eligible to participate in Study 44-01102. Detailed discussion of the inclusion and exclusion criteria and the procedures for their implementation is contained in the original protocol for Study 44-01102 (Appendix 20). With the exception of the definition of “*failure to receive benefit from the randomized treatment they had*

been assigned to” as defined below, the inclusion and exclusion criteria were identical to that contained in protocol 44-01101.

“Response is defined as a reduction in baseline total HAMDI7 score that is greater than or equal to 25%. This calculation is performed by comparing the total score at the study exit visit against the total score obtained at the baseline visit (the visit at which patients are randomized to treatment condition). In other words, if the exit score is 25% or more lower than the score seen at the baseline visit, then the patient is considered to have met criteria for response.”

If the patient fell below this criterion, i.e., they “*failed to receive benefit from the randomized treatment they had been assigned to*”, the remaining inclusion and exclusion criteria for the study was reviewed by the site, and if the patient remained eligible for enrollment, then the study was discussed with the patient and informed consent obtained, otherwise, the patient was discontinued from further study and referred for clinical treatment as appropriate.

20.2.5.5. Site Selection Procedures, Training Methods and Follow-Up Procedures for Study Device Operation and Clinician-Rates Assessments

All study sites were assessed with an on site visit and interview of potential staff, using established standard operating procedures at Neuronetics. Qualified study sites were provided an extensive training sequence prior to being permitted to utilize the Neuronetics TMS system in the study protocol. The processes for site qualification, training, rater training and site initiation are described further in the study report for Study 44-01102 in Section 3.2 (Appendix 20).

The HAMD and MADRS were assessed by clinical raters using a semi-structured interview developed for this study by Drs. Harold Sackeim, Judith Kiersky and Mark Demitrack, and modeled after the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) developed by Dr. Janet Williams at Columbia University (1988). This interview guide provides a verbatim leading question and a series of follow up questions designed to sequentially probe the symptom domains covered in the HAMD and MADRS interview, and permitted simultaneous scoring of the relevant items from both scales. Rater quality and reliability on the use of this interview was assessed during Study 44-01101 and only qualified raters were used for Study 44-01102.

20.2.5.6. Case Report Forms and Methods of Data Management

Data was entered from source data records into a web-based electronic case report form database, or electronic data capture (EDC) system, at all participating clinical sites. Only site staff trained in data entry using this EDC system were authorized to enter the data.

Neuronetics clinical study monitors verified entered data against source data records and queried all investigative site staff when needed for logical clarification of data or for missing data. The complete dataset for Study 44-01102 was locked on 02 March 2006, and final data was transferred from the electronic data capture (EDC) contract research organization [REDACTED] to N

[REDACTED] ion [REDACTED] on 07 March 2006.

20.2.5.7. Statistical Analysis Plan

Protocol 44-01102 was an uncontrolled, open-label, multicenter clinical trial. Of the 23 sites contributing patients to Protocol 44-01101, 22 sites contributed patients to Protocol 44-01102. Although the exact number of patients enrolled in this study was dependent upon the actual response rates in protocol 44-01101, it was estimated prior to the initiation of this protocol, that approximately 86 patients would be enrolled. At the study conclusion, 166 patients were enrolled in this clinical trial.

There are two potential routes of entry into study 44-01102, and they represent two separate Groups contained within the evaluable study population for purposes of study analysis and reporting. Unless otherwise stipulated, data will always be reported for the two Groups separately. The two Groups are:

Group A: Patients who were randomized to active TMS in study 44-01101, did not respond, and who agreed to enter study 44-01102

Group B: Patients who were randomized to sham TMS in study 44-01101, did not respond, agreed to enter study 44-01102

The patient and clinician remained masked to the original study 44-01101 treatment assignment, and did not know within which stratum the patient was grouped. All analyses are reported stratified by intake stratum for clarity of results.

The primary goal of the analysis was to assess the chance of subsequent response to open-label active treatment with the Neuronetics TMS System following failure of either active TMS or sham TMS to achieve response. In addition, the quantitatively measured course of patients

(mean scores on standardized rating scales) was assessed over time to complete the statistical description of the results of open-label active treatment with the Neuronetics TMS System. No inferences as to treatment effects are possible from such an open-label, uncontrolled trial, so all analyses are inherently descriptive in the statistical reports.

As noted in the original protocol, all site personnel were blinded to which efficacy measure was declared as the primary outcome and the time point at which this outcome was defined in order to improve the study's signal detection ability. Declaration of the primary outcome measure was documented in the study master file prior to interim data lock.

20.2.5.8. Results

20.2.5.8.1. Efficacy

The primary and secondary outcome measures used in the analyses for Study 44-01102 and the order of their sequential testing are listed above in Table 20.3. Key primary and secondary outcome measures are summarized in Table 20.10 below.

In all analyses, the primary study population of interest was declared as the *intent-to-treat population*, defined as including all subjects who signed an informed consent, were randomized to a treatment condition and received at least one treatment (whether partial or complete), and for whom at least one completed post-randomization observation was available for analysis.

PRIMARY OUTCOME MEASURE:

MADRS Total Score

- *After 4 weeks, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the MADRS total score that was numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment in study 44-01101.*
 - Patients previously allocated to active TMS showed a mean reduction in MADRS total score of -10.5 (95% CI: -12.7 to -8.4)
 - Patients previously allocated to sham TMS showed a mean reduction MADRS total score of -11.9 (95% CI: -14.1 to -9.7)

SECONDARY OUTCOME MEASURES:

HAMD24, HAMD17 (Weeks 4 and 6) and MADRS Total Score (Week 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in both the HAMD24 and HAMD17 total scores that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
 - Patients previously allocated to active TMS showed a mean reduction in HAMD24 total score of -9.0 (95% CI: -11.0 to -7.0) and a mean reduction in HAMD17 total score of -6.4 (95%CI: -7.9 to -5.0)
 - Patients previously allocated to sham TMS showed a mean reduction HAMD24 total score of -11.0 (95% CI: -12.8 to -9.2) and a mean reduction in HAMD17 total score of -8.2 (95%CI: -9.6 to -6.9)
- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in both the HAMD24 and HAMD17 total scores that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101
 - Patients previously allocated to active TMS showed a mean reduction in HAMD24 total score of -11.1 (95% CI: -13.5 to -8.6) and a mean reduction in HAMD17 total score of -8.2 (95%CI: -10.0 to -6.4)
 - Patients previously allocated to sham TMS showed a mean reduction HAMD24 total score of -14.5 (95% CI: -16.8 to -12.3) and a mean reduction in HAMD17 total score of -10.8 (95%CI: -12.5 to -9.0)
- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the MADRS total score that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101
 - Patients previously allocated to active TMS showed a mean reduction in MADRS total score of -12.5 (95% CI: -15.4 to -9.7)

- Patients previously allocated to sham TMS showed a mean reduction MADRS total score of -17.0 (95% CI: -19.9 to -14.0)

HAMD24, HAMD17, and MADRS Response Rate (Weeks 4 and 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the categorical clinical outcome of response rate ($\geq 50\%$ reduction from baseline score) on the MADRS, the HAMD24, and the HAMD17, that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
 - 15 of 68 (22.1%) of patients previously allocated to active TMS were responders on the MADRS (95% CI: 12.90 to 33.76) while 21 of 77 (27.3%) of patients previously allocated to sham TMS were responders on the MADRS (95% CI: 17.74 to 38.62).
 - 16 of 68 (23.5%) of patients previously allocated to active TMS were responders on the HAMD24 (95% CI: 14.09 to 35.38) while 24 of 77 (31.2%) of patients previously allocated to sham TMS were responders on the HAMD24 (95% CI: 21.09 to 42.74)
 - 16 of 68 (23.5%) of patients previously allocated to active TMS were responders on the HAMD17 (95% CI: 14.09 to 35.38) while 23 of 77 (29.9%) of patients previously allocated to sham TMS were responders on the HAMD17 (95% CI: 19.97 to 41.38)
- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the categorical clinical outcome of response rate ($\geq 50\%$ reduction from baseline score) on the MADRS, the HAMD24, and the HAMD17, that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
 - 19 of 61 (31.1%) of patients previously allocated to active TMS were responders on the MADRS (95% CI: 19.90 to 44.29) while 36 of 69 (52.2%) of patients previously allocated to sham TMS were responders on the MADRS (95% CI: 39.80 to 64.35)
 - 23 of 61 (37.7%) of patients previously allocated to active TMS were responders on the HAMD24 (95% CI: 25.61 to

- 51.04) while 36 of 69 (52.2%) of patients previously allocated to sham TMS were responders on the HAMD24 (95% CI: 39.80 to 64.35)
- 22 of 61 (36.1%) of patients previously allocated to active TMS were responders on the HAMD17 (95% CI: 24.16 to 49.37) while 32 of 69 (46.4%) of patients previously allocated to sham TMS were responders on the HAMD17 (95% CI: 34.28 to 58.80)

Functional Status Outcome (MOS SF-36 and Q-LES-Q) (Weeks 4 and 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement of at least 5 points on 4 of 8 factors on the SF-36 Scale and on the Q-LES-Q total score that were consistently *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement of at least 5 points on 5 of 8 factors of the SF-36 Scale and on the Q-LES-Q total score that were consistently *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.

HAMD24, HAMD17, and MADRS Remission Rate (Weeks 4 and 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the categorical clinical outcome of remission rate on the MADRS (total score < 10), the HAMD24 (total score < 11), and the HAMD17 (total score < 8), that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
 - 4 of 68 (5.9%) of patients previously allocated to active TMS were remitters on the MADRS (95% CI: 1.63 to 14.38) while 5 of 77 (6.5%) of patients previously allocated to sham TMS were remitters on the MADRS (95% CI: 2.14 to 14.51)

- 7 of 68 (10.3%) of patients previously allocated to active TMS were remitters on the HAMD24 (95% CI: 4.24 to 20.07) while 11 of 77 (14.3%) of patients previously allocated to sham TMS were remitters on the HAMD24 (95% CI: 7.35 to 24.13)
- 5 of 68 (7.4%) of patients previously allocated to active TMS were remitters on the HAMD17 (95% CI: 2.43 to 16.33) while 9 of 77 (11.7%) of patients previously allocated to sham TMS were remitters on the HAMD17 (95% CI: 5.49 to 21.03)
- After 6 weeks, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement in the categorical clinical outcome of remission rate on the MADRS (total score < 10), the HAMD24 (total score < 11), and the HAMD17 (total score < 8), that was *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
 - 8 of 61 (13.1%) of patients previously allocated to active TMS were remitters on the MADRS (95% CI: 5.84 to 24.22) while 17 of 69 (24.6%) of patients previously allocated to sham TMS were remitters on the MADRS (95% CI: 15.05 to 36.49)
 - 12 of 61 (19.7%) of patients previously allocated to active TMS were remitters on the HAMD24 (95% CI: 10.60 to 31.84) while 23 of 69 (33.3%) of patients previously allocated to sham TMS were remitters on the HAMD24 (95% CI: 22.44 to 45.71)
 - 11 of 61 (18.0%) of patients previously allocated to active TMS were remitters on the HAMD17 (95% CI: 9.36 to 29.98) while 18 of 69 (26.1%) of patients previously allocated to sham TMS were responders on the HAMD17 (95% CI: 16.25 to 38.06)

HAMD Factor Scores (Weeks 4 and 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement of at least 2 points on 5 of 6 factors of the HAMD (Anxiety/Somatization, Core Depression, Maier, Gibbons, and Retardation) that were consistently *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.

- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement of at least 2 points on 5 of 6 factors of the HAMD (Anxiety/Somatization, Core Depression, Maier, Gibbons, and Retardation) that were consistently *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.

Other Efficacy Measures (IDS-SR, CGI-Severity, PGI-Improvement) (Weeks 4 and 6)

- *After 4 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement on the IDS-SR total score, the CGI-Severity scale, and the PGI-Improvement scale that were consistently *numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.
- *After 6 weeks*, patients receiving open-label active TMS treatment using the Neuronetics TMS System showed a clinically significant improvement on the IDS-SR total score, the CGI-Severity scale, and the PGI-Improvement scale that were *consistently numerically greater in those patients previously allocated to sham TMS treatment compared with those patients previously allocated to active TMS treatment* in study 44-01101.

Table 20.10. Study 44-01102 Results: A Priori-Defined Outcome Measures

Efficacy Outcome Measures	Week 4 Study 101 Active TMS	Week 6 Study 101 Active TMS	Week 4 Study 101 Sham TMS	Week 6 Study 101 Sham TMS
MADRS Total Score Mean Change ¹	-10.5	-12.5	-11.9	-17.0
HAMD 24 Total Score Mean Change ¹	-9.0	-11.1	-11.0	-14.5
HAMD17 Total Score Mean Change ¹	-6.4	-8.2	-8.2	-10.8
MADRS Responder Rate (%) ^{2,6}	20.5	26.0	24.7	42.4
HAMD 24 Responder Rate (%) ^{2,6}	21.9	31.5	28.2	42.4
HAMD17 Responder Rate (%) ^{2,6}	21.9	30.1	27.1	37.6
MADRS Remission Rate (%) ^{3,6}	5.5	11.0	5.9	20.0
HAMD24 Remission Rate (%) ^{4,6}	9.6	16.4	12.9	27.1
HAMD17 Remission Rate (%) ^{5,6}	6.8	15.1	10.6	21.2

¹ Change in total score mean change from baseline at entry to Study 44-01102

² Responder is >50% change from baseline score at entry to Study 44-01102

³ MADRS Remission is defined as MADRS total score <10

⁴ HAMD24 Remission is defined as HAMD24 total score <11

⁵ HAMD17 Remission is defined as HAMD17 total score <8

⁶ Responder and Remission rates are calculated using total enrolled sample

20.2.5.8.2. Durability of Effect

At the conclusion of the acute treatment phase, all remaining patients were entered into a continuation phase referred to at the *post-treatment taper phase*. During this portion of the study, all patients began a scheduled taper of their open-label, active TMS treatment across a 3-week schedule. At the same time, *all patients were initiated on open-label pharmacotherapy with a single antidepressant medication* selected from a protocol-defined list.

Categorical responder and remission rates for the primary disease-specific efficacy outcome measures (the MADRS, the HAMD24 and the HAMD17) were collected for all patients continuing into the post-treatment taper phase and analyzed separately for Group A and Group B. These results are provided in more detail in Section 16 of the study report for Study 44-01102 (Appendix 20) and showed that:

- The clinical effect of active TMS is sustained during transition to single-drug antidepressant monotherapy (MADRS, HAMD

17 and HAMD 24 mean total score at 6 weeks was maintained through week 3 of taper). This indicates that patients may be appropriately transitioned to clinically relevant continuation treatment without loss of clinical benefit achieved in the acute treatment phase.

- Patients previously allocated to sham TMS treatment in study 44-01101 consistently showed a greater clinical benefit during this continuation period compared to those patients previously allocated to active TMS treatment.

20.2.5.8.3. Safety

The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and emergent suicidal ideation. A summary of MedDRA preferred term adverse events occurring with an incidence on active TMS of $\geq 2\%$ and greater than the incidence on sham TMS in study 44-01102 is provided in Table 20.11.

Serious Adverse Events

- There were no deaths or seizures reported in this study

Spontaneous Adverse Events During the Acute Treatment Phase

- There was a similar incidence of headaches seen in both TMS treatment groups.
- Application site pain was observed in both treatment groups, but the incidence was greater in the patient group that had previously been allocated to sham TMS treatment prior to entry into study 44-01102, suggesting that the prior exposure assisted in accommodation to this effect.
- For both headache and application site pain, the greatest incidence was observed during the first week of treatment with a substantial reduction in incidence of these common adverse events after the first week of treatment, consistent with a rapid accommodation to these commonly experienced events. This accommodation effect was more pronounced for application site pain.
- Adverse events and their temporal relationship in study 44-01102 were similar to that reported in study 44-01101.

Cognitive Function Testing During the Acute Treatment Phase

- There was no evidence of clinically significant cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System

Auditory Threshold Testing During the Acute Treatment Phase

- There was no evidence of clinically significant auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System

Emergent Suicidal Ideation During the Acute Treatment Phase

- There was no clinically meaningful difference in incidence of cases of worsening suicidal ideation in patients in either treatment group.
- There was no evidence that active TMS treatment was associated with worsening of suicidal ideation or emergent suicidal ideation during the acute treatment phase.

Table 20.11 Summary of MedDRA Preferred Term Adverse Events Occurring with an Incidence on Active TMS of $\geq 5\%$ Incidence on Active TMS Treatment in Either Group A or Group B in Study 44-01102

Body System (-)Preferred Term	Group A (N=73) N (%)	Group B (N=85) N (%)
Gastrointestinal disorders		
- Diarrhoea	6 (8.2)	7 (8.2)
- Nausea	10 (13.7)	6 (7.1)
- Toothache	3 (5.4)	1 (1.4)
- Vomiting	5 (6.8)	1 (1.2)
General disorders and site administration conditions		
- Application site discomfort	7 (9.6)	8 (9.4)
- Application site pain	8 (11.0)	27 (31.8)
- Facial pain	0	5 (5.9)
- Fatigue	6 (8.2)	5 (5.9)
- Pain	4 (5.5)	3 (3.5)
Infections and infestations		
- Nasopharyngitis	4 (5.5)	2 (2.4)
- Upper respiratory tract infection	4 (5.5)	1 (1.2)
Musculoskeletal and connective tissue disorders		
- Arthralgia	4 (5.5)	8 (9.4)
- Back pain	5 (6.8)	2 (2.4)
- Muscle twitching	15 (20.5)	18 (21.2)
- Pain in extremity	5 (6.8)	4 (4.7)
Nervous system disorders		
- Dizziness	6 (8.2)	7 (8.2)
- Headache	35 (47.9)	39 (45.9)
- Migraine	4 (5.5)	2 (2.4)
- Paraesthesia	5 (6.8)	4 (4.7)

Body System (-Preferred Term)	Group A (N=73) N (%)	Group B (N=85) N (%)
Psychiatric disorders		
- Anxiety	11 (15.1)	12 (14.1)
- Insomnia	22 (30.1)	22 (25.9)
Skin and subcutaneous tissue disorders		
- Pain of skin	1 (1.4)	5 (5.9)

20.2.5.8.4. Overall Safety and Efficacy Conclusions

- Patients with major depression who failed to receive adequate clinical benefit from medication therapy show a clinically meaningful response to open-label treatment with the Neuronetics TMS System:
 - After failure to receive benefit from their randomized treatment assignment in study 44-01101, patients previously assigned to sham TMS show *a consistent and numerically superior clinical benefit with open-label TMS treatment in comparison with patients previously assigned to active TMS.*
 - A clinically meaningful proportion of patients who failed to receive clinical benefit after at least 4 weeks of active TMS, respond successfully to an extended duration of active treatment with TMS.
- The clinical effect of active TMS is sustained during transition to single-drug antidepressant monotherapy (MADRS, HAMD 17 and HAMD 24 mean total score at 6 weeks was maintained through week 3 of taper). This indicates that patients may be appropriately transitioned to clinically relevant continuation treatment without loss of clinical benefit achieved in the acute treatment phase.
- Patients previously allocated to sham TMS treatment in study 44-01101 consistently showed a greater clinical benefit during this continuation period compared to those patients previously allocated to active TMS treatment.
- Active treatment with the Neuronetics TMS System is safe and well tolerated in patients with DSM-IV-defined major depression
 - Adverse events are consistent with those observed in the prior exploratory literature and also with the adverse events observed during treatment with active TMS in protocol 44-01101
 - There is no evidence of cognitive adverse effects, or adverse effects on auditory threshold

- Consistent with observations in protocol 44-01101, there is evidence of tolerance to common adverse events including headache and application site pain

20.2.6. Protocol 44-01103: “A 6-Month Open Label Maintenance Study of Patients with Major Depression Previously Responsive to rTMS Treatment with the Neuronetics Model 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) Device in Patients with Major Depression”

20.2.6.1. Objectives

Primary Study Objective:

- Evaluate the efficacy of maintenance antidepressant pharmacotherapy with or without TMS reintroduction in patients who have shown an acute clinical response to daily dose TMS administration

Secondary Study Objectives:

- Describe the efficacy of acutely administered TMS reintroduction of specified dose in those patients receiving maintenance pharmacotherapy for up to 6 months, who show a recurrence of depressive symptoms
- Determine the safety and tolerability of TMS as assessed by both spontaneous adverse events, auditory threshold testing, and formal assessment of cognitive function
- Assess the change in depressive symptomatology and functional capacities across the duration of maintenance antidepressant treatment and its clinical impact through use of additional observer and self-administered efficacy measures and measures of work status and functional capacity

20.2.6.2. Experimental Design

Protocol 44-01103 is an uncontrolled, open-label, multicenter clinical trial in outpatients who have previously participated in either or both of Protocols 44-01101 or 44-01102, and who showed sufficient clinical response to acute treatment with TMS, per protocol criteria, to enroll in Protocol 44-01103.

The study design is comprised of a *24-week maintenance of effect treatment phase*. During this treatment phase, all patients received maintenance antidepressant pharmacotherapy. The specific choice of pharmacotherapy was initiated upon the patient’s entry into the taper phase of either Protocol 44-01101 or 44-01102, in order to permit the patient to enter Protocol 44-01103 at an appropriate initial treatment

dose. The pharmacotherapy regimen was constrained in several ways, in order to minimize excessive heterogeneity of medication selection that may have precluded a meaningful assessment of safety and efficacy of TMS during this maintenance of effect study as follows:

- Only monotherapy was permitted, with the choice of medication restricted to a medication to which the patient had not previously been shown to have had a demonstrated failure of response.
- The dose of medication was to be optimized within the labeled dose range for the specific medication, based on clinical response to treatment.
- No switching of medication was permitted.
- No augmentation or medication combination regimens were allowed.

In the event that the patient's clinical status remained at the level observed at entry to Protocol 44-01103 or improved, no further clinical intervention was provided. However, in the event that the patient's clinical status met protocol-defined criteria, then TMS reintroduction was permitted as an add-on treatment to the existing antidepressant pharmacotherapy. The protocol-defined criteria that triggered reintroduction of TMS were based on the patient's CGI-S score and was stated in the original protocol as follows:

“In the event that the patient's CGI-S score worsens 1 point or more from the preceding visit, then the patient must be rescheduled for repeat clinical assessment within 1 week. If this symptom change is confirmed at that visit, then the patient is considered to have met criteria for clinical deterioration.”

Each reintroduction block of treatment with the Neuronetics TMS System consisted of two weeks of TMS administered twice weekly, followed by up to 4 weeks of 5x/week TMS administration. Dose parameters used were identical to those used in Protocols 44-01101 and 44-01102. If symptom improvement occurred during the course of TMS reintroduction, then TMS was stopped, and the patient continued in the study. TMS reintroduction was permitted an indefinite number of times during the duration of the study, based on these criteria.

In the event that a patient experienced relapse of their depression at any point, they were discontinued from the protocol and referred for clinical treatment. Relapse of depression was defined in two ways:

- Recurrence of full criteria for major depression as defined by DSM-IV criteria (confirmed upon two observations over a two week interval of time), or

- Failure of symptom improvement despite administration of a full course of TMS re-introduction as specified above

With regard to longitudinal symptom change, the primary and secondary outcome measures for Protocol 44-01103 and the order of their sequential testing is identical to the sequence for Protocols 44-01101 and 44-01102 as described above.

This study is designed to provide descriptive data of the time to symptom recurrence or disease relapse with concomitant pharmacotherapy in the aftermath of an acute response to treatment with TMS. Because this is an open-label, uncontrolled clinical trial, it is limited in its ability to provide inferential statistical comparisons. Nevertheless, the data reported has enormous clinical utility for the practicing clinician to inform potential approaches to patient management in the aftermath of successful acute treatment with the Neuronetics TMS System.

Specifically, this study will provide descriptive information to address several clinical questions, including:

- 1) What proportion of patients can be successfully maintained on monotherapy with antidepressant medications subsequent to a successful acute treatment course with TMS?*
- 2) What proportion of patients experience recurrence of symptoms or relapse of their illness subsequent to a successful acute course of TMS and transition to monotherapy with antidepressant medications?*
- 3) For those patients who experience recurrence of symptoms, what proportion of patients can be successfully treated with reintroduction of TMS?*
- 4) For those patients who experience recurrence of illness, what is the average time to first symptomatic worsening?*
- 5) For those patients who experience recurrence of illness, what is average time to relapse of illness?*

20.2.6.3. Data Collection and Analysis

A comprehensive set of measurement instruments were used in this study to confirm the diagnosis and illness severity of the patient population, and to define the symptomatic and functional response to acute treatment with TMS. All instruments used in this study are identical to those used in Protocols 44-01101 and 44-01102, and are well-accepted and psychometrically valid psychiatric assessments. These instruments are summarized in Table 20.3 above, and included both clinician-rated and patient-reported outcome measures.

Identical measures for the assessment of safety were used in Protocol 44-01103 as were used in Protocols 44-01101 and 44-01102, and are summarized in Section 20.2.3 above. These measures included assessment of adverse events and serious adverse events at each study visit, and additional targeted safety assessment of cognitive function and auditory threshold.

The study protocol and procedures are included in the original protocol for Study 44-01103 and are found in Appendix 2 of the final study report for Study 44-01103 (Appendix 21). A schedule of events for Study 44-01103 is provided in the final study report in Section 3.2.

20.2.6.4. Inclusion and Exclusion Criteria

Only patients who had been previously enrolled in study 44-01101 or study 44-01102 and who had received adequate clinical benefit, per *a priori*-defined criteria, from their randomized treatment assignment in that study were eligible to participate in study 44-01103. Detailed discussion of the inclusion and exclusion criteria and the procedures for their implementation is contained in the original protocol in Appendix 2 for Study 44-01103 (Appendix 21).

The specific criteria used to determine eligibility based on clinical response was declared *a priori* and stated as follows:

“Response is defined as a reduction in baseline total HAMDI7 score that is greater than or equal to 25%. This calculation is performed by comparing the total score at the study exit visit against the total score obtained at the baseline visit (the visit at which patients are randomized to treatment condition). In other words, if the exit score is 25% or more lower than the score seen at the baseline visit, then the patient is considered to have met criteria for response.”

If the patient fell above this criterion (and hence was deemed to have had a sufficient clinical response to their prior protocol participation), the remaining inclusion and exclusion criteria for the study was reviewed by the site, and if the patient remained eligible for enrollment, then the study was discussed with the patient and informed consent obtained, otherwise, the patient was discontinued from further study and referred for clinical treatment as appropriate.

With the exception of the definition of having received sufficient benefit from the randomized treatment they had been assigned to in protocol 44-01101 or the open-label treatment in protocol 44-01102, the inclusion and exclusion criteria were identical to that contained in protocol 44-01101.

20.2.6.5. Site Selection Procedures, Training Methods and Follow-Up Procedures for Study Device Operation and Clinician-Rates Assessments

All study sites were assessed with an on site visit and interview of potential staff, using established standard operating procedures at Neuronetics. Qualified study sites were provided an extensive training sequence prior to being permitted to utilize the Neuronetics TMS system in the study protocol. The processes for site qualification, training, rater training and site initiation are described further in the study report for Study 44-01103 in Section 3.2 (Appendix 21).

The HAMD and MADRS were assessed by clinical raters using a semi-structured interview developed for this study by Drs. Harold Sackeim, Judith Kiersky and Mark Demitrack, and modeled after the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) developed by Dr. Janet Williams at Columbia University (1988). This interview guide provides a verbatim leading question and a series of follow up questions designed to sequentially probe the symptom domains covered in the HAMD and MADRS interview, and permitted simultaneous scoring of the relevant items from both scales. Rater quality and reliability on the use of this interview was assessed during Study 44-01101 and only qualified raters were used for Study 44-01103.

20.2.6.6. Case Report Forms and Methods of Data Management

Data was entered from source data records into a web-based electronic case report form database system at all participating clinical sites. Study monitoring was conducted by Neuronetics clinical study monitors verifying entered data against source data records, querying all investigative site staff when needed for logical clarification of data or for missing data.

Enrollment for protocol 44-01103 has closed, but patient activity is still underway, and therefore, the final patient visit has not yet occurred. The interim dataset for Protocol 44-01103 was locked on 31 January 2006, and data was [redacted] contract research organization [redacted] contract research organization [redacted] on 06 February 2006.

20.2.6.7. Statistical Analysis Plan

Protocol 44-01103 was an uncontrolled, open-label, multicenter clinical trial. Of the 23 sites contributing patients to Protocols 44-01101 and 44-01102, 20 sites contributed patients to Protocol 44-01103. Although the exact number of patients participating in this study was dependent upon

the actual response rates in protocols 44-01101 and 44-01102, it was estimated prior to start of this study that approximately 115 patients would be enrolled after have experienced clinically significant benefit from treatment in one of the antecedent clinical trials. At the time of this report, enrollment in Protocol 44-01103 was 136 patients.

Patients in this study are considered to be members of one of 4 mutually exclusive groups, representing four separate populations for study analysis and reporting. The first three groups represent the various paths active TMS treated subjects took prior to entry into study 103, while the 4th group represents the sham TMS responders from Protocol 44-01101:

Group 1: Patients who were randomized to active rTMS in Protocol 44-01101, responded, and agreed to enter Protocol 44-01103 [Study 101 Active responders]

Group 2: Patients who were randomized to active rTMS in Protocol 44-01101, did not respond, and who agreed to enter Protocol 44-01102, received a course of open-label active rTMS, responded to that course of treatment and then agreed to enter Protocol 44-01103 [Study 101 Active non-responders/Study 102 responders]

Group 3: Patients who were randomized to sham rTMS in Protocol 44-01101, did not respond, agreed to enter Protocol 44-01102, received a course of open-label active rTMS, and then agreed to enter Protocol 44-01103 [Study 101 Sham non-responders/Study 102 responders]

Group 4: Patients who will have received sham rTMS in Protocol 44-01101, responded to treatment and subsequently agreed to enter Protocol 44-01103 [Study 101 Sham responders]

The statistical analysis plan was developed in order provide descriptive statistical information that would address the two major topics of this study, namely demonstration of durability of clinical effect of TMS, and the longitudinal pattern of symptom change, functional status outcome and safety assessment as defined in the sequential priority testing order in the original protocol. Subsequent to finalization of the initial protocol, but prior to data lock on 31 Jan 2006, a clarification in the analysis and reporting was made. Rather than pool the separate population groups that had previously been exposed to active TMS, the population groups were reported separately, without pooling. This provides a more accurate reflection of the separate datasets. The planned analyses for durability of effect, and the primary and secondary efficacy measures in the order of their priority testing are stipulated in the original protocol (Appendix 21).

20.2.6.7.1. Demonstration of Durability of Effect

As discussed with the FDA in our original IDE submission, the portion of the dataset that is of primary interest with regard to demonstration of durability of effect is the first four weeks of Protocol 44-01103 for the entire population of patients in Group 1. Group 1 contains all of the patients randomized to active TMS in Protocol 44-01101, and who subsequently responded to treatment sufficiently to meet criteria for entry into Protocol 44-01103. Coupled with the data for this Group shown from the taper phase of Protocol 44-01101, this allows a descriptive view of this cohort of patients across 7 weeks following their exit from the acute treatment phase. The data for Group 1 contained in this report is complete and final data as of the data cutoff date for the Protocol 44-01103 dataset.

In the remainder of the interim report for Protocol 44-01103, all other information is considered of secondary interest in addressing the information requested by the FDA pertaining to demonstration of durability of effect, and is reported on all available information present in the database on the data cutoff date used at the time of data base closure and lock for the submission dataset.

There are two time frames of interest for demonstration of durability of effect for TMS:

- the first 4 weeks of study 44-01103
- weeks 5 through 24 of the remainder of the study.

In all of the analyses presented here, these two time frames are summarized separately.

The primary analysis used to demonstrate durability of effect is the proportion of patients remaining relapse-free (using the criterion definitions summarized in Section 20.2.6.2 above). A secondary method of analysis used to demonstrate durability of effect is the proportion of patients who have not experienced the criterion of symptomatic worsening as determined by CGI-S score (see Section 20.2.6.2). Additional analyses consist of the longitudinal symptom scores observed for all Groups across the two time frames of interest following the sequence of priority testing as noted in the following section.

Durability of effect data is reported for the evaluable study population using the most conservative estimate of relapse, which is the protocol-defined evaluable patient definition of 'relapse' as discussed in Section 20.2.6.2 (i.e., including all patients

discontinuing from study for any reason through the first 4 weeks of Protocol 44-01103).

20.2.6.7.2. Descriptive Statistical Analysis of Longitudinal Symptom Scores

For all other efficacy variables, the analyses will summarize the longitudinal symptom scores and the change from baseline (i.e., the last assessment prior to entry into protocol 44-01103), where appropriate. No inferential statistics will be obtained.

20.2.6.8. Results

20.2.6.8.1. Efficacy

In all analyses, the primary study population of interest was declared as the *intent-to-treat population*, defined as including all subjects who signed an informed consent document.

DURABILITY OF ACUTE EFFICACY

Durability of acute efficacy was determined by *rate of relapse* of depression. Relapse of depression was captured on the case report form as discontinuation due to lack of efficacy, and was characterized clinically in two ways:

- Recurrence of full criteria for major depression as defined by DSM-IV criteria (confirmed upon two observations over a two week interval of time), or
- Failure of symptom improvement despite administration of a full course of TMS re-introduction.

All patients who discontinued due to lack of efficacy at any time point from week 4 through 24 were declared as having relapsed. In addition, to ensure a conservative estimate of the relapse during the primary interval of interest, namely weeks 1 through 4, during this time interval, patients who discontinued the study for any reason were also considered to have met criteria for relapse.

During discussions with the FDA at the time of IDE filing [REDACTED] [REDACTED] the Division requested that an alternative, exploratory definition of relapse be applied to this data in order to allow a closer comparative examination of the rate of relapse in study 44-01103 with the primary definition of relapse used in the published ECT literature. [ECT devices are the predicate devices for the Neuronetics TMS System that has been filed for clearance by premarket notification and this data contributes to the determination

of substantial equivalence to the predicate ECT devices].

The definition of relapse that is operationally applied in ECT studies is determined in terms of the HAMD24 total score:

- any patient who is observed to have a HAMD24 total score of at least 16, and an increase in HAMD24 total score of at least 10 points from that observed at entry into study 44-01103, observed on two consecutive visits, is considered to have met criteria for relapse (Sackeim, HA, 2001).

Note that this definition was not stipulated *a priori* as a criterion for relapse in study 44-01103, and therefore patients may not have been discontinued from the study even if they met this criterion, therefore this analysis represents a summary of the incidence of the first occurrence of this event for any patient, and ignores any recurrence of this criterion at later time points.

The data from these analyses demonstrated that the durability of the acute treatment response to active TMS is maintained over the first four weeks of TMS-free treatment expressed in terms of the incidence of illness relapse. Using the protocol-defined definition of discontinuation for all cause during this time interval, the cumulative incidence of relapse is 2.3% (range 0%-7.2%). Using the alternative definition of relapse, based on a definition of change in HAMD24 score as defined above (a relapse definition commonly used in the ECT literature), the cumulative incidence of relapse across the first 4 weeks of TMS-free treatment is 9.1%. These data compare favorably to the expected incidence of relapse in a difficult to treat patient population with major depression, as seen in the published ECT literature. After successful acute response to ECT, at four weeks of follow up, the incidence of relapse has been reported to range from 4.5% (Prudic, 2004) to 52% (Sackeim, 2001).

PRIMARY EFFICACY OUTCOME

The MADRS total score was used as the primary outcome measure in Study 44-01103. Table 20.12 shows the MADRS total score for Group 1, (i.e., patients who were responders in the active treatment group in Study 44-01101), which is the group of interest to determine maintenance of effect. As further discussed in Section 12.2 of the interim study report for Study 44-01103 (Appendix 21), MADRS mean scores for all Groups remain stable from study entry through week 4.

Table 20.12. Study 44-01103 Results: A Priori-Defined Outcome Measures for

Group 1¹

Efficacy Outcome Measures	Week 1	Week 2	Week 3	Week 4
MADRS Total Score Mean Change ²	-20.1	-21.4	-20.3	-21.2
HAMD24 Total Score Mean Change ²	-18.0	-19.0	-18.4	-19.6
HAMD17 Total Score Mean Change ²	-14.0	-14.4	-13.9	-14.6
MADRS Remission Rate ^{3,6} (%)	50	59.1	52.3	45.5
HAMD24 Remission Rate ^{4,6} (%)	47.7	54.5	47.7	43.2
HAMD17 Remission Rate ^{5,6} (%)	50	56.8	43.2	43.2

¹ Group 1 are patient who were responders in the active treatment group in Study 44-01101

² Baseline is defined as baseline of Study 44-01101

³ MADRS Remission is defined as MADRS total score <10

⁴ HAMD24 Remission is defined as HAMD24 total score <11

⁵ HAMD17 Remission is defined as HAMD17 total score <8

⁶ Remission rate is calculated using total enrolled sample

SECONDARY EFFICACY OUTCOMES

Secondary outcome measures for weeks 1-4 for HAMD 17 and 24 item total scores and for MADRS, HAMD 17 and HAMD 24 item response and remission rates are shown in Table 20.12 above. These outcome measures also demonstrate stability of response over 4 weeks.

TMS REINTRODUCTION TREATMENT CYCLES

Overall, 38.2% of all patients who have entered study 44-01103 have experienced at least one cycle of TMS reintroduction. Most treatments occur subsequent to the first month, with the median time to reintroduction ranging from 6.5 to 11 weeks after enrollment in study 44-01103.

These results suggest that symptomatic change sufficient to require protocol reintroduction occurs in less than half of the patients entering study 44-01103 overall, and that the time to reintroduction is not immediate, but occurs after approximately 1-3 months.

20.2.6.8.2. Safety

The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and emergent suicidal ideation. A summary of MedDRA preferred term adverse events occurring with an incidence on active TMS of $\geq 5\%$ incidence in any treatment group in Study 44-01103 is provided in Table 20.13.

There were no deaths, seizures or suicides reported at the time of database analysis for this interim report.

Table 20.13. Summary of MedDRA Preferred Term Adverse Events Occurring with an Incidence on Active TMS of $\geq 5\%$ Incidence in Any Treatment Group in Study 44-01103

Body System (-) Preferred Term	Group 1 (N=44) N (%)	Group 2 (N=27) N (%)	Group 3 (N=42) N (%)	Group 4 (N=23) N (%)
Gastrointestinal disorders				
- Constipation	0	5 (18.5)	2 (4.8)	0
- Diarrhoea	5 (11.4)	3 (11.1)	2 (4.8)	1 (4.3)
- Dry Mouth	1 (2.3)	4 (14.8)	5 (11.9)	1 (8.7)
- Nausea	7 (15.9)	4 (14.8)	3 (7.1)	4 (17.4)
- Vomiting	0	1 (3.7)	0	2 (8.7)
General disorders and site administration conditions				
- Application site pain	3 (6.8)	2 (7.4)	2 (4.8)	6 (26.1)
- Fatigue	2 (4.5)	2 (7.4)	5 (11.9)	3 (13.0)
- Pain	3 (6.8)	0	2 (4.8)	1 (4.3)
Immune System Disorders				
- Seasonal allergy	1 (2.3)	0	2 (4.8)	1 (4.3)
Infections and infestations				
- Upper respiratory tract infection	4 (9.1)	1 (3.7)	4 (9.5)	1 (4.3)
Musculoskeletal and connective tissue disorders				
- Arthralgia	8 (18.2)	4 (14.8)	8 (19.0)	1 (4.3)
- Back pain	5 (11.4)	2 (7.4)	3 (7.1)	0
- Muscle twitching	4 (9.1)	1 (3.7)	4 (9.5)	4 (17.4)
- Musculoskeletal stiffness	1 (2.3)	2 (7.4)	0	0
- Myalgia	1 (2.3)	1 (3.7)	5 (11.9)	0
- Pain in extremity	2 (4.5)	0	3 (7.1)	0
Nervous system disorders				
- Dizziness	5 (11.4)	1 (3.7)	2 (4.8)	1 (4.3)
- Headache	16 (36.4)	9 (33.3)	13 (31.0)	10 (43.5)

Body System (-) Preferred Term	Group 1 (N=44) N (%)	Group 2 (N=27) N (%)	Group 3 (N=42) N (%)	Group 4 (N=23) N (%)
Psychiatric disorders				
- Agitation	3 (6.8)	0	0	0
- Anxiety	7 (15.9)	2 (7.4)	6 (14.3)	3 (13.0)
- Depressive symptom	0	1 (3.7)	4 (9.5)	2 (8.7)
- Insomnia	13 (29.5)	10 (37.0)	14 (33.3)	7 (30.4)
- Irritability	2 (4.5)	2 (7.4)	2 (4.8)	0
- Libido decreased	4 (9.1)	3 (11.1)	1 (2.4)	0
Respiratory, Thoracic and Mediastinal Disorders				
- Nasal congestion	1 (2.3)	0	1 (2.4)	2 (8.7)
- Sinus congestion	2 (4.5)	0	1 (2.4)	2 (8.7)
Skin and subcutaneous tissue disorders				
- Hyperhidrosis	2 (4.5)	2 (7.4)	0	0
Uncoded verbatim terms				
- Increased frequency of headaches	0	1 (3.7)	0	0
- Menorrhea	0	0	0	1 (4.3)

20.2.6.8.3. Overall Safety and Efficacy Conclusions

- In patients who have shown an acute response to active treatment with the Neuronetics TMS System, the rate of protocol-defined relapse over a 4 week period of observation is 2.3%.
- The acute response to active TMS treatment can be effectively maintained in patients treated with antidepressant medication monotherapy during a 4 week period of follow up after their last TMS treatment, as shown by the pattern of symptom change over that period:
 - The mean change from baseline score prior to treatment shows a large, stable, and clinically meaningful reduction in total symptom burden over a 4 week period of maintenance treatment
 - A majority of patients maintain a criterion score of remission as measured by either the MADRS, HAM-D24 or the HAM-D17 that is stable over a 4 week period of maintenance treatment

Depending upon their treatment path prior for entry into study 44-01103, the percentage of subjects who experienced symptomatic worsening and were provided with reintroduction of active TMS treatment ranged from 33.3% to 47.8%

Active TMS was safe and well tolerated when administered in an adjunctive manner with antidepressant pharmacotherapy. Patients who showed an acute response to TMS treatment during either

controlled or open-label treatment with the Neuronetics TMS System show a pattern of adverse events during 24 week maintenance treatment with antidepressants that is:

- consistent with the expected profile of adverse events with medication use and
- consistent with the expected profile of adverse events associated with the episodic use of TMS as seen in Neuronetics' studies 44-01101 and 44-01102 (i.e., headache and application site pain were the most frequent events).

20.3. Conclusions Drawn from Studies 44-01101, 44-01102 and 44-01103

Transcranial magnetic stimulation (TMS) as delivered by the Neuronetics TMS System (NeuroStar™ System) is an effective, safe and well-tolerated antidepressant for the treatment for patients with major depressive disorder. The acute response to TMS treatment can be effectively maintained in a clinically meaningful manner during a follow up period of up to 24 weeks.

The most important source of support for this claim is derived from the results of the randomized, sham-controlled clinical trial, protocol 44-01101, which provides several important pieces of evidence that offer definitive support for the efficacy of TMS as delivered by the NeuroStar™ System in patients with major depression. Using accepted disease-specific measures of symptom change, active treatment with TMS was statistically significantly superior to sham TMS treatment at the primary outcome time point of 4 weeks (HAMD 17 and HAMD 24, MADRS with baseline adjustment). Importantly, the symptom change was also statistically significant for the traditional categorical outcomes of response (> 50% reduction of baseline scores) for all measures and for remission (successful resolution of clinical symptoms below accepted thresholds of wellness specific to each rating scale) at 6 weeks (MADRS and HAMD 24 item).

The pattern of symptom change observed in protocol 44-01101 was also accompanied by statistically significant evidence of functional improvement (Medical Outcomes Study SF-36), and by statistically significant evidence of patient-reported symptomatic and functional benefit (Q-LES-Q). These effects were broadly represented across the known symptom domains of the major depression syndrome, and followed a coherent temporal pattern.

Key evidence from the Neuronetics studies that demonstrates the safety and efficacy of the TMS therapy as delivered by the Neuronetics TMS System is as follows:

- First, the outcome on the major symptom rating scales in Study 44-01101 achieved statistically significant separation on both the continuous and the categorical outcomes.
- A second manner of analysis to support the clinical significance of the observed outcome on these rating scales is provided by the *statistically significant changes in key sub-factor scores of the HAMD and MADRS*.
- A third source of evidence to support the clinical significance of the observed changes is found in the pattern of *statistically significant change in patient-rated outcome measures*.
- A fourth source of evidence for the clinical significance of the results observed in protocol 44-01101 comes from the specific pattern of results observed in the accompanying open-label cross-over study, protocol 44-01102 which demonstrated *effectiveness in both non-responder populations exiting Study 44-01101* (active and sham treated) with higher rates of efficacy observed in the sham-treated group.
- The final source of evidence to support the clinical significance of the observed effect of active TMS is in the durability of the clinical response during the post-treatment taper phase of studies 44-01101 and 44-01102, and continuing into the first month of TMS-free follow up (interim study report; Study 44-01103).

In summary, TMS as delivered by the Neuronetics TMS System (NeuroStar™ System) is an effective and safe antidepressant for the treatment of patients with major depression who have not benefited from prior treatment with antidepressant medications. As described further in Section 12.6 of this submission, it compares favorably in clinical efficacy to the most commonly used options available for patients of this degree of clinical severity and provides a safety profile and evidence of clinical tolerability that also compares favorably to these other available options.

20.4. Statements of Compliance with 21 CFR part 56 (IRB), Part 50 (ICD) and Part 812

Studies 44-01101, 44-01102 and 44-01103 were conducted in compliance with 21 CFR part 56 (IRB), Part 50 (ICD) and Part 812.