NEURONETICS INTERIM STUDY REPORT
STUDY NO. 44-01103

14 April 2006

"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) System."

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Appendices

1.0 INTRODUCTION

The clinical development program for the Neuronetics TMS System consisted of three integrated clinical protocols as displayed in Figure 1.

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

Patients 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 1.

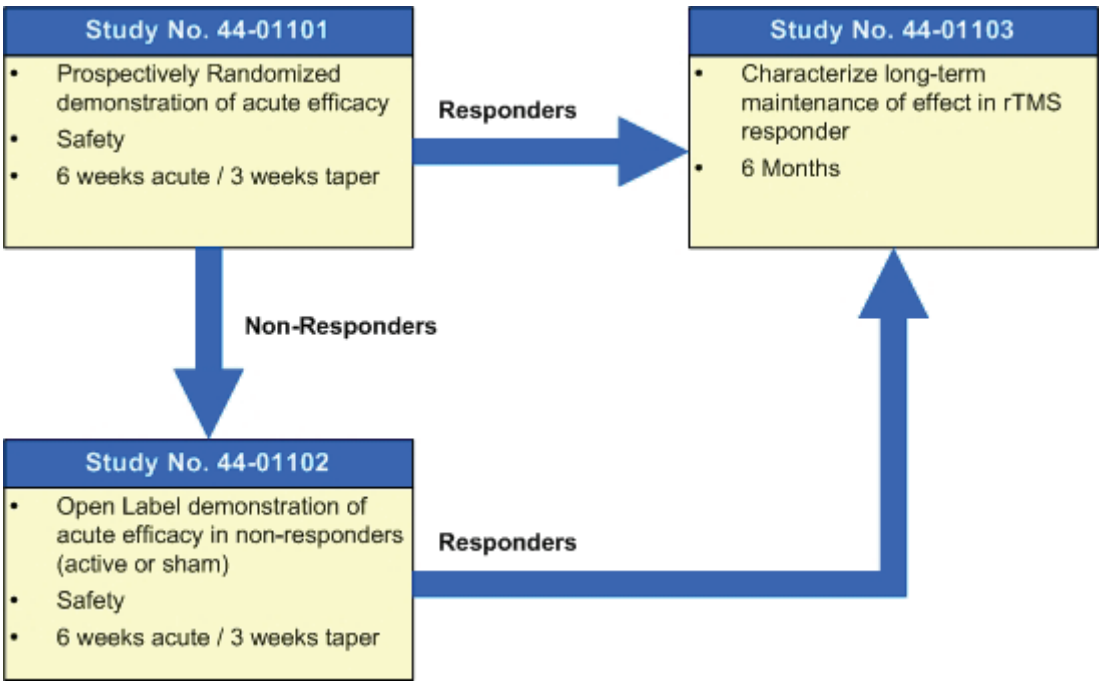


Figure 1. Neuronetics' Clinical Studies and Patient Allocation

Table 1. Summary of Neuronetics Clinical Studies 44-01101, 44-01102 and 44-01103

Study No.	Study Summary	Study Objective
44-01101	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. 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. During the taper phase, as TMS was tapered, monotherapy with oral anti-depressant medications was initi-ated. 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.	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 experi-mental conditions in patients meeting DSM-IV criteria for Major Depressive Episode, single or recurrent episode. Only patients meeting diagnostic criteria for Major De-pression were included in this study. Personnel at the study sites were blind to the choice of primary efficacy measure and to the point of declaration of the efficacy outcome. 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 sec-ondary outcome measures. Safety was assessed by adverse event reports, and by tar-geted safety evaluation of air-conduction auditory thresh-old. Cognitive function.was assessed with the Mini Mental Status Examination, the Buschke Selective Reminding Test, and the Autobiographical Memory Inventory-Short Form.
44-01102	An open-label, uncontrolled clinical trial for patients who do did not meet pre-defined criteria for re-sponse in Study 44-01101. This protocol was otherwise identical in design and treatment sequence to Study 44-01101.	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 recur-rent episode, who had not shown an acute clinical response to daily dose active of sham rTMS administered for up to 6 weeks. Personnel at the study sites were blind to the choice of primary efficacy measure and the point of declaration of the efficacy outcome.

Study No.	Study Summary	Study Objective
44-01103	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. 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.	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. To minimize study bias, the Investigator was blinded to the definition of response.

Protocol 44-01103 was conducted under Neuronetics' IDE No. G030185 that was conditionally approved by the FDA on 10 October 2003 and approved on 24 May 2004.

A list of investigators participating in Study 44-01103 is provided in Appendix 1. The study protocol and informed consent document for Study No. 44-01103 is provided in Appendix 2. All referenced data tables are provided in Appendix 3. SAE vignettes and related materials are provided in Appendix 4.

2.0 PROTOCOL SUMMARY

Enrollment for protocol 44-01103 has closed, but patient activity is still underway, and therefore, the final patient visit has not yet occurred. The data described in this study report represent an interim analysis, and the final data analysis will be included at the time of filing of the final study report. As this is an interim data summary, all data have undergone preliminary monitoring and review. The data reported here represent all data available for review on patients who were enrolled in study 44-01103 as of the final data cutoff date of 31 January 2006. These data may be revised based on ongoing patient visits and procedures, data completion, and data queries that are anticipated to occur prior to data lock and the preparation of the final study report for this protocol.

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 definition of *sufficient clinical response* used the same threshold criterion for meaningful clinical change as was used in protocol 44-01102. These criteria 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 HAMD17 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.

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 as given below, 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.

- 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 for symptomatic worsening, then TMS reintroduction was permitted as an add-on treatment to the existing antidepressant pharmacotherapy. The protocol-defined criterion that triggered reintroduction of TMS was 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 treatment block with TMS consisted of two weeks of TMS administered twice weekly, followed by up to 4 weeks of 5x/week TMS administration using the Neuronetics TMS System. 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 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 reintroduction 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, and is provided in section 17 (Statistical Analysis) of protocol 44-01103.

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 clinical utility for the practicing clinician to inform potential approaches to patient management in the aftermath of successful acute treatment with TMS. For example, this information will expand an understanding of the clinical significance of an acute response to TMS, and will allow a more informed position for the design of future controlled trials of maintenance of effect or relapse prevention with TMS. The use of a TMS re-introduction strategy also provides new information about the potential for intermittent TMS to serve as a clinically meaningful rescue intervention for patients who experience symptom breakthrough during maintenance pharmacotherapy.

Specifically, upon the conclusion of this study, it 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 successfully be 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?***

Based on the data available at the time of data cut-off for this interim report, and as previously agreed with the FDA, this interim report provides:

- Data summaries that characterize the pattern and course of symptom change and the pattern and timing of illness relapse during the first 4 weeks of the study, on the primary efficacy outcome measures, namely the MADRS, HAMD24 and HAMD17 total scores.
- Complete adverse event information available as of the data cutoff date.
- A summary of the available information on symptom outcome for weeks 8 through 24.

This interim data must be considered preliminary, particularly for data obtained past study week 4, since patients are in varying stages of study completion at these later time points, and it is expected that the final study report numbers will vary from the data reported here. Nevertheless, we believe that sufficient patient information has been accrued to allow major conclusions to be drawn at this time.

<u>Major Conclusions That Can Be Drawn From This Interim Study Include:</u>

- A majority of patients who experienced symptomatic response to acute TMS treatment in study 44-01101 showed a clinically meaningful and stable pattern of symptomatic response during *4 weeks* of maintenance antidepressant pharmacotherapy alone.

  - Depending upon their treatment path prior to entry into study 44-01103, the incidence of protocol-defined relapse ranged from 0% to 7.2%.

- Depending upon their treatment path prior to entry into study 44-01103, the percentage of subjects who experienced symptomatic worsening and were provided with *reintroduction of active TMS* treatment for at least one cycle observed at this interim report across 24 weeks ranged from 33.3% to 47.8%

3.0 METHODS OF DATA COLLECTION AND ANALYSIS

3.1. Clinical Assessment Instruments

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 2, and include both clinician-rated and patient-reported outcome measures.

Table 2. Diagnostic, Symptom Assessment, Functional Status and Quality of Life Instruments Used in Protocols 44-01101, 44-01102 and 44-01103

Assessment Tool	Description
Psychiatric Diagnostic Interview - Structured Clinical Interview for the DSM-IV (SCID-IV)	- 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
Treatment History - Antidepressant Treatment History Form (ATHF)	- 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.
Clinician-Rated Symptom Assessments - 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)	- 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.

Assessment Tool	Description
<u>Patient-Reported Symptom, Quality of Life, and Functional Status Assessments</u> - 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)	- 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.
<u>Patient-Reported Health Care Resource Utilization and Work Productivity Assessment</u> - Health Resource Utilization Questionnaire (HRQ)	- The HRQ is a multi-item self-reported questionnaire which assesses health care utilization, work status and productivity, and caregiver burden.

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 staff at Neuronetics' contracted vendor for electronic data capture (EDC [redacted] using the current version of the Medical Dictionary for Regulatory 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 3.

Table 3. 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

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.

3.2. Schedule of Events

A detailed discussion of the study protocol and procedures is included in Protocol 44-01103, Appendix 2, of this report. A synopsis of the study procedures is provided here, and the schedule of study events is outlined in Table 4.

Table 4. Schedule of Study Events for Protocol 44-01103

Phase	101 Study	6-Month Maintenance of Effect								
Week	Taper Wks 1,2,3	Wk 1	Wk 2	Wk 3	Wk 4[e]	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[c]
Day(s)		1-6	7-13	14-20	21-28	29-56	57-84	85-112	113-140	141-168
Informed Consent	X[a]									
Motor Threshold Determination	X[a,h]									
Efficacy Assessments										
HAM-D_{24}	X	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
MADRS	X	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
CGI-S	X	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
PGI-I	X	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
SF-36										X[e]
Q-LES-Q										X[e]
Health Resource Questionnaire										X
IDS-SR	X	X	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Neuropsychological Assessments										
Mini Mental Status Exam										X[e]
Buschke Selective Reminding Task										X[e]
Autobiographical Memory Interview										X[e]
Safety Assessments										
Pregnancy test[f]	X									
Audiometry assessment										X
Adverse Events[g]	X ----------									----------X
Concomitant Treatment	X ----------									----------X
rTMS Treatment Session Re-Introduction (2x/wk for 2 weeks, 5x/week for 4 weeks) See protocol text for description of reintroduction parameters		X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]	X--X[b,d]

a. **A minimum of 3 days and a maximum of 7 days may elapse between the last 44-01101/2 study visit and the baseline visit in this study.** NOTE: **An informed Consent for this study must be signed prior to initiating any study-related procedures. A Motor Threshold Determination and audiometry assessment must also be performed immediately prior to administration of the first rTMS treatment to a patient in this study. Subsequent Motor Threshold Determinations are done prior to the re-introduction of any rTMS treatment block, and weekly during that treatment block.**

b. **For re-introduction of rTMS, 2x/week, treatment should be Monday and Friday. For 5x/week treatment should occur on a Monday, with daily treatment sessions occurring on Monday through Friday of each week.**

c. **Patients who prematurely discontinue should complete all Week 24 procedures within 2 days after their last rTMS treatment session.**

d. **Efficacy assessments must be completed every other week during each rTMS treatment re-introduction**

e. **Efficacy and safety assessments to be performed the end of each month when visits are monthly.**

f. **If patient is a female of childbearing potential, a urine pregnancy test will be performed at baseline.**

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

h. **In addition to the indicated days, motor threshold may be repeated at any time during the course of the active rTMS treatment sessions based on clinical assessment of the supervising physician.**

4.0 INVESTIGATIVE SITES FOR NEURONETICS STUDY 44-01103

4.1. Investigative Sites and Subjects Per Investigative Site

A listing of the clinical study investigators whose sites were qualified to conduct Study 44-01103 as assessed by Neuronetics staff per standard operating procedure and who participated in this study is provided in Appendix 1 of this report.

The table in Appendix 1 lists all investigators who participated in the conduct of Study 44-01101 as well as those who participated in Neuronetics' continuation studies 44-01102 and 44-01103. Enrollment into protocol 44-01101 for each site and the number of patients who transitioned from protocol 44-01101 into the other two protocols, 44-01102 and 44-01103 is also shown in the listing.

One hundred and thirty-six patients (N=136) with MDD participated in Study 44-01103. Twenty sites contributed patients to protocol 44-01103.

Three sites were non-U.S. sites, two in Australia and one in Canada; a total of 15 patients were enrolled at these 3 sites. The non-U.S. studies were conducted under an Investigational Testing applications (Canada) or Clinical Trial Notifications (Australia) approved by the regulatory authorities in the countries of clinical testing.

All sites underwent a site-specific study initiation meeting, and all staff were trained in protocol procedures and device use as described below.

4.2. Site Selection Procedures, Training Methods and Follow-Up Procedures for Study Device Operation

All study sites participating in Study 44-01103 participated in the initial study 44-01101. All sites in Study 44-01103 were assessed for qualification in the Neuronetics clinical studies during the initial qualification for Study 44-01101.

In brief, qualified study sites were provided an extensive training sequence prior to being permitted to utilize the Neuronetics TMS System in the study protocol 44-01101, 44-01102, or 44-01103.

In November 2003, an investigator meeting held prior to the start of the protocol. During this meeting, study site personnel were provided a series of lectures that included a detailed review of the biophysics of magnetic stimulation, safety considerations and currently accepted safety practices, and a review of the safety procedures required for this study. For approximately half of one day, personnel participated in several hands-on didactic training stations that were set up with live demonstrations of the device equipment. All study staff were provided with written materials to review.

Subsequent to the initial training meeting, individual study site initiation visits were scheduled for each site. At these individual visits, all personnel who were expected to be using the Neuronetics TMS system during the trial were required to attend. No personnel were permitted to use the Neuronetics TMS System unless they obtained specific training conducted and documented by Neuronetics and demonstrated evidence of competence in the use of the device.

Following these training sessions, within-study follow up occurred in two ways. Neuronetics personnel were present for the first patient's baseline visit and first treatment in Study 44-01101 at each study site. During these visits, Neuronetics staff members were able to observe continued adherence to protocol technique as taught in the training sessions. In addition, Neuronetics staff returned on at least two different occasions within the duration of the study to review procedural technique with all study sites. Any evidence of training deficiency was noted and remediated by the Neuronetics trainer during these visits.

As a study requiring participation in protocol 44-01101, protocol 44-01103 initiation was conducted during the protocol 44-01101 training. Procedures were reviewed with sites upon verification of a patient eligible to transition to Study 44-01103.

4.3. Training Methods and Follow-Up Procedures for Clinician-Rated Assessments

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 in Study 44-01101, in two ways. All prospective raters were required to independently view and score a series of 5 videotapes of different patients interviewed using this structured guide. These tapes were prepared specifically for the Neuronetics by staff of the Department of Biological Psychiatry at Columbia University and included patients with a broad range of relevant clinical symptomatology. Each rater's scores were compared to a pooled expert score for each tape, and a minimum threshold intraclass correlation statistic was required to be achieved prior to permitting the rater to participate in the study.

In Study 44-01101, once the study ratings began, all patient HAMD/MADRS rating interviews for baseline, week 4 and week 6 assessments were videotaped, and a selected subset of these ratings for each rater were independently reviewed, and quantitatively scored for rater technique by an experienced rater at the New York State Psychiatric Institute. Any deficiencies in rater technique were identified, and if re-

quired, the rater was removed from the active rater pool. Details of the rater training program and documentation of the initial rater certification and the follow-up videotaped interviews is contained in the study master files at Neuronetics.

Only raters that were certified in Study 44-01101 were allowed to complete ratings for Study 44-01103.

4.4. 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 who were trained in data entry using this EDC system were authorized to enter the data.

Study monitoring was conducted by Neuronetics staff and contract research associates from MedSource, Inc., for all Neuronetics US and CA clinical study sites. The Australian sites were monitored by Quintiles, Inc. Both MedSource and Quintiles are qualified, contract research organizations. 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.

Enrollment for protocol 44-01103 has closed, but patient activity is still underway, and therefore, the final patient visit has not yet occurred. The data described in this study report represent an interim analysis, and the final data analysis will be included at the time of filing of the final study report. As this is an interim data summary, all data have undergone preliminary monitoring and review.

The data reported here represent data available through week 4 for all patients from Study 44-01101 who entered Study 44-01103, and all other data available in Study 44-01103 at other time points as of the final data cutoff date of 31 January 2006. This dataset for Study 44-01103 was e (EDC) contract research organization to naly on 06 February 2006. These data may be revised ta queries that are anticipated to occur prior to data lock and the preparation of the final study report for this protocol.

5.0 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 for study 44-01103.

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 HAMD17 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.

The definition of *sufficient clinical response* used the same threshold criterion for meaningful clinical change as was used in protocol 44-01102. These criteria 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.

6.0 STUDY POPULATIONS AND STATISTICAL ANALYSIS

6.1. Study Populations

All subjects who signed an informed consent form the ***evaluable study population***.

There are four potential routes of entry into study 44-01103, and they represent the four separate populations contained in the study analysis. The first three groups represent the various paths for active TMS-treated subjects to enter study 103, while the 4th group represents the sham TMS responders from study 44-01101.

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

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

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

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

6.2. Statistical Analysis Methods

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. Of the 23 sites contributing patients to Protocol 44-01101, 20 sites contributed patients to Protocol 44-01103. 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 115 patients would be enrolled. At the time of this report, 136 patients were enrolled in this clinical trial.

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 will be reported separately, without pooling. This is expected to provide 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 as stipulated in the original protocol are described below.

6.2.1. Demonstration of Durability of Effect

As discussed with the FDA during the review of [redacted] the portion of the Study 44-01103 dataset that is of primary in durability of effect is the first four weeks of Protocol 44-01103 for the entire population of patients in Group 1 as defined in section 6.1 above. 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 dataset allows a descriptive view of this cohort of patients across 7 weeks after their exit from the acute treatment phase. The data for Group 1 contained in this report is complete for all patients who entered Study 44-01103 and is the final data as of the data cutoff date of 31 January 2006.

All other data presented in Study 44-01103 is of secondary interest in addressing the information requested by the FDA pertaining to demonstration of durability of acute effect. This data is provided in this interim report for Study 44-01103 for all available information present in the database on the data cutoff date.

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 and therefore did not qualify for reintroduction of TMS. 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."

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 described above as determined by CGI-S score.

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' (i.e., including all patients discontinuing from study for any reason through the first 4 weeks of Protocol 44-01103).

6.2.2. Descriptive Statistical Analysis of Longitudinal Symptom Scores

For all other efficacy variables, the analyses 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.

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.

7.0 STUDY PERIOD AND EVALUABLE PATIENTS

As noted in the final study report for protocol 44-01101, the first site initiation for protocol 44-01101 occurred on 18 December 2003, and first patient was enrolled on 26 January 2004. The first patient entered protocol 44-01103 on 09 April 2004. As of the time of data lock for protocol 44-01101 on 31 Jan 2006, 136 patients had been consented and enrolled for study participation in protocol 44-01103 and constitute the ***evaluable patient population (n=136)*** for this interim report.

A summary of the specific reasons for patients to be declared non-evaluable for analysis will be summarized in the final study report for protocol 44-01103 and will not be discussed here.

8.0 PATIENT DEMOGRAPHICS AND BASELINE ILLNESS CHARACTERISTICS OF THE 44-01103 STUDY POPULATION

The evaluable study population included 136 patients. Demographic and clinical variables for this population are described Section 8.1 and shown in Table 5. Baseline illness characteristics are described in Section 8.2 and shown in Tables 6 and 7.

8.1. Patient Demographic and Clinical Variables

The baseline demographic features of the 4 treatment Groups did not differ in any clinically meaningful way from each other as shown in Table 5. These characteristics were also clinically similar to the demographic features observed in the overall patient population randomized into study 44-01101.

Table 5. Demographic Features for the Evaluable Population in Study 44-01103

Table 5. Demographic Features for the Evaluable Population in Study 44-01103

Variable	Treatment Group			
	Group 1 (N=44)	**Group 2 (N=27)**	**Group 3 (N=42)**	**Group 4 (N=23)**
Gender				
• Female	24 (54.5)	16 (59.3)	22 (52.4)	11 (47.8)
• Male	20 (45.5)	11 (40.7)	20 (47.6)	12 (52.2)
Age (Years, SD)	49.2 (9.7)	50.6 (11.5)	49.4 (8.9)	48.6 (10.2)
Ethnic Origin				
• Caucasian	39 (88.6)	27 (100)	39 (92.9)	19 (82.6)
• African-American	2 (4.5)	0	2 (4.8)	0
• Asian	0	0	0	0
• Hispanic	2 (4.5)	0		3 (13.0)
• Native American	1 (2.3)	0	0	0
• Other	0	0	1 (2.4)	1 (4.3)

8.2. Baseline Illness Characteristics

A summary of *illness history, characterization of treatment resistance history, and baseline symptom severity shown by illness descriptive variables* is included in Tables 6 and 7 for the evaluable study population.

Table 6. Illness History and Characterization of Treatment Resistance for the Evaluable Population in Study 44-01103

Variable	Treatment Group			
	Group 1 (N=44)	**Group 2 (N=27)**	**Group 3 (N=42)**	**Group 4 (N=23)**
Depression History				
- Single episode	2 (4.5)	1 (3.7)	0 (0)	3 (13.0)
- Recurrent episodes	42 (95.5)	26 (96.3)	42 (100.0)	20 (87.0)
Duration of current episode				
- Length [mean (SD)]	12.4 (8.8)	13.8 (10.5)	12.2 (8.9)	15.1 (9.4)
- < 24 months N(%)	37 (84.1)	20 (74.1)	37 (88.1)	19 (82.6)
- ≥24 months N(%)	7 (15.9)	7 (25.9)	5 (11.9)	4 (17.4)
Secondary Diagnoses N(%)				
- None	26 (59.1)	17 (63.0)	34 (81.0)	20 (87.0)
- Any Anxiety Disorder	18 (40.9)	10 (37.0)	8 (19.0)	3 (13.0)
ATHF Rating Summary (# of Level 3 Exposures)				
- 1	24 (54.5)	15 (55.6)	23 (54.8)	11 (47.8)
- 2	13 (29.5)	11 (40.7)	13 (31.0)	10 (43.5)
- 3	6 (13.6)	1 (3.7)	5 (11.9)	1 (4.3)
- 4	1 (2.3)	0 (0)	1 (2.4)	1 (4.3)
Mean # of ATHF Level 3 Exposures	1.6	1.5	1.6	1.7

The illness history was similar across the 4 treatment Groups, however there was a slightly lower incidence of recurrent illness, and the lowest incidence of anxiety disorder comorbidity in the Group 4 population. This is of interest, since these individuals were patients who had responded to sham TMS in study 44-01101, transitioned to antidepressant medication therapy and continued on to study 44-01103 in continuity. These patients may therefore be expected to show some clinical features of a less severe clinical course, which is seen in the reduced incidence of recurrent depression and a lower incidence of comorbid anxiety.

Table 7. Illness Descriptive Variables at Study Entry for the Evaluable Population in Study 44-01103

Variable	Treatment Group			
(Values observed at last visit prior to entry)	**Group 1 (N=44)**	**Group 2 (N=27)**	**Group 3 (N=42)**	**Group 4 (N=23)**
MADRS Total Score [mean (SD)]	9.0 (8.2)	10.6 (6.3)	11.0 (9.0)	10.9 (8.1)
HAMD24 Total Score [mean (SD)]	8.6 (6.6)	10.2 (5.2)	9.5 (6.3)	9.9 (6.6)
HAMD17 Total Score [mean (SD)]	6.5 (4.8)	7.9 (3.7)	7.4 (5.1)	7.5 (5.0)
CGI-Severity Score [mean (SD)]	1.9 (1.2)	2.4 (0.9)	2.2 (1.1)	2.3 (1.0)
IDS-SR Total Score [mean (SD)]	14.4 (9.8)	17.5 (9.4)	15.5 (10.5)	13.4 (9.4)

9.0 PATIENT DISPOSITION

At the time of this interim study report, 136 patients had been enrolled in protocol 44-01103. Of those patients, N=44 were allocated to Group 1, N=27 were allocated to Group 2, N=42 were allocated to Group 3, and N=23 were allocated to Group 4. At the end of Week 4, only four patients had discontinued treatment, and one patient was ongoing but had not yet reached the Week 4 time point, leaving N=131 patients available for analysis.

At the time of this interim study report, N=70 patients had completed study 44-01103 through Week 24, N=29 were allocated to Group 1, N=23 were allocated to Group 2, N=28 were allocated to Group 3, and N=15 were allocated to Group 4.

During the first four weeks of study 44-01103, the reasons for discontinuation were N=1 (protocol violation), N=3 (lost to follow up or failed to return). Overall, of the 155 patients who were allocated to active TMS in study 44-01101 (i.e., Group 1 in this report), 28.5% (44/155) continued on directly into study 44-01103, while of the N=146 patients who were allocated to sham TMS treatment in study 44-01101 (i.e., Group 4 in this report), 15.8% (23/146) continued directly into study 44-01103.

10.0 PATIENT DISPOSITION

Concomitant medication use in study 44-01103 will be provided in the final study report and is not discussed in this interim report.

11.0 EFFICACY OUTCOMES

The primary and secondary outcome measures used in the analyses for Study 44-01103 and the order of their sequential testing are listed in Section 17 of the protocol for Study 44-01103 (Appendix 2).

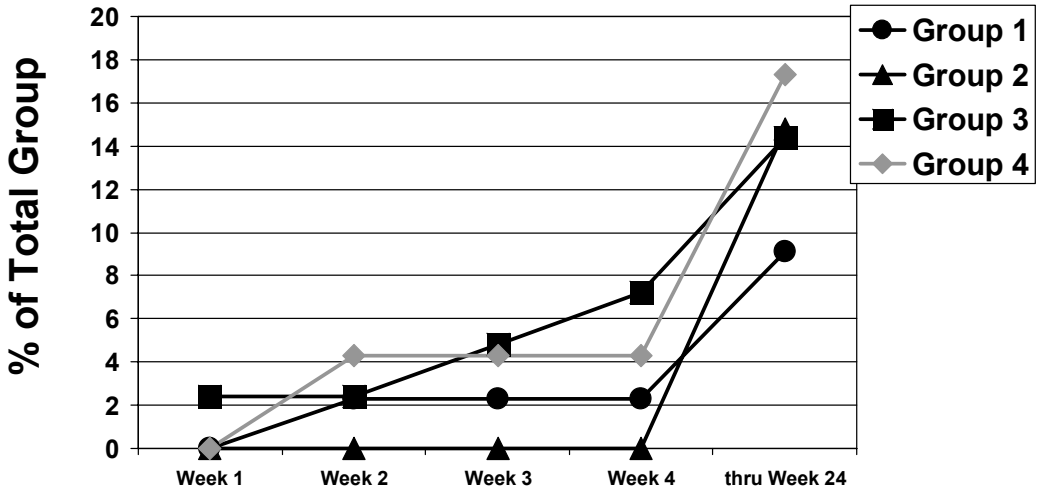
In all analyses, the primary study population of interest was declared as the *intent-to-treat population,* defined as including all subjects who signed an informed consent document.

11.1. Durability of Acute Efficacy

Durabilty 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. This *a priori* analysis is presented in Figure 2.



Relapse definition: Discontinuation due to lack of efficacy, and all cause discontinuation through Week 4

Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 2. Incidence of Relapse Using the *A Priori*-Defined Protocol Criterion During

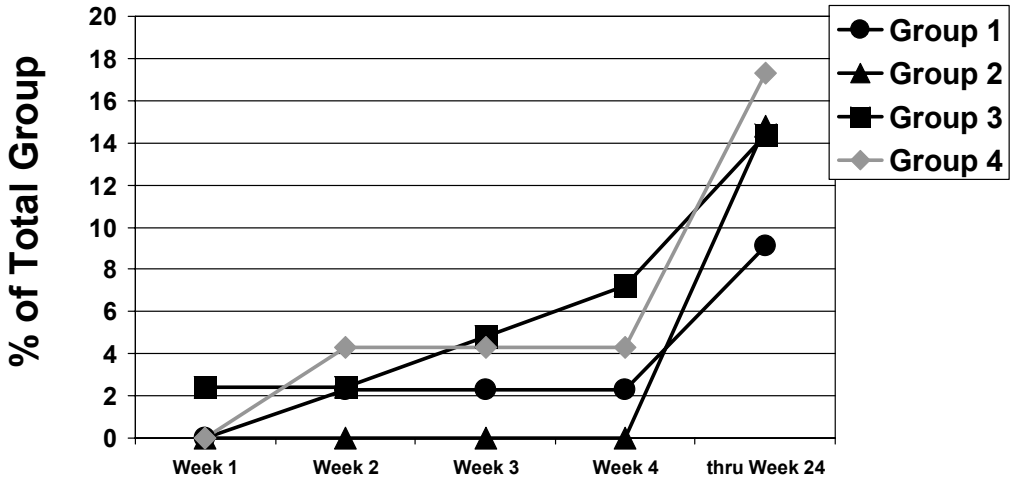
Weeks 1 through 4 and At Study Endpoint in Study 44-01103

During discussions with the FDA at the time of IDE filing [redacted] the Division requested that an alternative, exploratory definition [redacted] lied 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 notication 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 last 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. This analysis is presented in Figure 3.



Relapse definition: Discontinuation due to lack of efficacy, and all cause discontinuation through Week 4

Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 3. Incidence of Relapse Using the ECT Literature Definition Criterion During

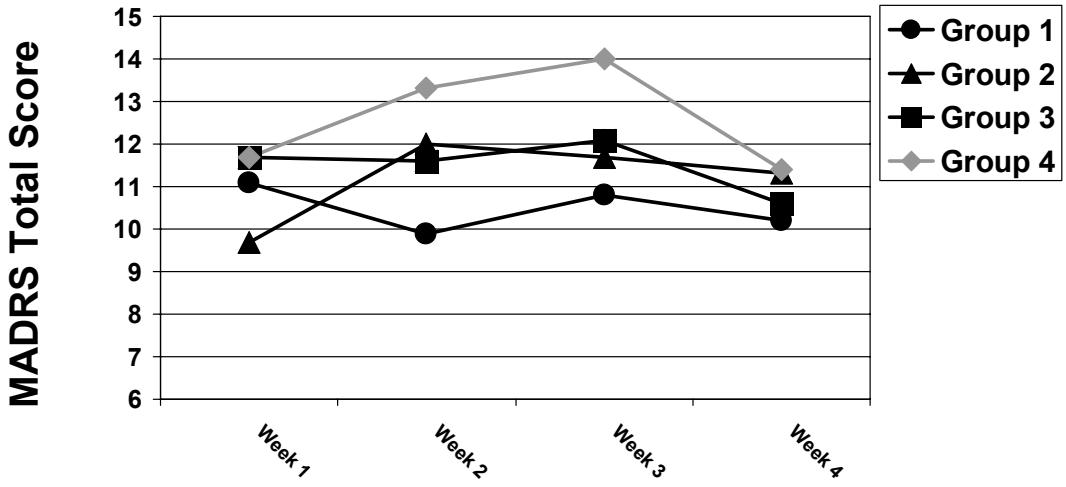
Weeks 1 through 4 and At Endpoint in Study 44-01103

Figure 3. Incidence of Relapse Using the ECT Literature Definition Criterion During Weeks 1 through 4 and At Endpoint in Study 44-01103

These data demonstrate 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%. An alternative definition was also applied in an exploratory manner over this same time interval, based on a definition of change in HAMD24 score derived (a relapse definition commonly used in the ECT literature). Based on this definition, 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).

11.2. Primary Efficacy Outcome

The MADRS total score was used as the primary outcome measure in study 44-01103. Tabular display of the MADRS total score at all time points from week 1 through week 24 is shown in Table 3.1 in Appendix 3. The MADRS total score is shown below in Table 8 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. Figure 4 displays the mean total score across weeks 1 through 4 for all Groups.



Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 4. MADRS Total Score (mean value) Observed Case Weeks 1 through 4 and At Endpoint in Study 44-01103

11.3. Secondary Efficacy Outcomes

The HAMD24 and HAMD17 total scores were used as secondary outcome measures in study 44-01103. Tabular display of the HAMD24 and HAMD17 total scores at all time points from week 1 through week 24 are given in Tables 3.2 and 3.3 in Appendix 3.

Figures 5 and 6 below display the mean total score for the HAMD24 and HAMD17, respectively, across weeks 1 through 4.

The HAMD24 and HAMD17 total scores and remission rates for MADRS, HAMD24 and HAMD 17 are shown in Table 8 for Group 1, i.e., patients who were responders in the active treatment group in Study 44-01101, which is the group of interest for determination of maintenance of effect.

Table 8. Study 44-01103 Results: A Priori-Defined Outcome Measures for Group 1[1]

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

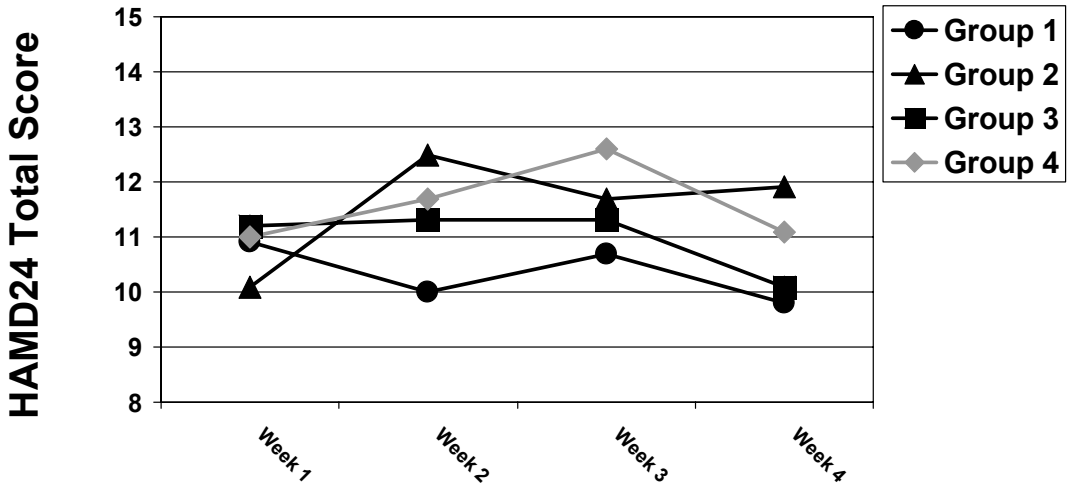
[3] MADRS Remission is defined as MADRS total score <10

[4] HAMD24 Remission is defined as HAMD24 total score <11

[5] HAMD17 Remission is defined as HAMD17 total score <8

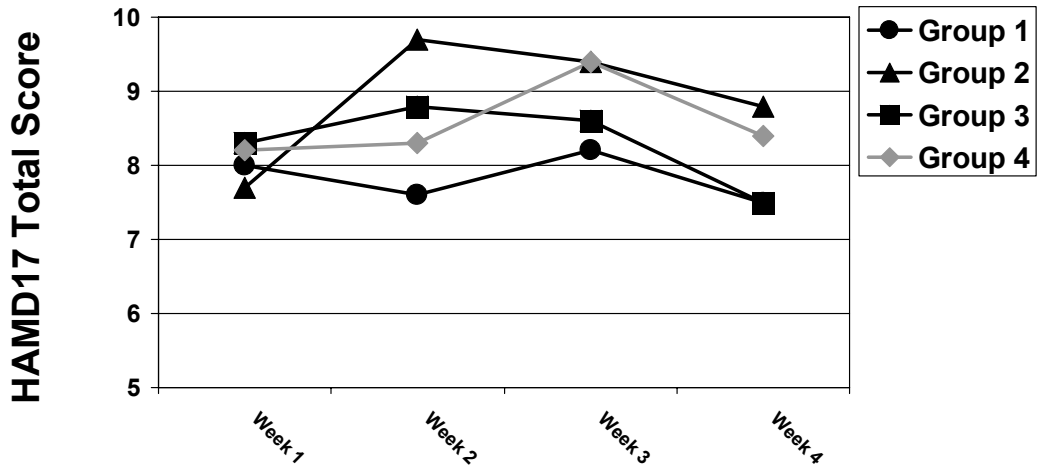
[6] Remission rate is calculated using total enrolled sample

Figures 7 through 9 display the percentage of patients achieving remission criterion on the MADRS, HAMD24 and HAMD17, respectively, across weeks 1 through 4 for all Groups. In these figures, a conservative estimate of remission rates are provided by using the sample size at entry for each treatment Group as the denominator in the computations. Because the study populations are currently at varying stages of study completion at time points beyond week 4, remission data for these later time points has not yet been generated. Detailed summary tables for remission are included in Tables 3.4, 3.5, and 3.6 in Appendix 3.



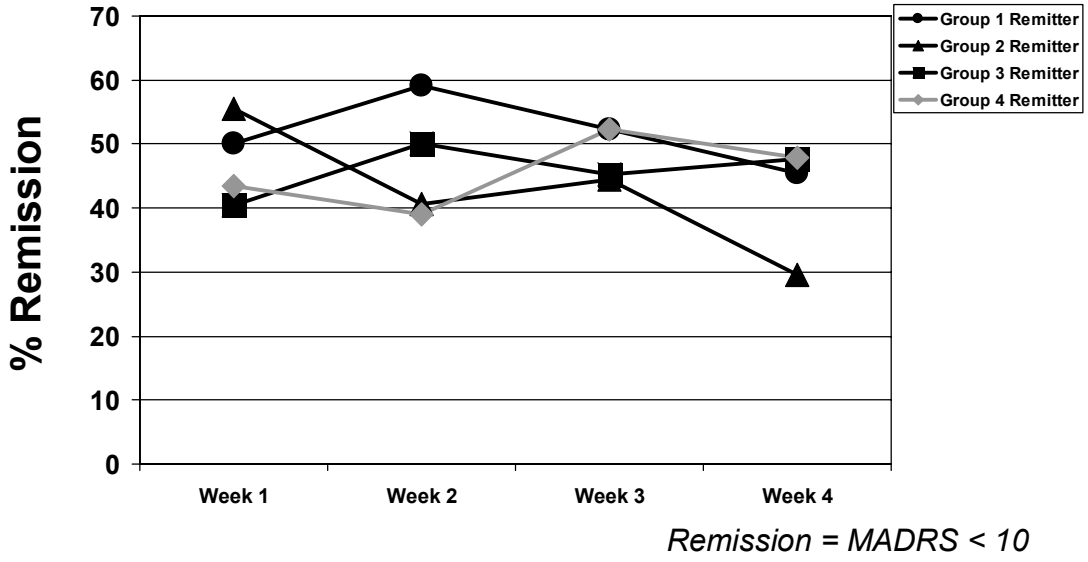
Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 5. HAMD24 Total Score (mean value) Observed Case Weeks 1 through 4 and At Endpoint in Study 44-01103



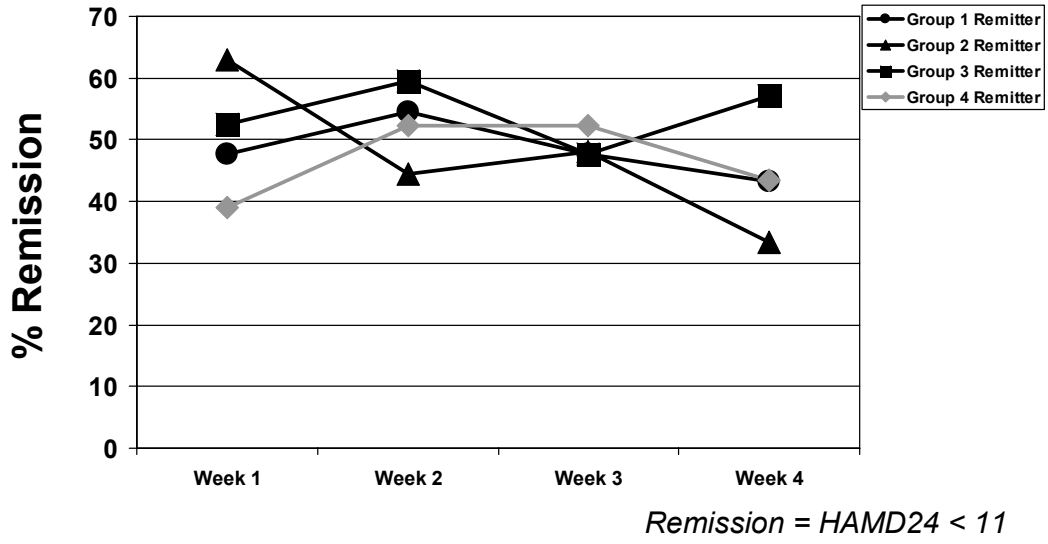
Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 6. HAMD17 Total Score (mean value) Observed Case Weeks 1 through 4 and At Endpoint in Study 44-01103



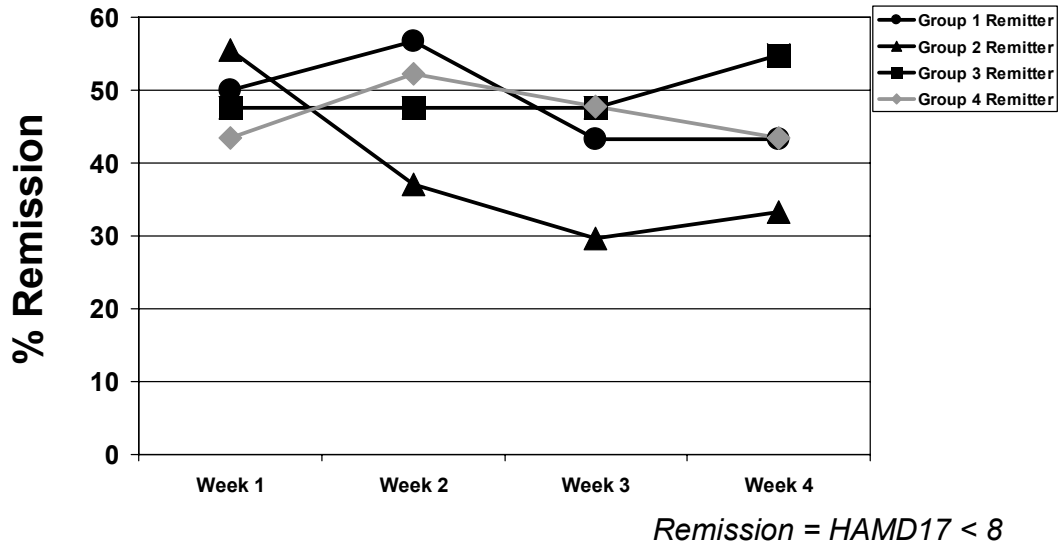
Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 7. MADRS Remission Rate Weeks 1 through 4 in Study 44-01103



Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 8. HAMD24 Remission Rate Weeks 1 through 4 in Study 44-01103



Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders; Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 9. HAMD17 Remission Rate Weeks 1 through 4 in Study 44-01103

11.4. Overall Conclusions Based on Interim Report of A-Priori Defined Efficacy Outcome Measures

- 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%
  - Using a literature-based alternative definition of relapse derived from the HAMD24 total score, the rate of relapse in this same population over the same 4 week time interval is 9.1%
- 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, HAMD24 or the HAMD17 that is stable over a 4 week period of maintenance treatment.

12.0 TMS RE-TREATMENT SCHEDULE, TMS TREATMENT PARAMETERS AND COMPLIANCE

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 for symptomatic worsening, then TMS reintroduction was permitted as an add-on treatment to the existing antidepressant pharmacotherapy. The protocol-defined criterion that triggered reintroduction of TMS was 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."

TMS re-treatment sessions were conducted using the Neuronetics Model 2100 TMS System as described in Section 2. The therapy coil used for TMS re-treatment was a known active coil used to determine motor thresholds (coil labeled 'MT Active'). This known, active coil was used for all treatments in the open-label study protocol 44-01103.

Treatment coil assignment for each patient was indicated by the electronic information previously recorded on flash memory embedded on the unique treatment card assigned to that patient. When inserted into the console, the operator was prompted to attach the specific coil defined by the treatment assignment, displayed on the console by the text: "Attach MT/Active Coil" for all patients entered into study 44-01103. The site staff then manually connected the MT/Active coil prior to proceeding with each TMS treatment session.

Each reintroduction treatment block with TMS consisted of two weeks of TMS administered twice weekly, followed by up to 4 weeks of 5x/week TMS administration using the Neuronetics TMS System. Dose parameters used were identical to those used in Protocols 44-01101 and 44-01102 as given below. If symptom improvement occurred during the course of TMS re-introduction, 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.

Treatment parameters were standardized for each treatment session using a magnetic field intensity of 120% of the patient's observed motor threshold, at a repetition rate of ten magnetic pulses per second. Treatment intensity could be adjusted to 110% of observed motor threshold if clinically indicated for tolerability. Pulses were grouped in 30 second cycles with a stimulation on-time of 4 seconds, and an off-time of 26 seconds. A treatment session lasted for 37.5 minutes for a total number of 3000 magnetic pulses per session.

Motor threshold was determined weekly during the acute treatment phase by visual observation of thumb or finger movement using MT Assist, a standardized mathematical algorithm that provided an iterated estimate of the motor threshold across four estimations (MT1 through MT4). The final motor threshold was computed as the average of the four iterations (Recommended MT).

The standardized treatment location was operationally defined in the protocol over the left prefrontal cortex, determined by a standard convention of movement of the TMS coil 5 cm anterior to the motor threshold location along a left superior oblique plane, with a rotation point about the subject's nose. Spatial coordinates of this position were recorded to allow precise placement of the coil in the same position for the next treatment session. Coordinates were reset weekly with each repeat motor threshold. Coil movement within a treatment session was permitted in a limited, pre-defined sequence for comfort as needed, to limit variability in placement.

Compliance with the treatment schedule will be reported in the final report for study 44-01103.

13.0 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 as noted in Figure 10 below. The distribution of this reintroduction course across the four treatment Groups is shown. 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.

There is insufficient information at this time to characterize the 2nd or 3rd TMS reintroduction cycles.

Variable	Treatment Group			
	Group 1 (N=44)	Group 2 (N=27)	Group 3 (N=42)	Group 4 (N=23)
Overall Population Receiving TMS Reintroduction N(%)	16 (36.4)	9 (33.3)	16 (38.1)	11 (47.8)
First reintroduction N (%) • No. of sessions (median) • Time to reintroduction in weeks (median) • Population continuing past first cycle N (%)	16 (36.4) 14 11 11 (68.8)	9 (33.3) 24 7 6 (66.7)	16 (38.1) 4 6.5 9 (56.3)	11 (47.8) 14 10 6 (54.5)
Second reintroduction cycle* N(%)	5 (11.4)	2 (7.4)	5 (11.9)	2 (8.7)
Third reintroduction cycle* N(%)	1 (2.3)	0	2 (4.8)	0

** Insufficient information at interim to characterize cycle performance at interim report*

Group 1 = 101 active responders; Group 2 = 101 active non-responders/102 responders;
Group 3 = 101 sham non-responders/102 responders; Group 4 = 101 sham responders

Figure 10. Overview of TMS Reintroduction Cycles in Study 44-01103

14.0 SAFETY DATA

14.1. Serious Adverse Events

In addition to the collection of all protocol-emergent adverse events, sites were instructed to collect and document all serious adverse events as defined in the study protocol.

Protocol 44-01103 defines a *serious adverse event* (SAE) as an adverse event that:

- Resulted in death,
- Was life threatening,
- Required inpatient hospitalization or prolongation of an existing hospitalization,
- Resulted in permanent impairment of a body function or permanent damage to a body structure,
- Necessitated medical or surgical intervention to preclude such impairment,
- Resulted in a congenital anomaly or birth defect,
- Additionally, *important medical events* that may not have resulted in death, or were not life-threatening, or did not require hospitalization, could have been considered SAEs, based upon appropriate medical judgment of the investigator,
- Seizures, and
- Any malfunction of an investigational device if it was likely to result in death, serious injury or other significant adverse event experience.

Overdose with the Neuronetics device as defined below was considered an adverse event of special interest for reporting purposes of this study. Neuronetics elected to pursue this conservative reporting strategy because the treatment parameters in use in this protocol were higher than previous studied in the TMS literature. This event was asked to be reported in the time frame of a serious adverse event and is reported within the serious adverse event case vignettes.

Clinical case vignettes for all serious adverse events are provided in Appendix 4. Detailed supporting documentation for each vignette, including serious adverse event reporting pages, and accompanying case report forms are also contained in Appendix 4.

14.1.1. Serious Adverse Events Reported for Study 44-01103

- No deaths or seizures have been reported as of the data cutoff date for this interim report.
- Six serious adverse events occurred after signing of the informed consent.

- The types of serious adverse events or other reportable events are shown in Table 9. The number of serious adverse events reported and the relationship to study device as determined by the investigator is also provided.

Table 9. Serious Adverse Events Reported for Study No. 44-01103

Serious Adverse Event	Number of SAEs	Relationship to Study Device
Worsening of depression and suicidal ideation	1	Not related
Hospitalization for coronary artery surgery	1	Not related
Hospitalization for bladder tumor removal	1	Not related
Overdose of TMS treatment (operator error)	1	Not related
Atrial fibrillation	1	Not related
Hospitalization for hip pain	1	Not related

14.1.2. Treatment-Emergent Adverse Events

All investigative sites were trained in the collection of adverse events at every study visit occurring after informed consent was obtained and through 30 days after the last study visit in all Neuronetics clinical protocols.

As defined in the protocol, an *adverse event* was:

- Any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person who has received treatment with a Neuronetics device or in a Neuronetics clinical study.

The event need not have been causally related to the Neuronetics device or Neuronetics clinical trial. An adverse event included, but was not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (i.e., a dose higher than that described in the protocol) of a Neuronetics device, whether accidental or intentional;
- An AE occurring from abuse (e.g., use for non-clinical reasons) of a Neuronetics device;
- An AE that has been associated with the discontinuation of the use of a Neuronetics device

Training in adverse event collection included instruction in proper terminology, as well as methods of assessment of causal relation of the event to study device. Sites recorded all adverse event information in complete form in source data re-

cords and on electronic case report forms. Verbatim adverse event terms as recorded by the investigative site staff were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and reported by MedDRA preferred terms.

Table 10 summarizes adverse events by MedDRA-preferred term that occurred at an incidence of $\geq$ 5% in any treatment Group. A detailed tabular summary of adverse events, including summary of investigator-assigned causal relationship to study device, and clinical severity are contained in Appendix 3, Tables 3.7-3.9.

Table 10. Summary of MedDRA Preferred Term Adverse Events Occurring with an Incidence on Active TMS of ≥ 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)
Psychiatric disorders				
- Agitation	3 (6.8)	0	0	0
- Anxiety	7 (15.9)	2 (7.4)	6 (14.3)	3 (13.0)
- Depressive su\ymptom	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)

14.1.3. Overall Conclusions Based on Interim Report of Safety Data for Study 44-01103

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

15.0 DEVICE FAILURES AND REPLACEMENTS

There were two failure modes that occurred during protocols 44-01101, 44-01102 and 44-01103. The failures involved a malfunction of the clinical trial Model 2100 TMS System console power supply due to a plating defect in the control board and a manufacturing defect of the E-shield that was caused by a shorted trace within the E-shield. The reporting of the failure modes is detailed below and is further defined in Table 11 and is described in further detail in the final study report for Study 44-01101.

Table 11. Reportable Device Malfunction Event and Regulatory Reporting for Studies 44-01101, 44-01102 and 44-01103

Device	Event	Device S/N	Event Date	[redacted] S/N	Report Date
E-Shield	Burn	01979	1 Jun 2004	009, 010, 011	4 Jun 2004
E-Shield	Burn	03645	26 Oct 2004	017	5 Nov 2004
E-Shield	Acute Pain	15021	8 Sep 2005	031, 033	4 Oct 2005
Console	Malfunction	1006	19 Jul 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1015	20 Jul 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1013	21 Jul 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1011	27 Jul 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1005	3 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1007	3 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1009	9 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1012	26 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1008	27 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	1010	30 Aug 2004	012, 014, 016	30 Aug 2004
Console	Malfunction	8006	7 Sep 2004	014, 016	30 Sep 2004
Console	Malfunction	1015	13 Sep 2004	014, 016	30 Sep 2004
Console	Malfunction	8028	21 Sep 2004	014, 016	30 Sep 2004
Console	Malfunction	8025	29 Oct 2004	016	19 Oct 2004
Console	Malfunction	8020	8 Nov 2004	016	19 Oct 2004

16.0 ADDITIONAL CLINICAL INFORMATION FROM THE STUDY

16.1. Deviations to the Protocol and Protocol Violations

A review of the protocol deviation log was conducted for assessment of potentially clinically significant events. This review revealed protocol deviations through the interim data cutoff date of the study as shown in Table 12. None of these deviations interfered with patient safety or the risk profile of the device, and none were expected to materially alter the results or interpretation of the study results.

Table 12. Protocol Deviations in Study 44-01103

Protocol Deviations	Number of Deviations
Excluded medications used	8
Documentation procedure	24
Protocol procedure	72
Reintroduction issues	28
Device issues	9