

**NEURONETICS FINAL STUDY REPORT**

**STUDY NO. 44-01102**

**14 April 2006**

**“A 9-week, Uncontrolled, Open-Label Study to Evaluate the Efficacy and Safety of the Neuronetics Model 2100 Repetitive Transcranial Magnetic Stimulation (rTMS) System in the Treatment of Patients with Major Depression Previously Non-Responsive to Active or Sham rTMS Treatment.”**

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## 1.0 INTRODUCTION

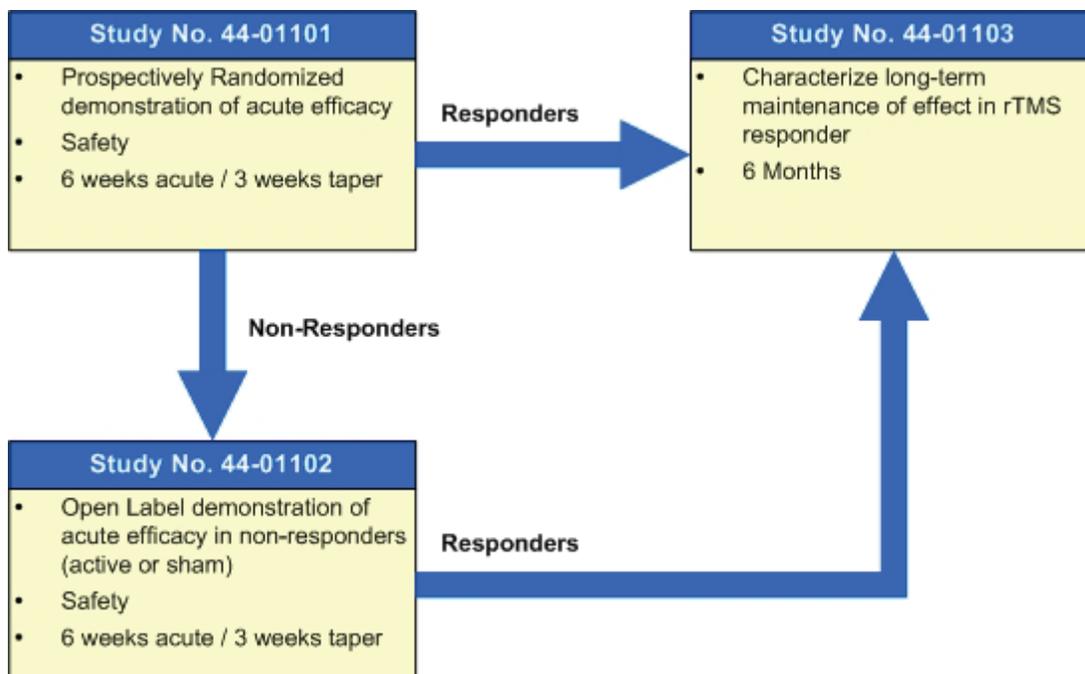
The clinical development program for the Neuronetics TMS System consisted of three integrated clinical protocols as displayed in Figure 1.

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
<b>44-01101</b>	<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 <u>and</u> 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>
<b>44-01102</b>	<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 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 the point of declaration of the efficacy outcome.</p>
<b>44-01103</b>	<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>

Protocol 44-01102 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 44-01102 is provided in Appendix 1. The study protocol and informed consent document for Study No. 44-01102 is provided in Appendix 2. All referenced data tables are provided in Appendix 3. SAE vignettes, SAE report, and patient case report form is provided in Appendix 4. An annotated case report form for Study 44-01102 is provided in Appendix 5.

## 2.0 PROTOCOL SUMMARY

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 TMS treatment 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 the MADRS, HAMD24, HAMD17 and CGI-S
- Point of exit total scores for the MADRS, HAMD24, HAMD17 and CGI-S
- Patient identification number and initials

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 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 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 all other respects, identical in formal structure to Protocol 44-01101. Protocol 44-01102 is provided in Appendix 2. 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.

Descriptive statistical analysis was conducted for Protocol 44-01102 due to its uncontrolled, open-label study design that limits the ability to provide inferential statistical comparisons. However, the descriptive statistical reports provide circumstantially supportive data that confirms the efficacy of TMS as provided in the randomized controlled study contained in Protocol 44-01101.

For purposes of analysis and reporting, subjects who entered Protocol 44-01102 are considered in one of two groups, based on the manner in which they arrived into this study:

**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 TMS and safety of additional TMS treatments, 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 order of the sequential testing of these questions is identical to the sequence for Protocol 44-01101, and is as outlined in Table 1 in Final Study Report 44-01101..

Major Conclusions Than Can Be Drawn from this Study Are:

- TMS therapy as delivered by the Neuronetics TMS System is an effective antidepressant for patients with DSM-IV defined major depression for those patients who had not previously received sufficient clinical benefit from treatment with pharmacotherapy for their illness:
  - Patients previously allocated to sham TMS show substantial and clinically meaningful improvement in symptom scores
  - In patients previously allocated to active TMS, a clinically meaningful proportion of patients show evidence of late response to treatment with continued active TMS.
- 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

Adherence to treatment with open-label active TMS using the Neuronetics TMS System is excellent

### 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
<u>Psychiatric Diagnostic Interview</u> - 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, 4 <sup>th</sup> edition
<u>Treatment History</u> - 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.
<u>Clinician-Rated Symptom Assessments</u> - 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
<p><u>Patient-Reported Symptom, Quality of Life, and Functional Status Assessments</u></p> <ul style="list-style-type: none"> <li>- Inventory of Depressive Symptoms – Self Report version (IDS-SR)</li> <li>- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q)</li> <li>- Medical Outcomes Study Short Form – 36 Item Questionnaire, version 1 (MOS SF-36)</li> <li>- Patient Global Impressions – Improvement of Illness Scale (PGI-I)</li> </ul>	<ul style="list-style-type: none"> <li>- 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.</li> <li>- 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.</li> <li>- 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.</li> <li>- The PGI-I is a well-recognized, self-administered, global rating scale that measures disease improvement on a 7-point Likert scale.</li> </ul>
<p><u>Patient-Reported Health Care Resource Utilization and Work Productivity Assessment</u></p> <ul style="list-style-type: none"> <li>- Health Resource Utilization Questionnaire (HRQ)</li> </ul>	<ul style="list-style-type: none"> <li>- The HRQ is a multi-item self-reported questionnaire which assesses health care utilization, work status and productivity, and caregiver burden.</li> </ul>

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 captured (EDC ) using the current version of the Medical Dictionary for  edDRA). 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 time-points 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 44-01102, 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.



## 4.0 INVESTIGATIVE SITES FOR NEURONETICS STUDY 44-01102

### 4.1. Investigative Sites and Subjects Per Investigative Site

A listing of the clinical study investigators whose sites were qualified to conduct Study 44-01102 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 sixty-six patients (N=166) with MDD participated in Study 44-01102. Twenty-two sites contributed patients to protocol 44-01102 as shown in the table in Appendix 1.

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 44-01102 participated in the initial study 44-01101. All sites in Study 44-01102 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 participating in protocol 44-01101, protocol 44-01102 initiation was conducted during the protocol 44-01101 training. Procedures were reviewed with sites upon verification of a patient eligible to transition to Study 44-01102.

#### **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 two ways in Study 44-01101. 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 intra-class 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 required, 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 44-01102.

**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. The complete dataset for Study 44-01102 was locked on 2 March 2006, and final data was

[redacted] e (EDC) contract research organization  
[redacted] to Neuronetics approved statistical  
[redacted]

on 07 March 2006.

## 5.0 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. With the exception of the definition of “*failure to receive benefit from the randomized treatment they had been assigned to*” in protocol 44-01101, the inclusion and exclusion criteria were identical to that contained in protocol 44-01101.

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 the MADRS, HAMD24, HAMD17 and CGI-S
- Point of exit total scores for the MADRS, HAMD24, HAMD17 and CGI-S
- Patient identification number and initials

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 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.

## 6.0 STUDY POPULATIONS AND STATISTICAL ANALYSIS

### 6.1. Study Populations

The *modified intent-to-treat study population* (also known as the evaluable study population) was defined as all subjects who signed an informed consent, and who received at least one treatment (whether partial or complete), and for whom a completed post-treatment observation is available for analysis.

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

For this study, the evaluable study population is the same as the *safety population*. Instruction on adverse event reporting for events occurring around or through the transition of a patient from study 44-01101 to 44-01102 are specifically described in the adverse event reporting for those studies in the protocols themselves. Specifically, an adverse event beginning after treatment has begun in study 44-01102, is reported in that study. Any events which began in study 44-01101 and continue into study 44-01102 are reported in both studies. Further instructions on use of the case report forms for these studies are found in the study protocols.

Serious adverse events were reported for all patients who signed an informed consent document.

### 6.2. Statistical Analysis Methods

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.

## 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 44-01102 on 23 February 2004. At the closure of study enrollment, 166 patients had been consented and enrolled for study participation in protocol 44-01102, while 158 patients were included in the final evaluable patient study population.

Among the all-randomized study population, there were 8 patients who were non-evaluable according to the operational criteria stipulated in the protocol, i.e., no post-baseline evaluations were obtained for these patients. Within this non-evaluable patient population, N=7 had been allocated to sham TMS treatment in protocol 44-01101, and N=1 had been allocated to active TMS treatment in that study. Patient identification, treatment arm allocation, age, gender, and reason for discontinuation for all of these patients are listed in Table 5.

**Table 5. Summary Patient ID, Treatment Arm Allocation, and Reason for Discontinuation among Non-Evaluable Patient Sample in Study 44-01102**

Patient ID	Treatment Arm Allocation	Age	Gender	Reason for Discontinuation
01-093	Sham	19	M	Protocol violation (use of excluded medication)
03-011	Sham	34	M	Adverse event (discomfort during treatment)
11-036	Sham	57	F	Lost to follow up
11-037	Sham	52	M	Adverse event (worsening depression)
15-025	Sham	29	F	Other (patient unable to tolerate treatment)
20-024	Sham	43	F	SAE (suicidal ideation)
21-013	Sham	46	F	Adverse event (worsening depression)
22-008	Active	48	M	Failed to return due to flu

## 8.0 PATIENT DEMOGRAPHICS AND BASELINE ILLNESS CHARACTERISTICS OF THE 44-01102 STUDY POPULATION

The evaluable study population included 158 patients. Demographic and clinical variables for this population are described Section 7.1. Baseline illness characteristics are described in Section 7.2.

### 8.1. Patient Demographic and Clinical Variables

A complete description of the demographic features for the intent-to-treat, evaluable study population (N=158) are described in Appendix 3, Table 3.1.

A brief summary of key observations from the demographic features and baseline clinical variables are shown in Table 6 for the intent-to-treat, evaluable study population. Please see Table 3.2 in Appendix 3 for further detail.

Please note that in all subsequent displays, information for patients in **Group A** (N=73, those patients previously allocated to active TMS treatment in study 44-01101), and **Group B** (N=85, those patients previously allocated to sham TMS treatment in study 44-01101) are shown separately for purposes of clarity, and demonstrate any areas of potentially clinically meaningful difference between these groups that may have relevance for interpretations of both efficacy and safety of active TMS.

**Table 6. Summary of Key Demographic and Clinical Variables Observed at Screening in the Intent-To-Treat, Evaluable Study Population in Study 44-01102**

Variable Name	Analysis Group		P-Value
	Group A (N=146)	Group B (N=155)	
Gender N(%)			
-Male	35 (47.9)	45 (52.9)	.632
-Female	38 (52.1)	40 (47.1)	
Age [yrs, mean (SD)]	47.8 (11.2)	50.0 (10.1)	.217
Ethnic Origin N(%)			
-Caucasian	71 (97.3)	78 (91.8)	.448
-African-American	1 (1.4)	2 (2.4)	
-Asian	1 (1.4)	1 (1.2)	
-Hispanic	0	3 (3.5)	
-Native American	0	0	
-Other	0	1 (1.2)	
Motor Threshold	51.1 (9.7)	55.5 (9.9)	.013

Data shown for evaluable study population

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

### 8.1.1. Conclusions Regarding Patient Demographics and Clinical Variables

- There were no statistically significant differences between the two patient groups using the Neuronetics TMS System on any demographic variables.
- The average age of patients was in their 5<sup>th</sup> decade of life, consistent with expectations for a more treatment-resistant population.
- There was a relatively equivalent representation of men and women in the two study population groups.
- There were no clinically meaningful differences on other clinical variables at study entry.

### 8.2. Baseline Illness Characteristics

A summary of *illness history, characterization of treatment resistance history, and baseline symptom severity* is included in Table 7 for the intent-to-treat, evaluable study population, with the two Groups displayed separately for comparison. A more complete description for this study population and a similar tabular summary for the all-randomized study population are provided in Appendix 3, Table 3.3 and shows a similar distribution of illness descriptive variables.

**Table 7. Key Observations for Illness History, Characterization of Treatment Resistance History and Baseline Symptom Severity for the Intent-To-Treat, Evaluable Study Population in Study 44-01102**

Variable Name	Analysis Group		P-Value
	Group A (N=73)	Group B (N=85)	
Depression History			
- Single episode	4 (5.5)	4 (4.7)	1.000
- Recurrent episodes	69 (94.5)	81 (95.3)	
Duration of current episode			
- Length [mean (SD)]	14.8 (10.27)	12.8 (9.05)	.1936
- < 24 months N(%)	54 (74.0)	74 (87.1)	.0431
- ≥24 months N(%)	19 (26.0)	11 (12.9)	
Secondary Diagnoses N(%)			
- None	46 (63.0)	56 (65.9)	.7407
- Any Other Anxiety Disorder	27 (37.0)	29 (34.1)	
ATHF Rating Summary (# of Level 3 Exposures)			
- 1	36 (49.3)	43 (50.6)	.8430
- 2	26 (35.6)	28 (32.9)	
- 3	7 (9.6)	11 (12.9)	
- 4	4 (5.5)	3 (3.5)	
Mean # of ATHF Level 3 Exposures	1.7	1.7	

Variable Name	Analysis Group		P-Value
	Group A (N=73)	Group B (N=85)	
MADRS Total Score [mean (SD)]	35.7 (5.9)	35.0 (5.8)	.4625
HAMD24 Total Score [mean (SD)]	30.5 (5.5)	30.0 (5.8)	.4862
HAMD17 Total Score [mean (SD)]	22.5 (3.8)	22.6 (3.8)	.9083
CGI-Severity Score [mean (SD)]	4.9 (0.8)	4.8 (0.8)	.6757
IDS-SR Total Score [mean (SD)]	40.1 (14.9)	40.8 (13.94)	.7534

### 8.2.1. Baseline Illness Characteristics Conclusions

- The overall pattern of illness history in the study patient population is consistent with a more severe treatment-resistant sample as reflected by the predominance of recurrent depression, and an ATHF assessment which yielded an average Level 3 resistance rating for 1.7 medications in both Groups A and B in the qualifying episode.
  - A statistically significantly greater number of patients in Group A had a current illness duration longer than 24 months ( $P < .05$ ) suggesting a slightly greater illness morbidity in this group.
- Baseline clinical symptom severity was consistent with this illness history as evidenced by the average scores at baseline on the HAMD24, HAMD17, MADRS, IDS-SR and CGI-Severity ratings, which suggest a moderate to severe clinical presentation in the current episode.
  - The MADRS total scores observed at entry to study 44-01102 were, on average, ~5 points higher than observed at entry into study 44-01101, suggesting that these two patient groups were clinically more symptomatic at entry to study 44-01102 than at the overall population at entry into study 44-01101.
  - A similar relative increase in scores was seen for the CGI-Severity, but not for the HAMD24, HAMD17 or the IDS-SR.

## 9.0 HEALTH RESOURCE UTILIZATION AND FUNCTIONAL STATUS

Functional status, work productivity, health resource utilization and quality of life satisfaction were appraised by patient-rated questionnaires at study entry into study 44-01101. A summary of key observations obtained from the Work Productivity and Health Resource Utilization Questionnaire for the two patient Groups (A and B) who entered study 44-01102, based on this earlier data is shown in Table 8. A complete, detailed tabular summary of all data measured for functional status, quality of life and health resource utilization is included in Table 3.4 in Appendix 3.

**Table 8. Work/Productivity and Health Resource Utilization in the All-Randomized Study Population at Study Entry into Study 44-01102**

Variable Name	Analysis Group	
	Group A (N=73)	Group B (N=85)
<b>Productivity/Work Loss due to Illness</b>		
- Work Status N(%)		
o Full time	25 (34.7)	27 (32.1)
o Part time	9 (12.5)	14 (16.7)
o Not working	38 (52.8)	43 (51.2)
- Disability payments		
o Yes	14 (33.3)	16 (34.8)
o No	28 (66.7)	30 (65.2)
<b>Health Utilization and Cost of Illness</b>		
- # visits to HCP for depression in last 3 mos (median)	3.5	3.0
- # visits to HCP for medical problem in last 3 mos (median)	2.0	2.0
<b>Caregiver Support</b>		
- Assisted by a caregiver? N(%)		
o Yes	13 (18.3)	12 (14.5)
o No	58 (81.7)	71 (85.5)
- # hours assisted each week by caregiver (median)	10.0	8.0

**9.1. Health Resource Utilization and Functional Status Conclusions**

- The pattern of health resource utilization and work productivity impairment are similar to those observed for the overall patient population in study 44-01101, and indicate a pattern of morbidity consistent with a more difficult to treat history; for example approximately half of the population in each treatment group were currently not working, with nearly 75% of each group reporting that this was due to depression;
  - In the two Groups entering study 44-01102, Group A showed a slightly greater degree of health resource impairment than Group B as reflected by a greater median number of health care provider visits for depression in the past 3 months, and a greater number of individuals who reported receiving the assistance of a caregiver at home for daily tasks, suggesting a slightly more impaired patient population in Group A compared to Group B
- On measures of functional health status, patients entering study 44-01102 showed a degree of functional morbidity consistent with their general illness history, presenting symptom severity and degree of treatment resistance.

## 10.0 PATIENT DISPOSITION

Subsequent to enrollment, there were two discrete phases in Protocol 44-01102, the *acute treatment phase*, and the *post-treatment taper phase*. Treatment through Week 4 of the acute treatment phase constituted the *a priori*-defined study period for the primary efficacy analysis.

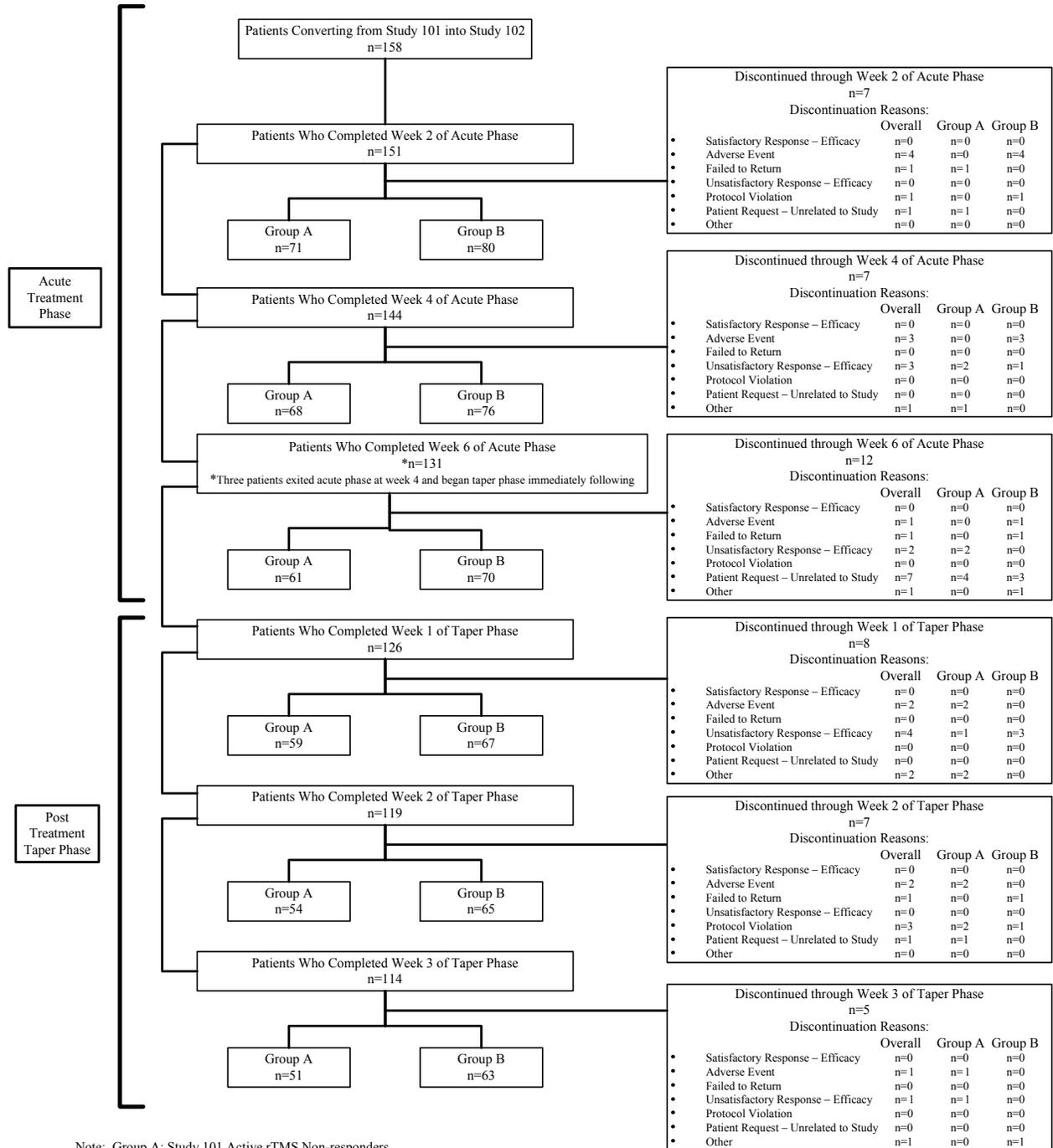
For those patients continuing on their assigned treatment beyond week 4, the time period between week 4 and week 6 served as an *a priori*-defined secondary analysis time point, and provides supportive information whether additional treatment sessions may confer added clinical benefit.

Subsequent to the conclusion of the acute treatment phase, durability of the acute effect of TMS was examined in the patients who proceeded on their assigned treatment into the 3-week, post-treatment taper phase.

The overall pattern of patient disposition across these various study phases is described in Table 9. The reasons for termination as recorded by the study investigator at the time of patient discontinuation are listed for each critical time point in the study. Per investigator request, three patients were permitted to exit the acute treatment phase at the end of acute treatment week 4, and directly transition to the taper phase and so are not counted in the week 6 totals.

**Table 9. Diagram of Patient Disposition Across Study Phases in Protocol 44-01102**

**Patient Disposition, Including Reasons for Study Termination  
(Patient Population: Evaluable)**



**10.1. Patient Disposition Conclusions**

- The overall adherence rate through week 4 of the acute treatment phase (the primary efficacy endpoint) was 91.1%.
- Discontinuation due to adverse events through week 4 of the acute treatment phase was 0% for patients previously allocated to active TMS treatment in study 44-01101 (Group A in this study), and 8.2% for patients previously allocated to sham TMS treatment in study 44-01101 (Group B in this study).

## 11.0 STUDY DEVICE AND TREATMENT RANDOMIZATION

### 11.1. Study Device: Neuronetics Model 2100 TMS System

All TMS treatments were delivered using [redacted] s Model 2100 TMS System. The system is described in detail in [redacted]

In brief, the Neuronetics Model 2100 TMS System is an electromechanical instrument that non-invasively produces and delivers brief duration (~200  $\mu$ sec) rapidly alternating, or pulsed, magnetic fields to the patient's head leading to the induction of electrical currents at spatially discrete regions of the cerebral cortex.

This method of cortical stimulation by application of brief magnetic pulses to the head is known as Transcranial Magnetic Stimulation or TMS. The peak magnetic field strength achieved with each pulse is approximately 0.5 Tesla in the cortex.

Neuronetics' clinical studies are intended to test the safety and efficacy of TMS as delivered by the Neuronetics Model 2100 TMS System for the treatment of Major Depressive Disorder (MDD). For treatment of MDD, TMS stimulation is directed to the left prefrontal cortex, a discrete region of the brain involved in mood regulation.

In commercial application, the Neuronetics TMS System will be provided on an out-patient basis by a licensed medical professional (i.e., psychiatrists and their staff) and by prescription only.

The Model 2100 TMS System consists of various hardware components, accessories and consumable supplies. The key components are the console which contains the controlling electronics of the system, the ferromagnetic coil that delivers the magnetic field to the patient's head and the E-Shield, which is a disposable circuit placed on the surface of the coil to decrease the induced electric field in the scalp in order to enhance patient tolerability.

Regarding the design of the Model 2100 TMS System may be found in [redacted]

### 11.2. Open-Label Treatment Assignment for Study 44-01102

Three separate "coded" magnetic coils were provided to each site for the initial Neuronetics study 44-01101. As described further in the final study report for study 44-01101, all coils were identical in weight, external appearance and acoustic properties when actively pulsed.

One coil was not blinded, and was used as a known active coil to determine motor thresholds (coil labeled 'MT Active'). This known, active coil was used for all treatments in the open-label study protocol 44-01102. The remaining two coils that

were distinguishable only by external labels as ‘coil B’ or ‘coil C’ , were used only in the blinded, randomized sham-controlled protocol 44-01101 and were not used in study 44-01102.

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 44-01102. The site staff then manually connected the MT/Active coil prior to proceeding with each TMS treatment session.

## 12.0 TMS TREATMENT SCHEDULE, TMS TREATMENT PARAMETERS AND COMPLIANCE

TMS treatment sessions were conducted using the Neuronetics Model 2100 TMS System in sequential five-day treatment blocks, generally administered Monday through Friday, during the acute treatment phase. Six additional treatments were administered across the 3 week post-treatment taper phase. A maximum of 36 treatments could have been given to any patient who completed all assigned treatment sessions in this study.

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. During the first week of the acute phase only, 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).

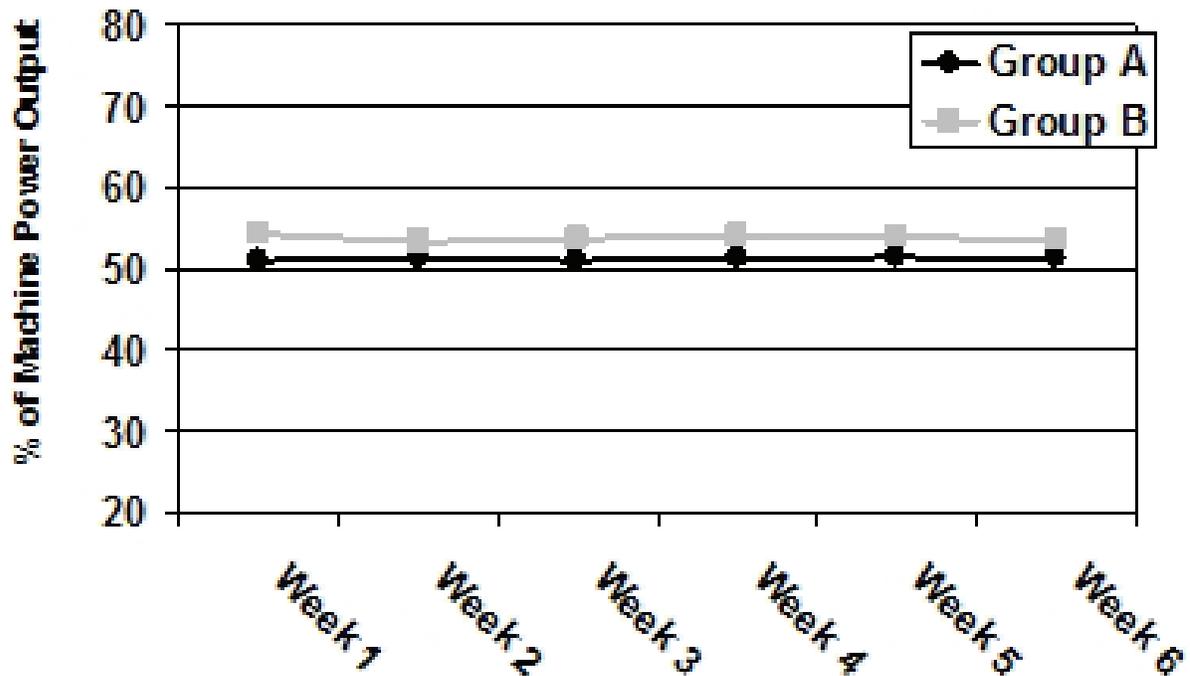
The standardized treatment location was operationally defined in the protocol over the left prefrontal cortex, determined by a standard convention of movement of the TMS coil 5 cm anterior to the motor threshold location along a left superior oblique plane, with a rotation point about the subject's nose. 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.

All patients were assessed for compliance with the intended treatment schedule during the acute treatment phase. Compliance was defined as missing less than 3 treatments in daily sequence, or missing less than 20% of the total number of treatment sessions as outlined in the schedule of events to be administered during the acute treatment phase for that patient.

Detailed tabular summaries of the weekly information obtained for all relevant treatment variables are contained in Tables 3.5 and 3.6 in Appendix 3. The mean number of patient treatment sessions conducted and treatment compliance are summarized in Table 10. The pattern of weekly recommended motor thresholds obtained during the study is shown in Figure 2.

**Table 10. Number of Patient Treatments and Overall Treatment Compliance in Protocol 44-01102**

Treatment Characteristic	Treatment Group A (N=73)	Treatment Group B (N=85)
# of Sessions Administered During the Acute Treatment Phase (mean [SD])	26.6 (6.35)	26.0 (7.55)
Treatment Session Compliance		
• Missed > 2 consecutive sessions N(%)	9 (12.3)	14 (16.5)
• Missed > 20% of total intended sessions N(%)	2 (2.7)	5 (5.9)



Note: Average value for recommended MT at the indicated time point is shown based on MT Assist algorithm

**Figure 2. Weekly Motor Thresholds Observed During the Acute Treatment Phase of Protocol 44-01102**

**12.1. Patient TMS Treatment and Compliance Conclusions**

- Overall compliance in study 44-01102 with the scheduled treatment parameters was excellent (7/158 missed > 20% of the intended number of treatment sessions = 95.6% adherence).
- Motor thresholds demonstrated a stable pattern across the acute treatment phase, and showed no clinically meaningful difference between the two treatment groups at any time point.

### 13.0 CONCOMITANT MEDICATION USE

Psychotropic medication use during the study was strictly limited. All patients were free of antidepressants or other psychotropic medications directed at treatment of their study diagnosis. Patients were allowed limited use of either sedative/hypnotics or daytime anxiolytics for treatment emergent insomnia or anxiety, respectively, subsequent to the initiation of treatment. These medications were permitted for up to 14 daily doses (of either or both types of medications) during the acute treatment phase. Any clinical indication for use beyond these limitations required discontinuation from study participation in the interests of patient care and so as not to unduly influence the efficacy and safety assessments in the study.

Table 11 summarizes the frequency of anxiolytic and hypnotic use during the acute treatment phase. As shown, ~30% of patients had some anxiolytic use in both active and sham TMS treatment groups.

**Table 11. Frequency of Protocol-Approved Anxiolytic or Hypnotic Medication Use During the Acute Treatment Phase in Study 44-01102**

Body System Preferred Term	Group A (N=73) N (%)	Group B (N=85) N (%)
<b>Subjects With At Least One Anxiolytic/Hypnotic Medication</b>	<b>30 (41.1)</b>	<b>34 (40)</b>
• Alpraxolam	0	3 (3.5)
• Lorazepam (Ativan)	20 (27.4)	19 (22.4)
• Zaleplon (Sonata)	1 (1.4)	0
• Zolpidem (Ambien)	15 (20.5)	21 (24.7)
• Zopiclone (Immovane)	1 (1.4)	0
• Temazepam	1 (1.4)	0
• Valium	0	1 (1.2)

Group A= Study 101 active TMS nonresponder; Group B = Study 101 Sham TMS nonresponder

During the post-treatment taper phase, oral antidepressant medication was initiated. The choice of medication was limited to a monotherapy selected from among a protocol-approved list, and also was limited to a medication for which the patient had not previously been shown to have failed to receive benefit. A summary of the antidepressant medications chosen for use during the post-treatment taper phase are listed in Table 12.

The pattern of use of these medications did not differ substantially between treatment groups.

Because of a history of medication intolerance, 14 patients were approved to proceed through the post-treatment taper phase, but were not initiated on antidepressant medication. These patients were not, therefore, eligible to continue into Protocol 44-01103.

**Table 12. Antidepressant Medications Used During the Post-Treatment Taper Phase**

Antidepressant Medication	Drug Name	Group A (N=73) N (%)	Group B (N=85) N (%)
Selective Serotonin Reuptake Inhibitors	Citalopram (Celexa)	2 (2.7)	3 (3.5)
	Escitalopram (Lexapro)	4 (5.5)	6 (7.1)
	Fluoxetine (Prozac)	1 (1.4)	0
	Fluvoxamine (Luvox)	0	1 (1.2)
	Paroxetine (Paxil)	1 (1.4)	0
	Sertraline (Zoloft)	3 (4.1)	0
Serotonin/Norepinephrine Reuptake Inhibitors	Duloxetine (Cymbalta)	17 (23.3)	10(11.8)
	Venlafaxine (Effexor)	7 (9.6)	8 (9.4)
Other Antidepressants	Clomipromine	1 (1.4)	0
	Bupropion (Wellbutrin)	11 (27.5)	11 (17.2)
	Mirtazapine (Remeron)	4 (10.0)	4 (6.3)
	Nardil	1 (1.4)	0
	Parnate	1 (1.4)	0
	Tofranil	1 (1.4)	0
	Trazodone (Desyrel)	1 (1.4)	0

Group A= Study 101 active TMS nonresponder; Group B = Study 101 Sham TMS nonresponder

## 14.0 EFFICACY OUTCOMES

The primary and secondary outcome measures used in the analyses for Study 44-01102 and the order of their sequential testing are listed in Table 13 and are also described in the original protocol provided in 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, 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.

**Table 13. Primary Outcome Measure and Secondary Outcome Measures in Protocol 44-01102 and Their Sequential Order of Importance in Testing**

Measurement	Evaluation
<b><u>Primary Outcome Measure</u></b>	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 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, stratified by Groups A or B.
<b><u>Secondary Outcome Measures</u></b>	<ol style="list-style-type: none"> <li>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, stratified by Groups A or B</li> <li>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 , stratified by Groups A or B</li> <li>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, stratified by Groups A or B</li> <li>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, stratified by Groups A or B</li> <li>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, stratified by Groups A or B</li> <li>6) Evaluate the antidepressant effect of treatment with the Neuronetics TMS System, using categorical outcome of remission/recovery (percent of patients</li> </ol>

Measurement	Evaluation
	<p>achieving HAMD17 total symptom score &lt; 8, HAMD24 total symptom score &lt; 11, and MADRS total symptom score &lt; 10 at the last post-treatment visit through week 4 and week 6, of a specified course of active treatment, stratified by Groups A or B</p> <p>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, of a specified course of active treatment, stratified by Groups A or B</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, stratified by Groups A or B</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, stratified by Groups A or B</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, stratified by Groups A or B</p>

#### 14.1. Primary Efficacy Outcome – Acute Treatment Phase

The *a priori*-defined primary outcome measure in Study 44-01102 was based on the last post-treatment total symptom score on the Montgomery-Asberg Depression Rating Scale (MADRS) through week 4 of the acute treatment phase. This was to be conducted on the intent-to-treat, evaluable study population as defined above. The results of this analysis are shown in Table 14 and in Figure 3.

**Table 14. Primary Outcome Measure (MADRS Total Score) for the Evaluable Study Population in Study 44-01102**

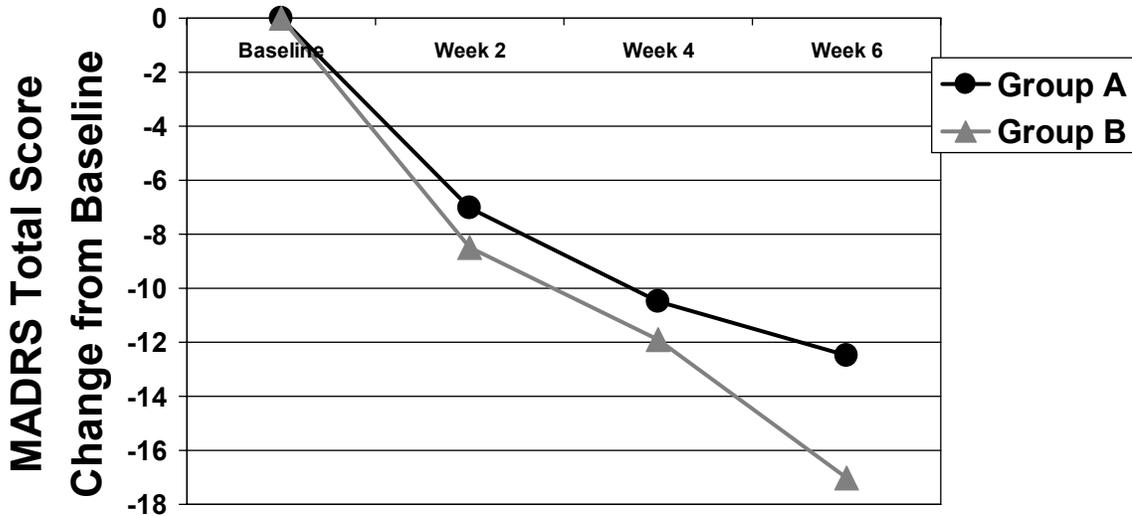
Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Total Score	N	73	73	68	61	85	85	77	69
	Mean	35.7	28.7	25.3	23.5	35	26.5	23.1	18
	SD	5.84	8.92	10.16	12.24	5.82	9.78	9.67	11.65
	Median	35	30	27	24	35	26	23	17
	Min	24	0	0	0	21	2	0	0
	Max	51	49	45	49	48	50	46	50
	Low 95% CI	34.3	26.6	22.8	20.4	33.7	24.4	20.9	15.2
	Higher 95% CI	37	30.8	27.8	26.6	36.3	28.6	25.3	20.8
Change from Baseline	N		73	68	61		85	77	69
	Mean		-7	-10.5	-12.5		-8.5	-11.9	-17
	SD		8	8.84	11.11		8.63	9.74	12.25
	Median		-5	-10.5	-12		-8	-11	-17
	Min		-32	-30	-40		-31	-34	-42
	Max		6	4	10		10	14	7
	Low 95% CI		-8.8	-12.7	-15.4		-10.4	-14.1	-19.9
	Higher 95% CI		-5.1	-8.4	-9.7		-6.6	-9.7	-14

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline values are defined as the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the mean MADRS total score and for the mean change from baseline is computed at the time points indicated



Data shown for evaluable study population  
 Group A = Study 101 active TMS; Group B = Study 101 sham TMS

**Figure 3. Primary Outcome Measure (MADRS Total Score) Baseline to Endpoint Change for the Evaluable Study Population in Study 44-01102**

**14.2. Secondary Efficacy Outcomes – Acute Phase**

Tabular results for all secondary outcomes measures in their *a-priori*-defined order of priority testing are shown from Tables 15 through 40 below. Graphical outcome of the baseline to endpoint change on the HAMD24 and the HAMD17 are displayed in Figures 4 and 5, respectively. Graphical outcome of the responder and remission rates for the MADRS, HAMD24 and HAMD17 are displayed in Figures 6, 7, and 8.

Additional Tables 3.7 and 3.8 are included in Appendix 3 and summarize the individual item change scores for the MADRS and HAMD across the acute treatment phase of the study.

**Table 15. Secondary Outcome Measure (HAM24 Total Score) Last-Observation Carried Forward Analysis**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Total Score	N	73	73	68	61	85	85	77	69
	Mean	30.5	23.9	21.7	19.8	30	22.5	19.3	15.9
	SD	5.53	6.85	7.98	10.11	5.18	7.49	8.58	9.21
	Median	30	24	22	19	30	23	19	15
	Min	20	5	3	2	20	3	2	1
	Max	49	38	39	48	44	37	46	41
	Low 95% CI	29.3	22.3	19.7	17.2	28.8	20.9	17.4	13.7
	Higher 95% CI	31.8	25.5	23.6	22.4	31.1	24.1	21.2	18.1
Change from Baseline	N		73	68	61		85	77	69
	Mean		-6.7	-9	-11.1		-7.4	-11	-14.5
	SD		6.87	8.26	9.69		6.73	8	9.34
	Median		-4	-9	-9		-6	-11	-15
	Min		-30	-34	-35		-23	-27	-34
	Max		4	6	6		6	13	7
	Low 95% CI		-8.3	-11	-13.5		-8.9	-12.8	-16.8
	Higher 95% CI		-5.1	-7	-8.6		-6	-9.2	-12.3

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

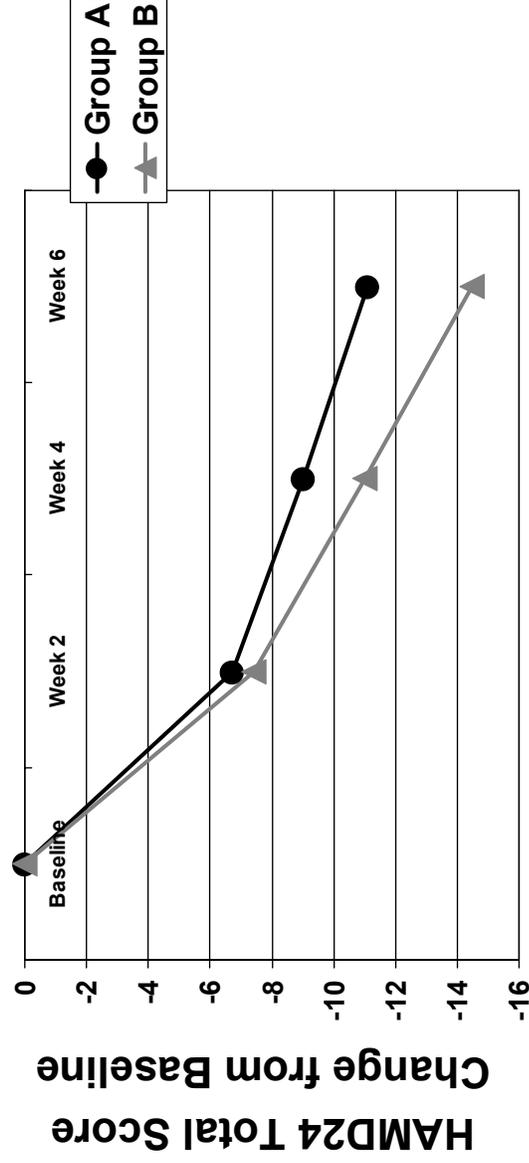
Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline values are defined as the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the mean MADRS total score and for the mean change from baseline is computed at the time points indicated

Figure 4. Secondary Outcome Measure (HAM24 Total Score) Baseline to Endpoint Change for the Evaluable Study Population in Study 44-01102

## HAMD24 Baseline to Endpoint Change Score



Data shown for evaluable study population  
Group A = Study 101 active TMS; Group B = Study 101 sham TMS

**Table 16. Secondary Outcome Measure (HAM-D17 Total Score) for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Total Score	N	73	73	68	61	85	85	77	69
	Mean	22.5	17.6	16.1	14.6	22.6	16.9	14.7	12.2
	SD	3.76	5.08	5.76	7.36	3.8	5.52	6.24	7.02
	Median	22	18	17	14	22	17	15	12
	Min	15	4	3	2	14	2	1	1
	Max	34	28	28	33	34	28	32	29
	Low 95% CI	21.6	16.4	14.7	12.7	21.8	15.7	13.2	10.5
	Higher 95% CI	23.4	18.8	17.5	16.4	23.4	18.1	16.1	13.9
Change from Baseline	N		73	68	61		85	77	69
	Mean		-4.9	-6.4	-8.2		-5.7	-8.2	-10.8
	SD		5	6.02	7.01		5.18	5.95	7.24
	Median		-3	-6	-7		-5	-8	-11
	Min		-21	-25	-26		-17	-21	-28
	Max		3	3	7		6	9	6
	Low 95% CI		-6.1	-7.9	-10		-6.8	-9.6	-12.5
	Higher 95% CI		-3.8	-5	-6.4		-4.6	-6.9	-9

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

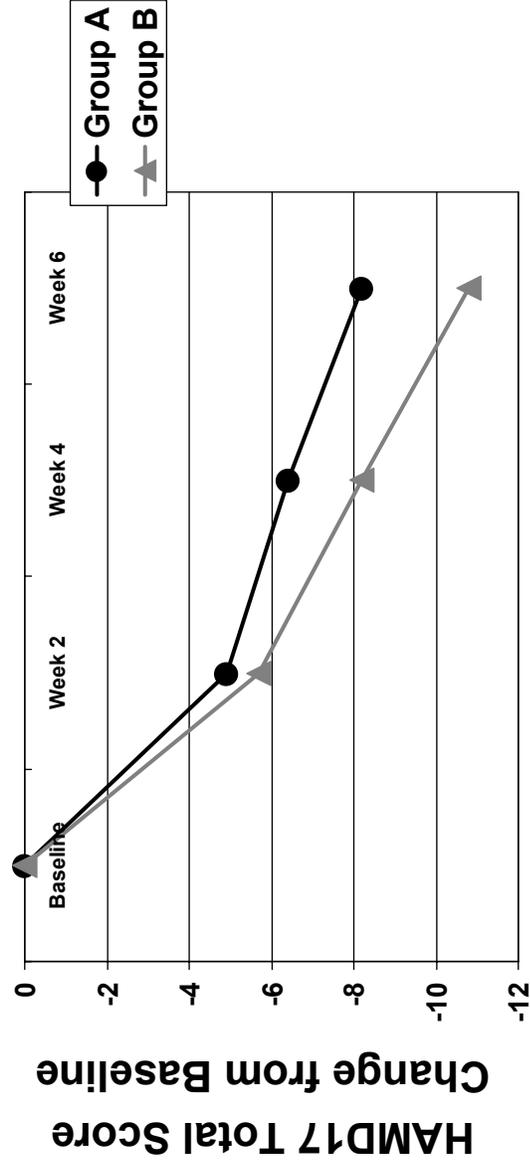
Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline values are defined as the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the mean MADRS total score and for the mean change from baseline is computed at the time points indicated

Figure 5. Secondary Outcome Measure (HAMD17 Total Score) Baseline to Endpoint Change for the Evaluable Study Population in Study 44-01102

## HAMD17 Baseline to Endpoint Change Score



Data shown for evaluable study population  
Group A = Study 101 active TMS; Group B = Study 101 sham TMS

Table 17. Secondary Outcome Measure (MADRS Responders) for the Evaluable Study Population in Study 44-01102

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Responder	N (%)	6 (8.2)	12 (14.1)
		95% C.I.	(%, %)	( 3.08, 17.04)	( 7.51, 23.36)
	Non-Responder	N (%)	67 (91.8)	73 (85.9)	
Week 4	Responder	N (%)	15 (22.1)	21 (27.3)	
	95% C.I.	(%, %)	( 12.90, 33.76)	( 17.74, 38.62)	
Week 6	Non-Responder	N (%)	53 (77.9)	56 (72.7)	
		Responder	N (%)	19 (31.1)	36 (52.2)
	95% C.I.	(%, %)	( 19.90, 44.29)	( 39.80, 64.35)	
	Non-Responder	N (%)	42 (68.9)	33 (47.8)	

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Response rate is defined as  $\geq 50\%$  reduction from baseline total score, using the last assessment obtained in study 44-01101, prior to entry into study 44-01102 as the baseline reference

95% confidence interval for the proportion of subjects that responded at the time points indicated

**Table 18. Secondary Outcome Measure (MADRS Remission Rate) for the Evaluable Study Population in Study 44-01102**

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Remission	N (%)	2 (2.7)	6 (7.1)
		95% C.I.	(%, %)	( 0.33, 9.55)	( 2.63, 14.73)
	Week 4	Non-Remission	N (%)	71 (97.3)	79 (92.9)
		Remission	N (%)	4 (5.9)	5 (6.5)
	Week 6	95% C.I.	(%, %)	( 1.63, 14.38)	( 2.14, 14.51)
		Non-Remission	N (%)	64 (94.1)	72 (93.5)
	Remission	N (%)	N (%)	8 (13.1)	17 (24.6)
		95% C.I.	(%, %)	( 5.84, 24.22)	( 15.05, 36.49)
	Non-Remission	N (%)	N (%)	53 (86.9)	52 (75.4)

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

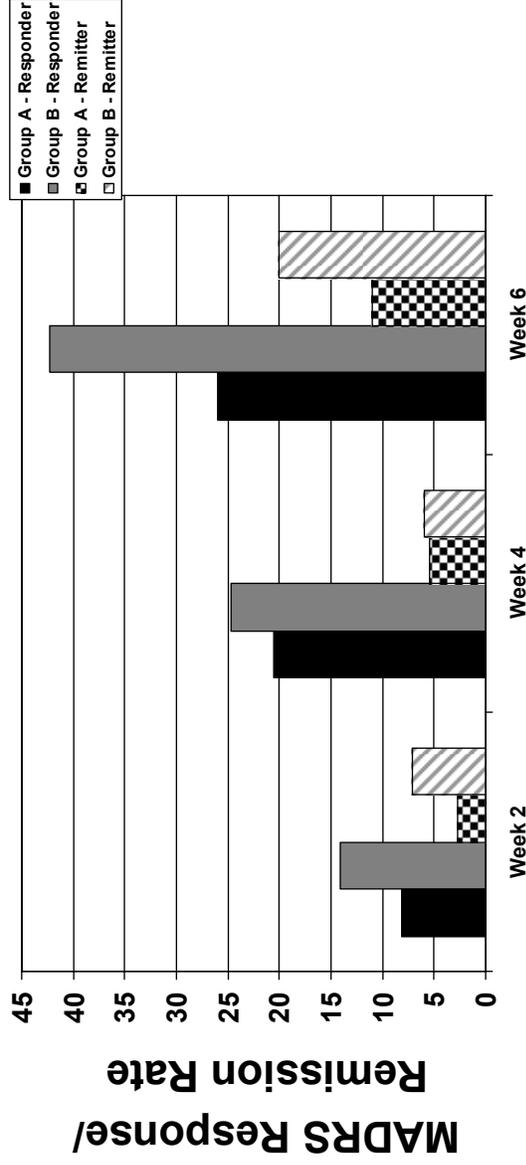
Group B = Patients previously allocated to sham TMS in study 44-01101

Remission is defined as a MADRS total score < 10

95% confidence interval for the proportion of subjects that responded at the time points indicated

Figure 6. Secondary Outcome Measures (MADRS Responder and Remission Rates) Last-Observation Carried Forward Analysis in Study 44-01102

## MADRS Categorical Clinical Outcomes



Data shown for evaluable study population  
Group A = Study 101 active TMS; Group B = Study 101 sham TMS  
Outcome displayed as a percentage of the total study population in the Group at entry

Table 19. Secondary Outcome Measure (HAM24 Responders) for the Evaluable Study Population in Study 44-01102

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Responder	N (%)	7 (9.6)	14 (16.5)
		95% C.I.	(%, %)	( 3.94, 18.76)	( 9.31, 26.09)
		Non-Responder	N (%)	66 (90.4)	71 (83.5)
	Week 4	Responder	N (%)	16 (23.5)	24 (31.2)
		95% C.I.	(%, %)	( 14.09, 35.38)	( 21.09, 42.74)
		Non-Responder	N (%)	52 (76.5)	53 (68.8)
	Week 6	Responder	N (%)	23 (37.7)	36 (52.2)
		95% C.I.	(%, %)	( 25.61, 51.04)	( 39.80, 64.35)
		Non-Responder	N (%)	38 (62.3)	33 (47.8)

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Response rate is defined as  $\geq 50\%$  reduction from baseline total score, using the last assessment obtained in study 44-01101, prior to entry into study 44-01102 as the baseline reference

95% confidence interval for the proportion of subjects that responded at the time points indicated

**Table 20. Secondary Outcome Measure (HAMD24 Remission Rate) for the Evaluable Study Population**

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Remission	N (%)	3 (4.1)	5 (5.9)
		95% C.I.	(%, %)	( 0.86, 11.54)	( 1.94, 13.20)
		Non-Remission	N (%)	70 (95.9)	80 (94.1)
	Week 4	Remission	N (%)	7 (10.3)	11 (14.3)
		95% C.I.	(%, %)	( 4.24, 20.07)	( 7.35, 24.13)
		Non-Remission	N (%)	61 (89.7)	66 (85.7)
	Week 6	Remission	N (%)	12 (19.7)	23 (33.3)
		95% C.I.	(%, %)	( 10.60, 31.84)	( 22.44, 45.71)
		Non-Remission	N (%)	49 (80.3)	46 (66.7)

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

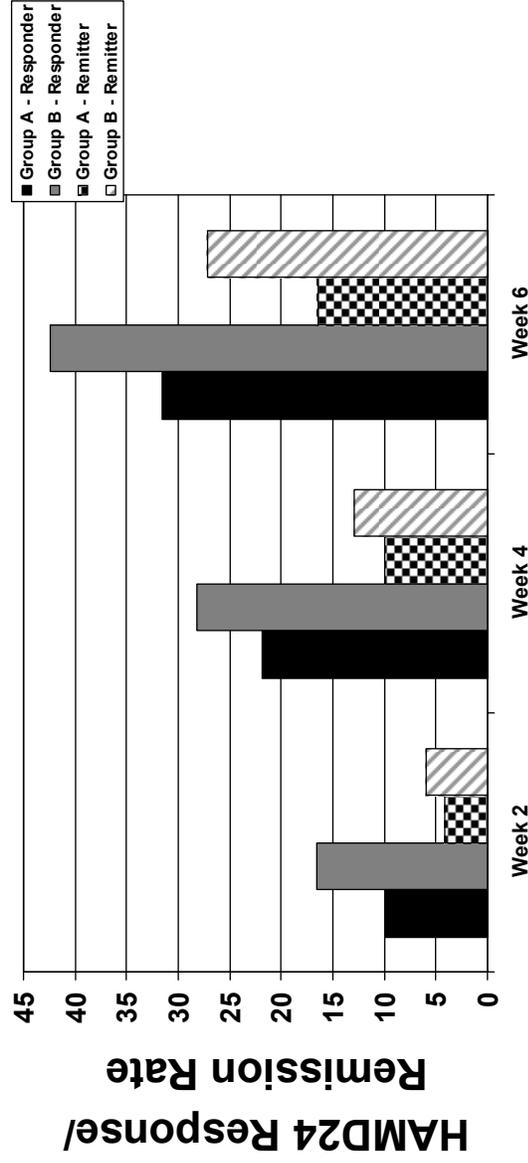
Group B = Patients previously allocated to sham TMS in study 44-01101

Remission is defined as a HAMD24 total score < 11

95% confidence interval for the proportion of subjects that responded at the time points indicated

Figure 7. Secondary Outcome Measures (HAM24 Responder and Remission Rates) for the Evaluable Study Population in Study 44-01102

## HAM24 Categorical Clinical Outcomes



Data shown for evaluable study population

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

Outcome displayed as a percentage of the total study population in the Group at entry

**Table 21. Secondary Outcome Measure (HAMD17 Responders) for the Evaluable Study Population in Study 44-01102**

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Responder	N (%)	9 (12.3)	11 (12.9)
		95% C.I.	(%, %)	( 5.80, 22.12)	( 6.64, 21.98)
		Non-Responder	N (%)	64 (87.7)	74 (87.1)
	Week 4	Responder	N (%)	16 (23.5)	23 (29.9)
		95% C.I.	(%, %)	( 14.09, 35.38)	( 19.97, 41.38)
		Non-Responder	N (%)	52 (76.5)	54 (70.1)
	Week 6	Responder	N (%)	22 (36.1)	32 (46.4)
		95% C.I.	(%, %)	( 24.16, 49.37)	( 34.28, 58.80)
		Non-Responder	N (%)	39 (63.9)	37 (53.6)

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Response rate is defined as  $\geq 50\%$  reduction from baseline total score, using the last assessment obtained in study 44-01101, prior to entry into study 44-01102 as the baseline reference

95% confidence interval for the proportion of subjects that responded at the time points indicated

**Table 22. Secondary Outcome Measure (HAMDI7 Remission Rate) for the Evaluable Study Population**

Phase	Time Point	Response	Statistics	Group A (N=73)	Group B (N=85)
Acute	Week 2	Remission	N (%)	3 (4.1)	6 (7.1)
		95% C.I.	(%, %)	( 0.86, 11.54)	( 2.63, 14.73)
	Week 4	Non-Remission	N (%)	70 (95.9)	79 (92.9)
		Remission	N (%)	5 (7.4)	9 (11.7)
	Week 6	95% C.I.	(%, %)	( 2.43, 16.33)	( 5.49, 21.03)
		Non-Remission	N (%)	63 (92.6)	68 (88.3)
		Remission	N (%)	11 (18.0)	18 (26.1)
		95% C.I.	(%, %)	( 9.36, 29.98)	( 16.25, 38.06)
		Non-Remission	N (%)	50 (82.0)	51 (73.9)

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

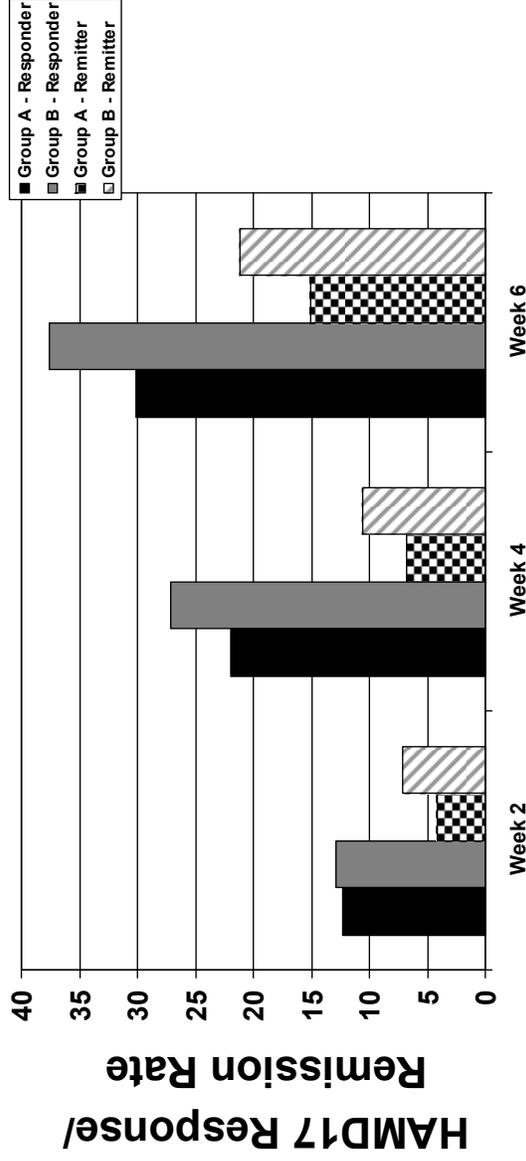
Group B = Patients previously allocated to sham TMS in study 44-01101

Remission is defined as a HAMDI7 total score < 8

95% confidence interval for the proportion of subjects that responded at the time points indicated

Figure 8. Secondary Outcome Measures (HAMD17 Responder and Remission Rates) for the Evaluable Study Population in Study 44-01102

## HAMD17 Categorical Clinical Outcomes



Data shown for evaluable study population

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

Outcome displayed as a percentage of the total study population in the Group at entry

**Table 23. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Physical Functioning Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Physical Functioning Score	N	73	71	61	85	81	70
	Mean	46.1	47.2	46.3	43.2	46.1	47
	SD	10.52	9.6	11.54	11.28	11.02	11.22
	Median	48.8	48.8	50.9	46.7	48.8	52.9
	Min	17.3	19.4	15.2	17.3	17.3	15.2
	Max	57.1	57.1	57.1	57.1	57.1	57.1
	Low 95% CI	43.6	44.9	43.3	40.8	43.6	44.3
	Higher 95% CI	48.5	49.5	49.2	45.6	48.5	49.7
Change from Baseline	N		71	61		81	70
	Mean		1.4	1.1		3.1	4.6
	SD		7.86	9.27		7.39	10.03
	Median		0	0		2.1	2.1
	Min		-25.2	-25.2		-21	-42
	Max		21	27.3		29.4	29.4
	Low 95% CI		-0.5	-1.2		1.4	2.2
	Higher 95% CI		3.2	3.5		4.7	7

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 24. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Role Physical Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Role Physical Score	N	73	71	61	85	81	70
	Mean	38.5	42.3	40.9	38.5	38.8	42.8
	SD	12.2	12.36	11.78	12.71	12.15	11.5
	Median	35	42.1	42.1	28	35	42.1
	Min	28	28	28	28	28	28
	Max	56.2	56.2	56.2	56.2	56.2	56.2
	Low 95% CI	35.7	39.4	37.9	35.8	36.1	40.1
	Higher 95% CI	41.4	45.2	44	41.3	41.5	45.5
Change from Baseline	N		71	61		81	70
	Mean		4.2	4.3		0.5	3.9
	SD		13.02	13.44		11.17	12.89
	Median		0	0		0	0
	Min		-28.3	-28.3		-28.3	-28.3
	Max		28.3	28.3		28.3	28.3
	Low 95% CI		1.1	0.8		-1.9	0.9
	Higher 95% CI		7.3	7.7		3	7

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 25. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Bodily Pain Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Bodily Pain Score	N	73	71	61	85	81	70
	Mean	44.4	45.6	45.2	43	44.8	46.9
	SD	9.74	9.76	10.03	8.89	9.51	8.76
	Median	45.6	45.6	45.6	45.6	45.6	45.6
	Min	19.9	24.2	19.9	19.9	24.2	19.9
	Max	58.5	58.5	58.5	58.5	58.5	58.5
	Low 95% CI	42.2	43.3	42.6	41.1	42.7	44.8
	Higher 95% CI	46.7	47.9	47.8	44.9	46.9	49
Change from Baseline	N		71	61		81	70
	Mean		1.3	1.8		2	4.2
	SD		7.39	7.83		6.7	6.44
	Median		0	4.3		0	4.3
	Min		-25.7	-21.4		-17.1	-8.6
	Max		17.1	17.1		21.4	21.4
	Low 95% CI		-0.5	-0.3		0.5	2.6
	Higher 95% CI		3	3.8		3.4	5.7

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 26. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: General Health Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
General Health Score	N	73	71	61	85	81	70
	Mean	39.5	42	42.6	38.6	41.7	44.1
	SD	9.82	9.61	10.27	9.87	10.28	9.8
	Median	40.6	40.6	42.9	40.6	42.9	45.3
	Min	21.9	21.9	21.9	19.5	19.5	19.5
	Max	64	64	64	61.7	61.7	64
	Low 95% CI	37.2	39.8	40	36.5	39.5	41.7
	Higher 95% CI	41.8	44.3	45.2	40.7	44	46.4
Change from Baseline	N		71	61		81	70
	Mean		2.9	4		3.4	5.6
	SD		6.65	8.07		6.32	6.73
	Median		2.3	4.7		2.3	4.7
	Min		-21.1	-14.1		-14.1	-7
	Max		23.4	35.1		21.1	23.4
	Low 95% CI		1.3	1.9		2	4
	Higher 95% CI		4.5	6		4.8	7.2

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 27. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Vitality Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Vitality Score	N	73	71	61	85	81	70
	Mean	31	36.5	38.1	29.5	35.4	39.7
	SD	7.29	9.88	10.3	5.97	10.01	11.54
	Median	30.1	34.9	37.2	27.8	32.5	39.6
	Min	23	23	23	23	23	23
	Max	53.8	68	63.3	49.1	58.5	63.3
	Low 95% CI	29.3	34.2	35.5	28.2	33.2	36.9
	Higher 95% CI	32.7	38.9	40.8	30.7	37.7	42.4
Change from Baseline	N		71	61		81	70
	Mean		5.8	7.8		6.2	9.9
	SD		8.72	10.76		8.95	10.81
	Median		4.7	4.7		4.7	9.5
	Min		-14.2	-14.2		-16.6	-14.2
	Max		28.4	40.2		30.8	33.1
	Low 95% CI		3.7	5.1		4.2	7.3
	Higher 95% CI		7.9	10.6		8.1	12.5

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 28. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Social Functioning Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Social Functioning Score	N	73	71	61	85	81	70
	Mean	25.9	31.1	33.7	27.7	32.1	36.8
	SD	7.62	9.54	12.17	10.77	10.71	11.3
	Median	24.6	30.2	35.4	24.6	30.2	35.4
	Min	13.7	13.7	13.7	13.7	13.7	13.7
	Max	46.3	57.1	57.1	51.9	57.1	57.1
	Low 95% CI	24.1	28.9	30.6	25.4	29.7	34.1
	Higher 95% CI	27.7	33.4	36.8	30	34.4	39.5
Change from Baseline	N		71	61		81	70
	Mean		5.3	8.3		4.8	9.5
	SD		10.26	12.91		9.54	11.04
	Median		5.2	5.7		5.2	10.9
	Min		-26.9	-21.7		-21.7	-21.7
	Max		32.6	43.4		32.6	38.2
	Low 95% CI		2.9	5		2.7	6.9
	Higher 95% CI		7.8	11.6		6.9	12.2

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 29. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Role Emotional Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Role Emotional Score	N	73	71	61	85	81	70
	Mean	26.3	30.3	32.5	25.8	31.5	33.8
	SD	5.48	9.65	12.19	5.32	11.53	11.7
	Median	23.7	23.7	23.7	23.7	23.7	34.2
	Min	23.7	13.3	23.7	23.7	2.6	23.7
	Max	44.9	55.3	55.3	55.3	55.3	55.3
	Low 95% CI	25	28	29.4	24.7	29	31
	Higher 95% CI	27.6	32.5	35.7	27	34.1	36.6
Change from Baseline	N		71	61		81	70
	Mean		3.9	6.4		5.9	8
	SD		11.16	12.5		12.37	12.37
	Median		0	0		0	0
	Min		-21.2	-10.8		-21.2	-21.2
	Max		31.6	31.6		31.6	31.6
	Low 95% CI		1.2	3.2		3.1	5
	Higher 95% CI		6.5	9.6		8.6	10.9

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 30. Secondary Outcome Measure Medical Outcomes Study Short Form-36 Item Questionnaire v1: Mental Health Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
MH Score	N	73	71	61	85	81	70
	Mean	24.4	30.1	32.8	23	29.5	35.1
	SD	8.88	11.02	11.53	8.33	10.18	12.64
	Median	23.2	30	32.3	23.2	27.7	36.8
	Min	7.3	11.8	11.8	7.3	9.6	7.3
	Max	48.2	57.3	55	45.9	52.7	59.5
	Low 95% CI	22.3	27.5	29.8	21.3	27.3	32.1
	Higher 95% CI	26.4	32.7	35.7	24.8	31.8	38.1
Change from Baseline	N		71	61		81	70
	Mean		5.9	8.4		6.6	11.6
	SD		11.11	12		9.12	11.7
	Median		4.5	6.8		6.8	9.1
	Min		-27.3	-27.3		-11.4	-11.4
	Max		31.8	40.9		31.8	31.8
	Low 95% CI		3.2	5.3		4.6	8.8
	Higher 95% CI		8.5	11.5		8.6	14.3

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the SF 36 component score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 31. Secondary Outcome Measure Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) Total Score in Study 44-01102**

Values	Statistics	Group A (73)			Group B (85)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
Q-LES-Q Total Score	N	73	71	61	85	81	70
	Mean	35.8	42.8	44.7	35.7	43.9	48.7
	SD	8.93	10.78	11.77	7.97	10.46	10.68
	Median	36	42	45	36	44	49
	Min	18	17	18	19	19	20
	Max	60	71	72	55	70	75
	Low 95% CI	33.8	40.3	41.7	34	41.6	46.2
	Higher 95% CI	37.9	45.4	47.7	37.4	46.2	51.3
Change from Baseline	N		71	61		81	70
	Mean		7.2	9.2		8.6	13.3
	SD		10.82	12.05		9.98	11.6
	Median		6	8		7	13.5
	Min		-23	-14		-10	-6
	Max		39	37		32	47
	Low 95% CI		4.7	6.2		6.4	10.5
	Higher 95% CI		9.8	12.3		10.8	16

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the Q-LES-Q total score at baseline and for the mean change from baseline is computed at the time points indicated

**Table 32. Secondary Outcome Measure HAMD Anxiety/Somatization Factor Score for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Anxiety/Somatization Factor	N	73	73	68	61	85	85	77	69
	Mean	7	5.3	5	4.7	7.4	5.7	4.8	4.1
	SD	2.19	2.36	1.97	2.66	1.95	2.31	2.23	2.66
	Median	7	5	5	4	7	5	4	3
	Min	3	1	2	1	3	0	0	0
	Max	13	13	10	14	12	12	11	12
	Low 95% CI	6.5	4.8	4.5	4	7	5.2	4.3	3.4
	Higher 95% CI	7.6	5.9	5.5	5.3	7.8	6.2	5.3	4.7
Change from Baseline	N		73	68	61		85	77	69
	Mean		-1.7	-2.1	-2.7		-1.8	-2.6	-3.3
	SD		2.13	2.25	2.45		2.15	2.13	2.62
	Median		-1	-2	-3		-2	-3	-3
	Min		-7	-7	-9		-8	-8	-10
	Max		3	2	3		2	3	3
	Low 95% CI		-2.2	-2.6	-3.3		-2.2	-3.1	-4
	Higher 95% CI		-1.2	-1.6	-2		-1.3	-2.1	-2.7

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAMD factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAMD Anxiety/Somatization Factor = HAMD Items 10, 11, 12, 13, 15 and 17

**Table 33. Secondary Outcome Measure HAMD Core Depression Factor Score for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Core Depression Factor	N	73	73	68	61	85	85	77	69
	Mean	9.7	7.6	6.8	6	9.6	7	5.9	4.6
	SD	2.07	2.58	3.08	3.53	1.95	3.04	3.03	3.33
	Median	9	8	7	5	10	7	5	4
	Min	5	1	1	0	4	0	0	0
	Max	15	13	13	13	14	14	14	13
	Low 95% CI	9.2	7	6.1	5.1	9.2	6.3	5.2	3.8
	Higher 95% CI	10.2	8.2	7.6	6.9	10	7.7	6.6	5.4
Change from Baseline	N		73	68	61		85	77	69
	Mean		-2.1	-2.8	-3.6		-2.6	-3.7	-5.1
	SD		2.55	2.68	3.26		2.89	2.99	3.45
	Median		-2	-2	-4		-2	-4	-5
	Min		-9	-9	-11		-12	-11	-12
	Max		3	2	3		3	5	3
	Low 95% CI		-2.7	-3.5	-4.5		-3.2	-4.4	-5.9
	Higher 95% CI		-1.5	-2.2	-2.8		-2	-3.1	-4.2

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAMD factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAMD Core Depression Factor = HAMD Items 1, 2, 3, 7 and 8

Table 34. Secondary Outcome Measure HAM-D Maier Factor Score for the Evaluable Study Population in Study 44-01102

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Factor Score	N	73	73	68	61	85	85	77	69
	Mean	11.4	8.9	8	6.9	11.3	8.2	7	5.6
	SD	2.08	2.87	3.08	3.39	2.11	3.12	3.24	3.71
	Median	11	9	8	6	11	9	7	6
	Min	6	1	1	0	7	0	0	0
	Max	17	15	15	14	17	14	15	15
	Low 95% CI	10.9	8.2	7.3	6	10.9	7.6	6.3	4.7
	Higher 95% CI	11.8	9.5	8.7	7.7	11.8	8.9	7.7	6.5
Change from Baseline	N		73	68	61		85	77	69
	Mean		-2.5	-3.3	-4.4		-3.1	-4.4	-5.7
	SD		2.78	3.08	3.13		3.13	3.33	3.99
	Median		-2	-3.5	-5		-3	-4	-6
	Min		-11	-10	-11		-11	-13	-14
	Max		3	2	2		3	4	4
	Low 95% CI		-3.1	-4	-5.2		-3.8	-5.2	-6.7
	Higher 95% CI		-1.8	-2.5	-3.6		-2.4	-3.6	-4.7

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAM-D factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAM-D Maier Factor = HAM-D Items 1, 2, 7, 8, 9 and 10

**Table 35. Secondary Outcome Measure HAMD Gibbons Factor Score for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Factor Score	N	73	73	68	61	85	85	77	69
	Mean	14.9	12.1	10.9	9.6	15	11.4	9.8	8.1
	SD	2.83	3.81	4.05	4.64	2.66	3.99	4.34	4.9
	Median	15	13	11	9	15	11	9	8
	Min	7	3	2	2	10	2	1	0
	Max	23	20	20	22	22	19	22	19
	Low 95% CI	14.3	11.2	9.9	8.4	14.4	10.5	8.8	6.9
	Higher 95% CI	15.6	13	11.9	10.8	15.6	12.2	10.8	9.3
Change from Baseline	N		73	68	61		85	77	69
	Mean		-2.8	-4	-5.4		-3.6	-5.4	-7
	SD		3.39	4	4.29		3.52	4.2	5.03
	Median		-3	-4	-5		-3	-5	-8
	Min		-14	-14	-15		-11	-15	-18
	Max		4	4	2		4	7	6
	Low 95% CI		-3.6	-5	-6.5		-4.4	-6.3	-8.3
	Higher 95% CI		-2.1	-3	-4.3		-2.9	-4.4	-5.8

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAMD factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAMD Gibbons Factor = HAMD Items 1, 2, 3, 7, 9, 10, 11 and 14

**Table 36. Secondary Outcome Measure HAM-D Retardation Factor Score for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Factor Score	N	73	73	68	61	85	85	77	69
	Mean	8.2	6.6	5.9	5.2	8.1	6.2	5.2	4.2
	SD	1.77	2.15	2.41	2.69	1.58	2.3	2.35	2.7
	Median	8	7	6	5	8	6	5	4
	Min	4	2	1	0	5	2	0	0
	Max	13	10	10	10	12	12	11	10
	Low 95% CI	7.8	6.1	5.3	4.5	7.8	5.7	4.7	3.6
	Higher 95% CI	8.6	7.1	6.5	5.9	8.5	6.7	5.8	4.9
Change from Baseline	N		73	68	61		85	77	69
	Mean		-1.7	-2.3	-2.9		-1.9	-2.9	-3.9
	SD		2.25	2.47	2.74		2.31	2.42	3.02
	Median		-1	-2	-3		-2	-3	-4
	Min		-7	-7	-9		-8	-11	-11
	Max		4	2	2		3	3	4
	Low 95% CI		-2.2	-2.8	-3.6		-2.4	-3.5	-4.6
	Higher 95% CI		-1.1	-1.7	-2.2		-1.4	-2.4	-3.2

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAM-D factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAM-D Retardation Factor = HAM-D Items 1, 7, 8 and 14

**Table 37. Secondary Outcome Measure HAMD Sleep Factor Score for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)						Group B (85)					
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
Factor Score	N	73	73	68	61	85	77	69					
	Mean	3.5	2.7	2.6	2.3	3.3	2.3	2.1					
	SD	1.59	1.78	1.7	1.86	1.75	1.84	1.81					
	Median	4	3	2	2	3	2	2					
	Min	0	0	0	0	0	0	0					
	Max	6	6	6	6	6	6	6					
	Low 95% CI	3.1	2.3	2.2	1.9	2.9	2.2	1.7					
	Higher 95% CI	3.9	3.1	3	2.8	3.7	2.9	2.6					
Change from Baseline	N		73	68	61	85	77	69					
	Mean		-0.8	-0.9	-1.2	-0.8	-1.2	-1.4					
	SD		1.98	1.85	2.14	1.51	1.7	1.92					
	Median		0	-1	-1	-1	-1	-1					
	Min		-6	-6	-6	-5	-6	-6					
	Max		3	3	4	3	3	3					
	Low 95% CI		-1.2	-1.4	-1.8	-1.1	-1.6	-1.8					
	Higher 95% CI		-0.3	-0.5	-0.7	-0.4	-0.8	-0.9					

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the HAMD factor score at baseline and for the mean change from baseline is computed at the time points indicated

HAMD Sleep Factor = HAMD Items 4, 5 and 6

**Table 38. Secondary Outcome Measure Inventory of Depressive Symptoms-Self Report (IDS-SR) for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
IDS-SR Total Score	N	73	72	68	62	85	77	70	70
	Mean	40.1	35.7	33	30	40.8	30.4	25.1	25.1
	SD	14.86	11.18	13.13	15.13	13.94	13.08	14.98	14.98
	Median	43	36	34	29.5	42	30	23	23
	Min	0	7	5	0	0	4	0	0
	Max	74	70	66	64	64	66	67	67
	Low 95% CI	36.6	33	29.8	26.1	37.8	27.4	21.5	21.5
	Higher 95% CI	43.5	38.3	36.1	33.8	43.8	33.4	28.7	28.7
Change from Baseline	N	72	68	68	62	85	77	70	70
	Mean	-4.3	-6.8	-6.8	-9.9	-5.6	-11.4	-16.8	-16.8
	SD	16.56	17.38	17.38	19.24	13.17	14.68	18.49	18.49
	Median	-4	-7	-7	-8	-4	-11	-17	-17
	Min	-48	-49	-49	-50	-37	-41	-56	-56
	Max	51	48	48	45	43	35	42	42
	Low 95% CI	-8.2	-11	-11	-14.8	-8.4	-14.7	-21.2	-21.2
	Higher 95% CI	-0.4	-2.6	-2.6	-5.1	-2.8	-8.1	-12.4	-12.4

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the IDS-SR total score at baseline and for the mean change from baseline is computed at the time points indicated

IDS-SR total score = Sum of 30 items

**Table 39. Secondary Outcome Measure Clinician Global Impressions-Severity (CGI-S) for the Evaluable Study Population in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
CGI-S Score	N	73	72	68	61	85	77	69	69
	Mean	4.9	4.3	4	3.5	4.8	3.7	3.1	3.1
	SD	0.79	1	1.04	1.3	0.75	0.99	1.24	1.24
	Median	5	4	4	3	5	4	3	3
	Min	2	1	2	1	4	1	1	1
	Max	6	6	6	6	7	6	6	6
	Low 95% CI	4.7	4.1	3.7	3.2	4.7	4	2.8	2.8
	Higher 95% CI	5	4.6	4.3	3.9	5	4.4	3.4	3.4
Change from Baseline	N	72	68	61	61	85	77	69	69
	Mean	-0.5	-0.8	-1.3	-1.3	-0.6	-1.1	-1.8	-1.8
	SD	0.9	0.95	1.3	1.3	0.8	0.94	1.19	1.19
	Median	0	-1	-1	-1	-1	-1	-2	-2
	Min	-4	-3	-4	-4	-3	-3	-4	-4
	Max	1	1	1	1	1	1	1	1
	Low 95% CI	-0.7	-1	-1	-1.6	-0.8	-1.4	-2.1	-2.1
	Higher 95% CI	-0.3	-0.6	-0.9	-0.9	-0.5	-0.9	-1.5	-1.5

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the CGI-S total score at baseline and for the mean change from baseline is computed at the time points indicated

CGI-S total score = integer score on 7-point scale

**Table 40. Secondary Outcome Measure Patient Global Impressions-Improvement (PGI-I) Total Score Last Observation Carried Forward Analysis in Study 44-01102**

Values	Statistics	Group A (73)				Group B (85)			
		Baseline	Week 2	Week 4	Week 6	Baseline	Week 2	Week 4	Week 6
PGI-I Score	N	73	71	68	61	85	77	68	68
	Mean	4.6	3.5	3.3	3	4.6	3	2.6	2.6
	SD	1.08	1.04	1.38	1.44	1.1	1.08	1.12	1.12
	Median	5	3	3	3	4	3	2	2
	Min	2	2	1	1	2	1	1	1
	Max	7	7	7	7	7	7	5	5
	Low 95% CI	4.4	3.2	3	2.6	4.3	3.3	2.3	2.3
	Higher 95% CI	4.9	3.7	3.6	3.4	4.8	3.8	2.9	2.9
Change from Baseline	N	71	68	68	61	85	77	68	68
	Mean	-1.1	-1.3	-1.6	-1.6	-1	-1.5	-2	-2
	SD	1.43	1.59	1.68	1.68	1.41	1.44	1.55	1.55
	Median	-1	-1	-2	-2	-1	-1	-2	-2
	Min	-5	-6	-6	-6	-5	-5	-5	-5
	Max	2	2	2	2	2	2	1	1
	Low 95% CI	-1.4	-1.7	-2	-2	-1.3	-1.9	-2.3	-2.3
	Higher 95% CI	-0.7	-0.9	-1.2	-1.2	-0.7	-1.2	-1.6	-1.6

Notes: Group A = Patients previously allocated to active TMS in study 44-01101

Group B = Patients previously allocated to sham TMS in study 44-01101

Baseline is defined using the last assessment obtained in study 44-01101, prior to entry into study 44-01102

95% confidence interval for the PGI-I total score at baseline and for the mean change from baseline is computed at the time points indicated

PGI-I total score = integer score on 7-point scale

### 14.3. Overall Efficacy Conclusions Based on the *A Priori*-Defined Efficacy Outcome Measures

#### 14.3.1. 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)

#### 14.3.2. 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.

#### 14.3.3. Overall Efficacy Conclusions (Table 41)

- Patients with major depression who have 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.
  - Open-label TMS treatment with the Neuronetics TMS System resulted in a *response rate of 29.5% and 50.3% at 4 and 6 weeks, respectively, and a remission rate of 10.8% and 28% at 4 and 6 weeks, respectively, using an average of MADRS, HAMD 17 and HAMD 24 item scores for patients previously allocated to sham TMS treatment in study 44-01101*.
  - Open-label TMS treatment with the Neuronetics TMS System resulted in a *response rate of 23.0% and 35.0% at 4 and 6 weeks, respectively, and a remission rate of 7.9% and 16.9% at 4 and 6 weeks, respectively, using an average of MADRS, HAMD 17 and HAMD 24 item scores for patients previously allocated to active TMS treatment in study 44-01101*.

**Table 41. Open-Label TMS Study 44-01102: A Priori-Defined Outcome Measures**

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

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

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

<sup>3</sup> MADRS Remission is defined as MADRS total score <10

<sup>4</sup> HAMD24 Remission is defined as HAMD24 total score <11

<sup>5</sup> HAMD17 Remission is defined as HAMD17 total score <8

<sup>6</sup> Responder and Remission rates were calculated using total enrolled sample

## 15.0 SUBSET ANALYSES

An exploratory descriptive analysis that was not previously stipulated in the protocol-defined statistical plan was conducted on specific demographic and illness severity measures. These analyses were intended to determine if the study results could be generalized across the broad population of patients with major depression regardless of fixed population characteristics (e.g., gender and age), and whether the observed treatment effect when analyzed by baseline severity is also broadly generalized within the overall treatment population.

Specifically, continuous outcome on the total score for the 3 principal disease-specific efficacy instruments, the MADRS, the 24-item HAMD, and the 17-item HAMD was examined for 3 specific patient subsets: gender, age (< 55 or > 55 years), and baseline HAMD17 severity (using a median split of the observed baseline score = 22).

Detailed tabular summary of these results are shown in Appendix 3, Tables 3.9-3.11. No inferential statistical comparisons were performed on these subsets since they are presented as exploratory analyses.

### 15.1. Subset Analyses Conclusions

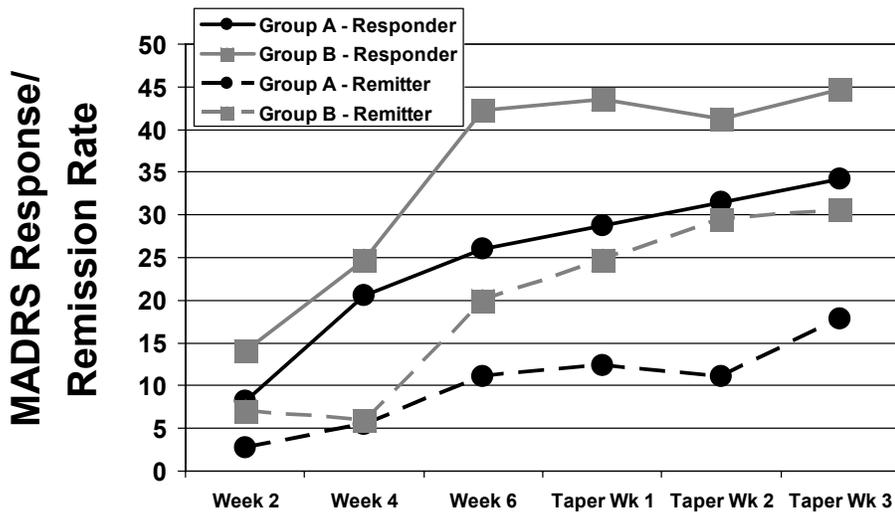
Inspection of the exploratory analyses subset by gender, age and baseline HAMD17 severity do not suggest any clinically meaningful differential effect of active TMS on any of the observed population features.

**16.0 DURABILITY OF EFFECT OF TMS TREATMENT**

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 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. No patient was to be treated with an antidepressant medication for which they had previously been shown to have failed to receive benefit.

Figures 9, 10, and 11 summarize the categorical responder and remission rates for the primary disease-specific efficacy outcome measures (the MADRS, the HAMD24 and the HAMD17) for all patients continuing into the post-treatment taper phase, displayed separately for Group A and Group B. Detailed supportive tables for these figures are included in Appendix 3, Tables 3.12-3.17.

**MADRS Categorical Clinical Outcomes**  
 - Durability of Effect in Taper Phase



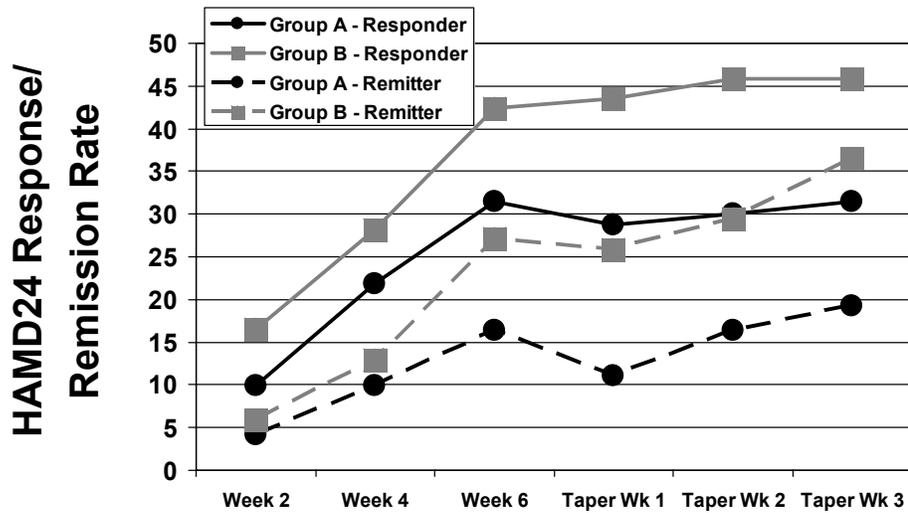
Data shown for evaluable study population  
 Group A = Study 101 active TMS; Group B = Study 101 sham TMS  
 Outcome displayed as a percentage of the total study population in the Group at entry

Notes: MADRS Responder =  $\geq 50\%$  reduction from baseline total score  
 MADRS Remission = total score < 10

**Figure 9. Responder and Remission Rates for the MADRS for Patients Continuing into the Post-Treatment Taper Phase in Study 44-01102**

# HAMD24 Categorical Clinical Outcomes

## - Durability of Effect in Taper Phase



Data shown for evaluable study population

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

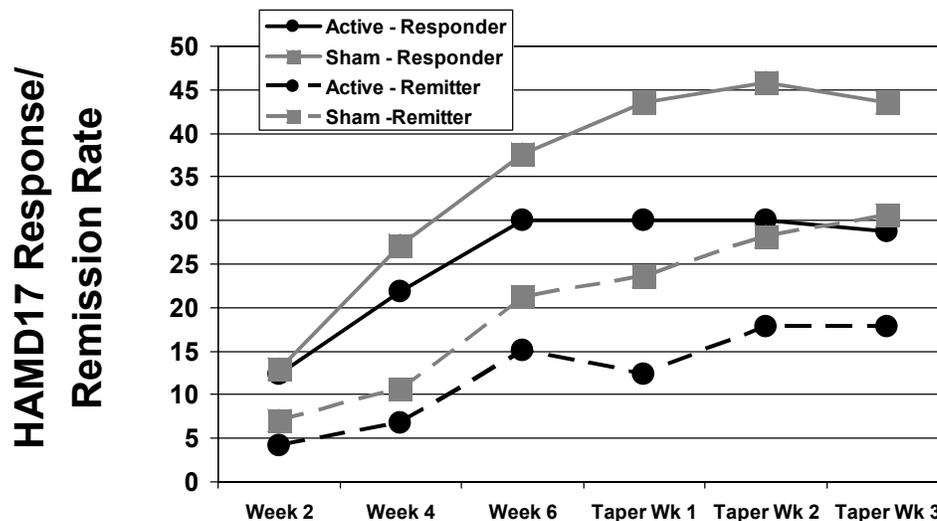
Outcome displayed as a percentage of the total study population in the Group at entry

Notes: HAMD24 Responder =  $\geq 50\%$  reduction from baseline total score  
 HAMD24 Remission = total score < 11

**Figure 10. Responder and Remission Rates for the HAMD24 for Patients Continuing into the Post-Treatment Taper Phase in Study 44-01102**

# HAMD17 Categorical Clinical Outcomes

## - Durability of Effect in Taper Phase



Data shown for evaluable study population

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

Outcome displayed as a percentage of the total study population in the Group at entry

Notes: HAMD17 Responder =  $\geq 50\%$  reduction from baseline total score  
 HAMD17 Remission = total score < 8

**Figure 11. Responder and Remission Rates for the HAMD17 for Patients Continuing into the Post-Treatment Taper Phase in Study 44-01102**

### 16.1. Durability of TMS Effect in Taper Phase Conclusions

- 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 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.

## 17.0 SAFETY DATA

### 17.1. 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 44-01102 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 below.

#### 17.1.1. Listing of Serious Adverse Events Reported for Study 44-01102

- No deaths or seizures were reported.
- Ten (10) events occurred during the acute treatment phase, and two (2) adverse events occurred in the post-treatment taper phase.
- The types of SAEs or other reportable events are shown in Table 42. The number of SAEs reported and the relationship to study device as determined by the investigator is also provided.

**Table 41. Serious Adverse Events Reported for Study No. 44-01102**

Serious Adverse Event	Number of SAEs	Relationship to Study Device
Left-sided facial numbness	1	Probably Related
Worsening Depression/Suicidal Ideation	2	Not Related
Overdose	4	Not Related
Tinnitus	1	Probably Not Related
Worsening of Major Depression	1	Not Related
Atrial Fibrillation	2	Not Related
Suicidal Ideation	1	Not Related

### 17.1.2. Serious Adverse Event Clinical Case Vignettes for Study 44-01102

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

## 17.2. 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 records 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 43 summarizes adverse events by MedDRA-preferred term that occurred at an incidence of  $\geq 5\%$  in either treatment Group A or Group B. 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 3.18-3.23.

**Table 42. 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**

<b>Body System (-) Preferred Term</b>	<b>Group A (N=73) N (%)</b>	<b>Group B (N=85) N (%)</b>
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)
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)

**17.2.1. Time Course of Common Adverse Events**

The most common adverse events experienced by patients were headache (47.9% Group A vs 45.9% sham TMS treatment) and application site pain (11.0% Group A vs 31.8% Group B). A comparable proportion of patients in Group A classified their headache severity as ‘severe’ as compared to Group B (Group A 6.8% vs Group B 5.9%). With regard to application site pain, a greater percentage of patients in Group B classified this event as ‘severe’ compared to Group A (Group A 0% vs Group B 9.4%).

Inspection of the investigator-assigned causal relation of the event to the study device revealed that for headache, 24.6% of Group A patients reported their headache as of ‘probable’ or ‘definite’ relation to the study device compared to 18.8% of Group B patients. In the instance of application site pain, all patients in both treatment groups considered the event of probable or definite relationship to the study device.

In order to determine the time course of incidence of these common adverse events, which were expected to show adaptation and diminishing incidence over time, an exploratory analysis of these symptoms was performed with regard to the time of event within the course of the clinical trial. These data are displayed in Figures 12 and 13. Supporting data tables for these figures are contained in Appendix 3, Tables 3.24-3.25.

Number of Patients Reporting Headaches per Week

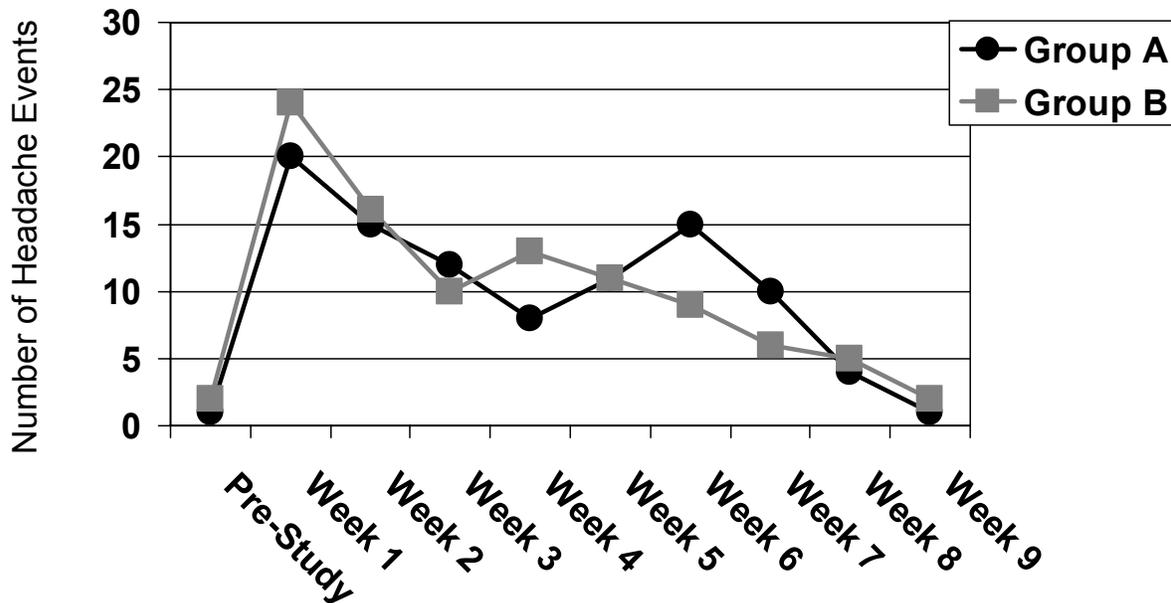


Figure 12. Time Course Incidence of Headache (Any Severity) in Study 44-01102

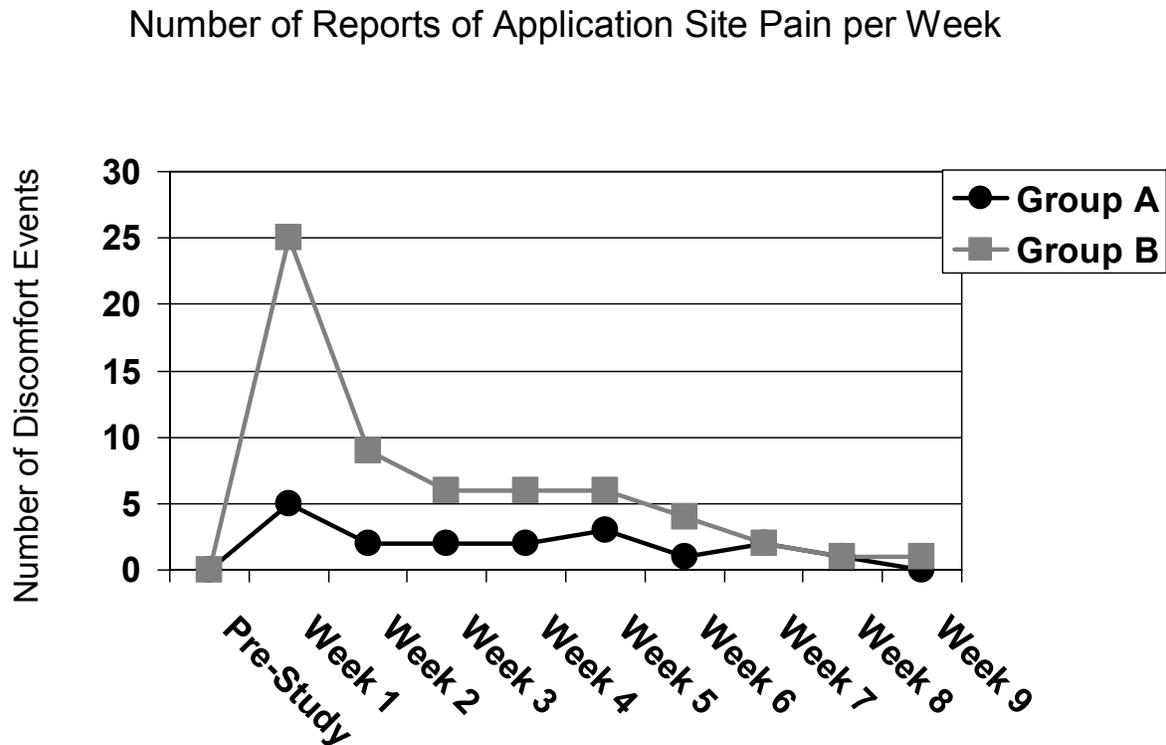


Figure 13. Time Course Incidence of Application Site Pain (Any Severity) in Study 44-01102

### 17.2.2. Treatment-Emergent Adverse Events Conclusions

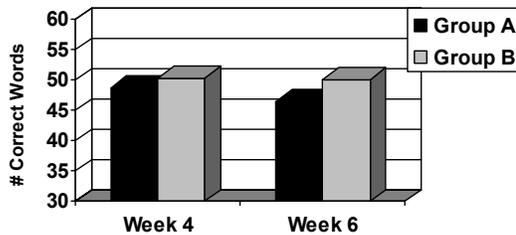
- There was a similar incidence of headaches seen in both TMS treatment groups.
- Application site pain was observed in both treatment groups, but the incidence was greater in the patient group that had previously been allocated to sham TMS treatment prior to entry into study 44-01102, suggesting that 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 was similar to that reported in study 44-01101.

**17.3. Cognitive Function Testing**

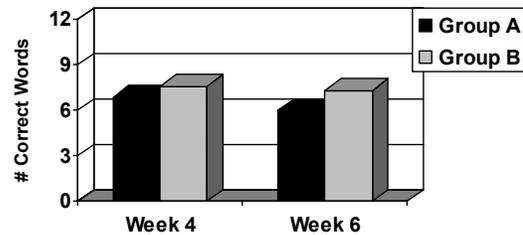
Cognitive function was assessed using the modified Mini Mental Status Examination (MMSE), the Buschke Selective Reminding Test (BSRT), and the Autobiographical Memory Inventory-Short Form (AMI-SF) at baseline, week 4 and week 6. Multiple versions of the MMSE and BSRT were used to allow repeat administrations and to deter learning effects.

Results of these tests comparing baseline assessment with 4 and 6 week observations during the acute treatment phase are shown in Figure 14. Detailed tabular summaries of these tests are contained in Appendix 3, Tables 3.26-28.

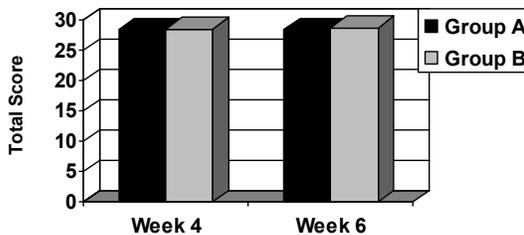
BSRT Short Term Recall



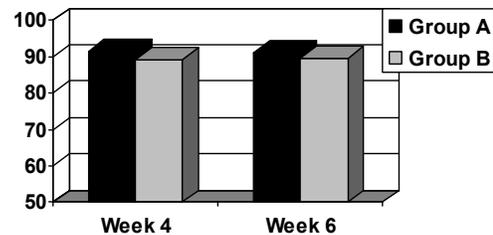
BSRT Delayed Recall



Mini Mental Status Exam Scores



AMI-SF Amnesia Scores (%)



Data shown for evaluable study population  
 Group A = Study 101 active TMS; Group B = Study 101 sham TMS

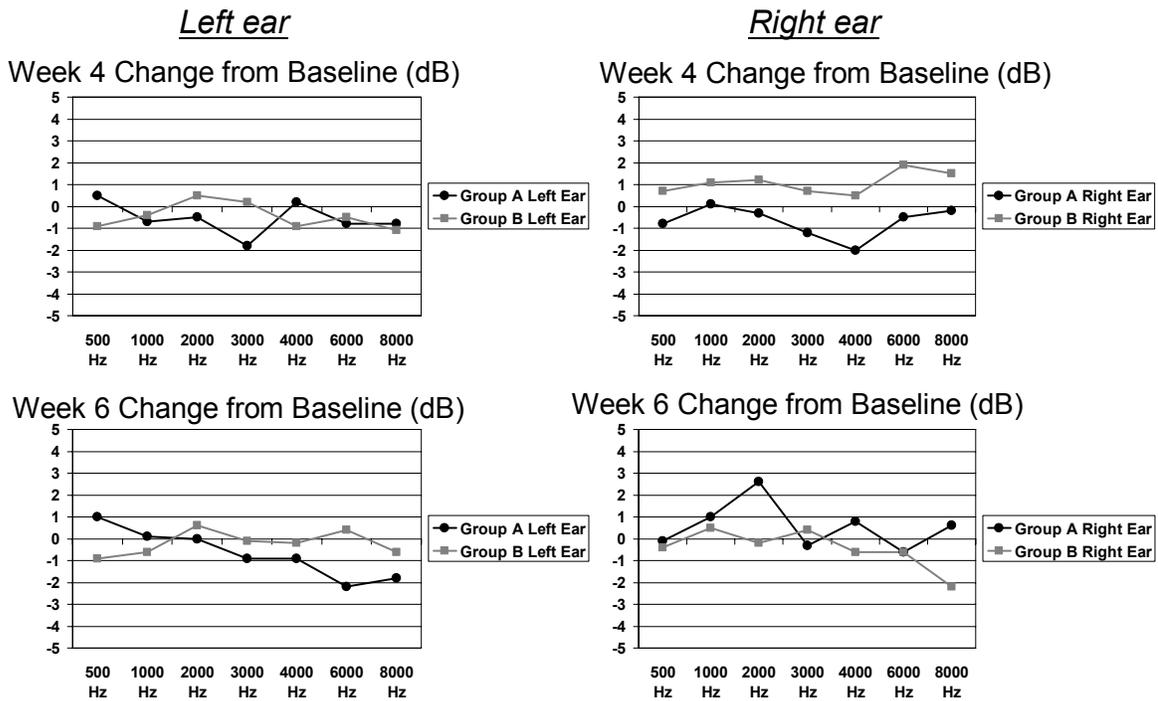
**Figure 14. Cognitive Function Testing Results for Study 44-01102**

**17.3.1. Cognitive Function Testing Conclusions**

- There was no evidence of an acute effect of TMS on any measure of cognitive function tested.
- Both treatment groups showed essentially stable cognitive function on the standard test measures used throughout the acute treatment phase of the study.

**17.4. Auditory Threshold Testing**

Air-conduction auditory threshold was assessed at baseline, week 4 and week 6. A desktop audiometer (Micro Audiometrics, Inc,) was used, with a standard test sequence that examined the threshold decibel level at which a pure tone signal could be perceived by the patient. Results of these tests are shown in Figure 15. Contrasts within treatment group examining change in decibel level (auditory threshold) are shown for left and right ears. Note that all patients wore ear protection rated at a minimum decibel level reduction of 30 during TMS treatment. Detailed tabular summaries of these tests are contained in Appendix 3, Tables 3.29-3.35.



Data shown for evaluable study population  
 Group A = Study 101 active TMS; Group B = Study 101 sham TMS

**Figure 15. Auditory Threshold Testing Results for Study No. 44-01102**

**17.4.1. Auditory Threshold Testing Conclusions**

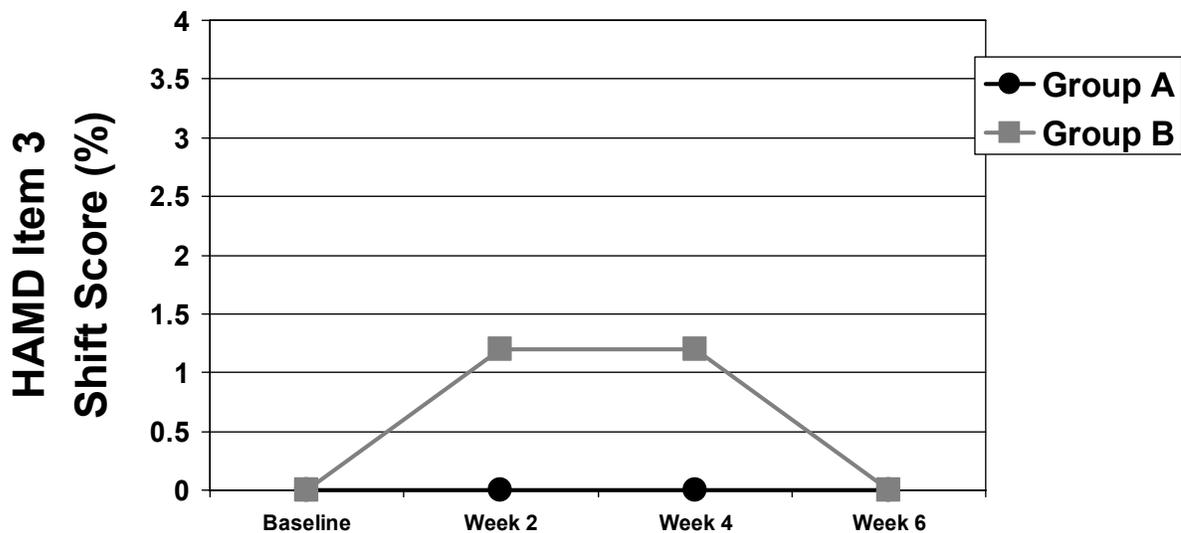
- There was no evidence of a short-term alteration of auditory threshold with acute treatment in either treatment group when earplugs (30 db) were worn during TMS treatment.
- Both treatment groups showed essentially stable air conduction auditory threshold throughout the acute treatment phase of the study.

**17.5. Emergent Suicidal Ideation**

Major depression is a potentially lethal disease. It has been speculated that in some patient populations, antidepressant treatment may be associated with a paradoxical aggravation of the illness, with a resulting abrupt incidence of suicidal ideation. In order to assess if TMS treatment may similarly be associated with a risk for paroxysmal suicidal ideation, an exploratory safety analysis was performed to examine this risk for active TMS treatment.

The Item 3 score on the HAMD (Suicidal Ideation) was examined for incidence of abrupt worsening of this item from a score of 0 or 1 at the baseline assessment to a shift in score to 3 or 4 at any later time point. Results of this analysis are shown in Figure 16, and detailed tabular summary of these results are provided in Appendix 3, Table 3.36.

**HAMD Item 3: Suicidal Ideation**



Shift Score indicates the % of subjects who experienced a change in Item 3 score from 0 or 1 at baseline to 3 or 4 at later points

Group A = Study 101 active TMS; Group B = Study 101 sham TMS

**Figure 16. Incidence of Emergent Suicidal Ideation in Study No. 44-01102**

**17.5.1. Emergent Suicidal Ideation Conclusions**

- 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.

## 17.6. Overall Conclusions Based on the *A Priori*-Defined Safety Outcome Measures

### Serious Adverse Events

- There were no deaths or seizures reported in Study 44-01102.

### 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 TMS literature and as reported in study 44-01101.
- The most frequently reported events were headache and application site pain. Headache was equally represented in both treatment groups. Application site pain was more frequently represented in Group B, patients who had not previously been exposed to active TMS. Both headache and application site pain lessened with time over the TMS treatment course.

### 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 (with use of earplugs during TMS treatment).

## 18.0 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 44.

### 18.1. Console Failure

Fifteen console failures at nine clinical sites were reported in Ser. No. 012 on 30 August 2004 and in the IDE Annual Report 2004 (Ser. No. 014). A root cause analysis report for the console failures was submitted as Ser. No. 016 on 19 Oct 2004. The console replacement process concluded on 15 October 2005 with the replacement of all affected consoles.

### 18.2. E-Shield Failure: first degree scalp burn and E-shield Recall

A single report of overheating of an E-Shield that resulted in a first degree scalp burn was reported to the FDA in Ser. No. 009 on 04 June 2004 as stated in the 2004  Annual Report (Ser. No. 014).

As a result of the E-Shield malfunction, a recall of 41 E-Shields was initiated (Ser. No. 009 dated 04 June 2004). The recall was expanded to include an additional 6 E-shields as described in Ser. No. 010 dated 23 July 2004. A root cause analysis was performed and reported in Ser. No. 011 dated 18 August 2004. Unreleased E-shields that met the requirements of the recall were destroyed by the contract manufacturer, DMSI.

A second report of a first degree scalp burn was reported by the Medical University of South Carolina on 26 October 2004 and was reported in Ser. No. 017, dated 05 November 2004. The root cause analysis report for the device malfunction was submitted in Ser. No. 011 on 18 August 2004. The informed consent documents for protocols 44-01101, 44-01102 and 44-01103 had previously been revised to include the risk of scalp burn. They were revised further to indicate that more than one event of scalp burn had occurred (Ser. Nos. 022, 023, 024 dated 07 Feb 2005, 10 Feb 2005, 02 Mar 2005, respectively). The changes to the informed consent documents and the investigational plan were approved in an FDA letter dated 14 April 2005.

One incident of “acute pain” under the treatment coil that was relieved by replacement of the E-Shield occurred on 08 September 2005 at Rush University. The patient’s scalp was examined and there was no evidence of skin irritation, erythema or burn. The event was reported in Ser. No. 031, dated 4 October 2005. The root cause analysis report for the device malfunction was submitted in Ser. No. 033 on 21 October 2005. Based on the findings, the event did not require the alteration of the risk profile of the device or modification of the informed consent documents.

**Table 43. Reportable Device Malfunction Event and Regulatory Reporting**

Device	Event	Device S/N	Event Date	<input type="text"/> 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

## 19.0 MODIFICATIONS TO THE PLANNED STATISTICAL ANALYSIS

All *a priori*-defined statistical analyses were conducted as planned. Additional analyses were conducted as follows:

- Subset analyses that were not prospectively defined in the protocol for study 44-01102 were conducted for gender, age and severity to determine if TMS treatment was biased to a demographic subset.

## **20.0 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR USE**

Safety data obtained from the conduct of Study 44-01102 are provided in the Neuronetics TMS System User Manual. New safety information obtained from study 44-01102 that was not previously included in IDE documents regarding the contraindications, warnings and precautions for use are as follows.

- A listing of adverse events reported with an incidence on active TMS of  $\geq 2\%$  and greater than the incidence on sham TMS is included in the Neuronetics TMS System User Manual.

## 21.0 ADDITIONAL CLINICAL INFORMATION FROM THE STUDY

### 21.1. Deviations to the Protocol and Protocol Violations

During the final database analysis, a summary of the potentially clinically important protocol violations was reviewed and summarized. These are listed in tabular form in Table 3.37 in Appendix 3, as shown for the evaluable study population (N=158).

In general, the pattern of protocol violations was distributed equally across the two treatment groups. The largest group of observations concerned subjects missing more than two treatment sessions in sequence, or >20% of the number of sessions intended during their study participation as discussed in Section 11.

The overall pattern of protocol violations listed was small relative to the overall sample size, and therefore was not considered to have substantially affected the interpretation of the results, therefore, no post-hoc analyses excluding these data were deemed appropriate.

In addition to these clinically important protocol deviations, a review of the protocol deviation log and of the final data listings used for the development of the data tables was conducted for assessment of potentially clinically non-significant events. This review revealed protocol deviations at the conclusion of the study as shown in Table 45. 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 44. Protocol Deviations in Study 44-01102**

Protocol Deviations	Number of Deviations
Excluded medications used	15
Documentation procedure	24
Protocol procedure	107
Device procedure	52

### 21.2. Post-Data Lock Errata and Data Handling Issues

Data for this clinical study was collected via  electronic data capture system (EDC). Clinical site, monitor, and sponsor were each provided with an individual log in ID. Site personnel entered the data that was collected on patient source documents, patient chart. The data on the EDC was monitored 100% against source document and was additionally reviewed for consistency and clarity. Upon completion of review, patient's data was soft locked by the investigator at the site.

Throughout the study, all adverse events [redacted] concomitant medications were coded via an autoencoder and manually a [redacted] to MedDRA and WHODrug, respectively. Neuronetics reviewed all assigned coding after each run and for the entire dataset, upon completion.

After the database was complete [redacted] removed database change access to all users, allowing read only access. [redacted] base was then converted to SAS datasets and qual [redacted] ch field. The dataset was then transferred to [redacted] for completion of the statistical analysis.

Incomplete start dates were provided by the sites for adverse events and concomitant treatments. For missing start months and days with year provided, the worst case scenario was used of January 1 of the year. For missing days with month and year provided, the first of the month was used.

After lock of the database, there were a few patients with adverse events starting in the year 2005, although the patients participation was completed in 2004. We changed the data in the derived dataset for calculation to 2004 without changing the original dataset.