

Transcranial Magnetic Stimulation: Effectiveness and Safety in a Randomized, Controlled Multisite Trial and an Open-Label Extension Study

[The TMS Therapy Study Group]
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Abstract

Background: Transcranial magnetic stimulation (TMS) is a method of using powerful, pulsed magnetic fields to induce electrical currents directed at a specific target location. A large body of work supports the view that TMS may have therapeutic potential in the treatment of major depression. However, definitive conclusions of true efficacy of TMS have been hampered by criticisms of several aspects of prior study designs, including variable dose selection, insufficient duration of treatment, single center study design, inferior sham condition and inadequate sample size. In this report, we describe the outcome of a large, multisite (23 site) randomized controlled clinical trial of 6 weeks duration, administered at fixed treatment parameters over the left dorsolateral prefrontal cortex, compared to a sham TMS treatment condition of identical procedure to the active condition.

Methods: Eligible patients (N=301) met DSM-IV criteria for unipolar major depression, and had failed to receive benefit from at least one but no more than four antidepressant treatments in their current episode (ATHF criteria). All patients were medication-free during the course of the acute treatment period. Treatment parameters were standardized at 120% of motor threshold, 10 pulses/sec, with a 4 sec on/26 off cycle, for a total of 3000 pulses per session. Coil position was determined by external landmarks using a mechanical coordinate system. An innovative sham coil design was used that was acoustically matched to allow a similar procedural experience to patient and clinician. Outcome was determined by clinician and patient rated instruments. Safety was assessed by adverse event report and by targeted assessment of cognitive function and auditory threshold.

Results: Active TMS showed a significant benefit over sham TMS on continuous outcome measures at 4 and 6 week time points (MADRS total score: P = 0.057 and 0.058, HAMD24 total score: P=0.012 and 0.015, HAMD17 total score: P=0.006 and P=0.005). Similarly significant outcomes for contrasts between active and sham TMS were observed on categorical responder rates at 4 and 6 weeks (MADRS: 4 weeks, 18.1% vs 11.0%, P=0.045 and 6 weeks, 23.9% vs 12.3%, P=0.007; HAMD24: 4 weeks, 19.4% vs 11.6%, P=0.030 and 6 weeks, 29.9% vs 15.1%, P=0.042; HAMD17: 4 weeks, 20.6% vs 11.6%, P=0.018 and 6 weeks, 24.5% vs 13.7%, P=0.015). Patients who failed to receive benefit from treatment in the randomized trial were offered enrollment in the open-label extension trial without un-blinding of prior treatment assignment. Patients crossing from prior treatment with sham TMS achieved response rates ~42-44% after 6 weeks of active TMS. Discontinuation rates due to adverse events were less than 5% and of similar incidence in either active or sham treatment groups.

Discussion: TMS was demonstrated to be an effective treatment for patients with major depression who had failed to receive adequate benefit from prior antidepressant therapy. TMS was well-tolerated, with a low discontinuation rate due to adverse events.

Introduction

Major depression is a common, recurrent, and frequently chronic disorder that is a leading contributor to functional impairment and disability. Treatment is often challenging, as an estimated 20% to 40% of patients do not benefit sufficiently from, or are intolerant to, existing antidepressant interventions, including trials of medication and psychotherapy. Indeed, a substantial proportion of patients manifest a chronic, treatment-resistant course of illness. The need for a new and more diverse array of therapies is clear.

Transcranial magnetic stimulation (TMS) is a method of using powerful, briefly pulsed magnetic fields to induce electrical currents in a focused manner in a conducting substrate. Applied to the brain as a target electrical conductor, TMS is unlike other methods of electrical stimulation because the effects can be directed in a more localized manner than for instance, is done during electroconvulsive therapy. TMS can be administered as single pulses, or in repetitive pulses, sometimes referred to as 'trains', of short (ie, several seconds) duration. It is now well-established that TMS can affect brain function in the direct area of the induced electric currents, and also that these local effects may produce broader, indirect functional effects in brain areas distant from the site of direct stimulation.

A number of empirical and theoretical observations led investigators to study whether TMS has therapeutic utility in the treatment of major depression. Arguing in favor of its potential use as an antidepressant are preclinical data demonstrating effects on receptor targets, gene expression and neurotransmitter turnover which are reminiscent of known antidepressants. In addition, animal behavioral models, such as the Porsolt forced swim test, show activity of TMS during chronic administration. In addition to these preclinical observations, there is sufficient evidence from small, single-site clinical studies demonstrating positive evidence that TMS can produce improvements in mood in patients diagnosed with major depression.

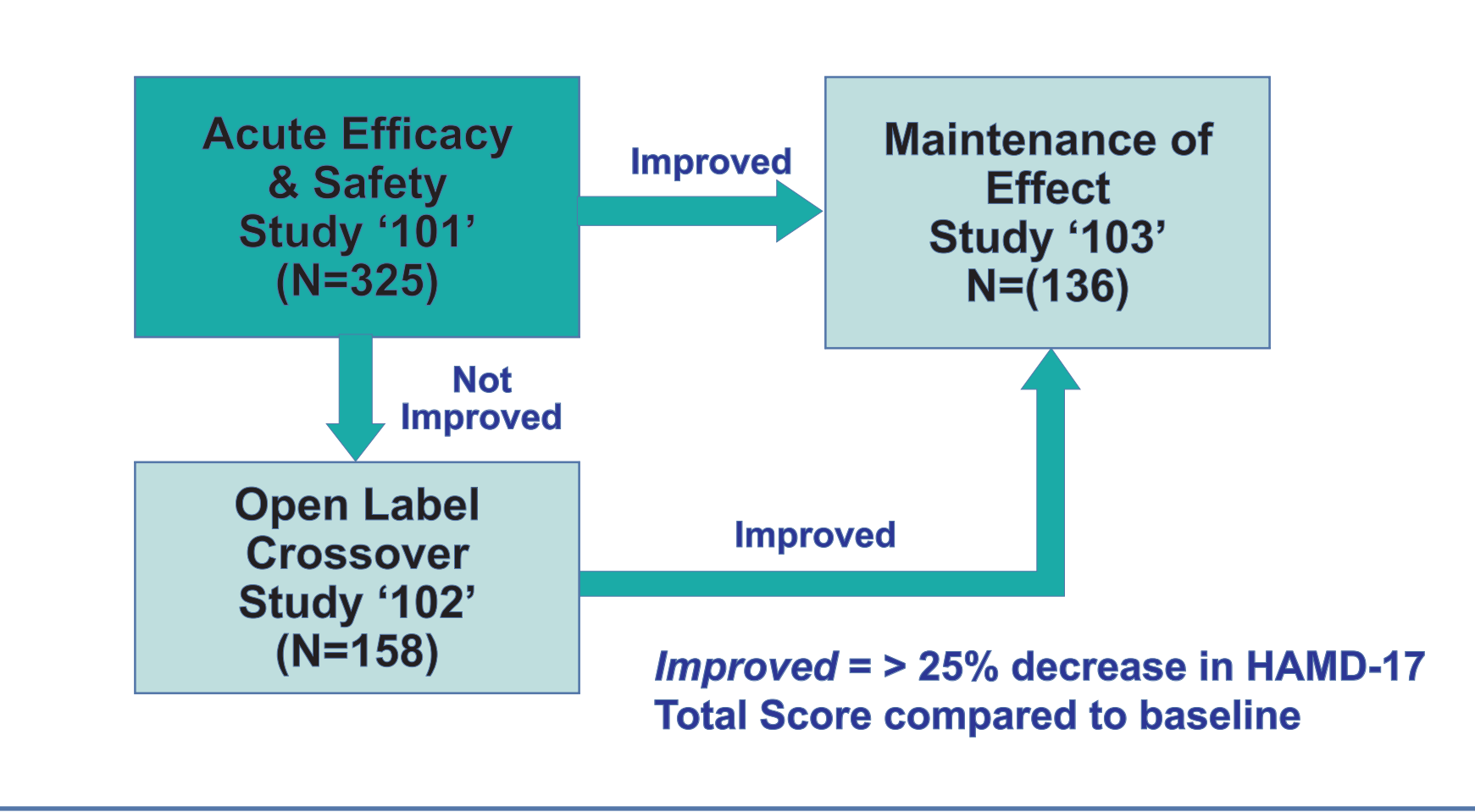
The present studies were designed to provide confirmatory evidence of this antidepressant effect, to refine our understanding of the clinical significance of these effects, and to define an optimal clinical treatment regimen for the use of TMS in patients with major depression.

Methods - Study Design

Overview of Clinical Development Program

The overall clinical development program was composed of three separate clinical protocols that were related in temporal sequence to one another (see Figure 1). Study 101 was a randomized controlled clinical trial designed to examine the efficacy of the NeuroStar TMS Therapy System compared to a sham TMS treatment condition. Treatment parameters and study duration (up to 6 weeks) were selected to represent a maximum feasible dose study design in order to test as exhaustively as possible the evidence for efficacy of TMS. Treatment parameters included stimulation at 120% of observed motor threshold, applied at a pulse frequency of 10 pulses per second (4 seconds on and 26 seconds off), for a total of 3000 pulses per treatment session. Because there was no prior work to guide estimates of patient adherence under study designs extending longer than 3 weeks, a consensus decision by the study development team was made to declare the primary efficacy outcome time point at 4 weeks to ensure that patient attrition was kept within an acceptable limit, while extending treatment for up to 6 weeks of acute treatment as a secondary endpoint to gain a better understanding of the benefit obtained from more extended treatment.

Figure 1. NeuroStar™ TMS Clinical Development Program



Methods - Study Design

A second, open-label study (Study 102) was incorporated that followed the same treatment sequence as the randomized controlled trial, and was available upon request for all patients who had: 1) participated in the first study for at least 4 weeks of acute treatment, 2) who had received no clinical benefit from their randomized assignment, and 3) who were electing to discontinue study participation. The blinded treatment assignment received in Study 101 was not revealed upon entry to Study 102. In addition, an a priori criterion defining failure of clinical benefit in Study 101 was established, however, that specific criterion definition was concealed from the investigator in order to minimize likelihood of rating bias. A three-week period of treatment transition, or Taper Phase, was included at the conclusion of the acute phase of either Study 101 or Study 102. The purpose of this Taper Phase was to determine whether the acute response to TMS could be maintained without abrupt loss of effect for a sufficient interval to allow continuation treatment on a known active antidepressant medication. Choice of medication in this phase was restricted to antidepressant monotherapy.

A final, open-label, continuation of effect study (Study 103) was included for up to 24 weeks of clinical follow up. Results for Studies 101 and 102 only are reported here.

All TMS sessions were delivered using the Neuronetics Model 2100 Therapy System investigational device. Three separate magnetic coils, similar in weight, external appearance and acoustic properties when actively pulsed, were used at each site, with one coil unblinded, and used as the known active coil to determine motor thresholds. The other two coils differed in that the sham coil had an embedded magnetic shield. The latter limited the magnetic energy reaching the cortex to 10% or less than the active coil, but nevertheless allowed the active and sham coils to have similar appearance, placement and acoustic properties. All treatment personnel were blind as to coil assignment. All efficacy outcome measures were assessed by blinded study personnel (raters) who were not permitted access to the treatment sessions. Raters underwent certification in which their study participation was contingent on demonstrating adequate reliability in the conduct and scoring of interviews to derive HAMD and MADRS scores. Quality of ongoing ratings was assessed through the use of video monitoring reviewed by an independent expert. Patients were instructed not to disclose any details of the treatment session with the study raters during rating sessions. Further, neither raters nor other study personnel at the specific centers were aware of the declared primary efficacy measure during the trial.

Methods - Patient Selection Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Primary Diagnosis: <ul style="list-style-type: none">DSM-IV Major Depressive EpisodeCurrent episode < 3 years	Psychiatric: <ul style="list-style-type: none">PsychosisBipolar DisorderObsessive compulsive disorderPost-traumatic stress disorder (past year)Prior ECT failure or recent ECT Rx
Symptom Severity: <ul style="list-style-type: none">HAMD17 ≥ 20 (Item 1 ≥ 2)CGI-S ≥ 4 (moderate or greater severity)	Non-Psychiatric: <ul style="list-style-type: none">Immediate risk of suicideUnable to discontinue psychotropic medsUnstable medical diseaseNeurological disease (incr in seizure risk)Metal objects in head
Prior Treatment Failure: <ul style="list-style-type: none">History of > 1 and < 4 antidepressant rx's of adequate dose and duration in current episode (by ATHF criteria)	

Methods - Study Outcomes

Efficacy and Safety Outcomes
The primary efficacy outcome was the difference between active and sham TMS using the last visit MADRS score through week 4 of the acute treatment phase. Secondary outcome measures included the MADRS score at 6 weeks, 24-item and 17-item Hamilton Depression Rating Scale (HAMD17 and HAMD24) scores at 4 and 6 weeks, and categorical endpoints using MADRS, HAMD17 and HAMD24 at 4 and 6 weeks. Response was defined as at least 50% reduction from baseline score. Remission was defined by an absolute score-specific total score (MADRS < 10, HAMD24 < 11, HAMD17 < 8).

Additional secondary outcome measures obtained are shown in Table 1.

Safety was assessed at every treatment visit by recording spontaneous adverse event reports that were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Auditory threshold and cognitive function were also assessed and are not reported in this abstract.

Analysis Methods

Efficacy analyses were performed on the strict intent-to-treat sample of all evaluable patients, defined in the protocol as those with a baseline and at least one post-baseline observation available for analysis. The null hypothesis for the primary outcome was tested with an analysis of covariance, using baseline score, and ATHF medication resistance level as fixed effect covariates, adjusting for site differences using a random effect. Secondary outcome analyses for continuous measures were conducted in a similar fashion. All analyses were conducted in a last-observation carried forward (LOCF) manner through the indicated time points.

Table 1. Primary and Secondary Efficacy Outcomes

- Primary outcome**
- MADRS Total Score Change from Baseline
- Secondary Outcomes**
- HAMD24 Total Score Change from Baseline
 - HAMD17 Total Score Change from Baseline
 - Response Rate (50% reduction: MADRS, HAMD24, HAMD17)
 - SF-36 and Q-LES-Q (Functional Status and Quality of Life Outcomes)
 - Remission Rate (MADRS <10, HAMD24 <11, HAMD17 <8)
 - HAMD Scale Factor Scores Change from Baseline
 - IDS-SR Total Score Change from Baseline
 - CGI-Severity Change from Baseline
 - PGI-Improvement Change from Baseline

Clinician-rated outcomes = blue
Patient-rated outcomes = black

Results

Subject Characteristics

Demographic and clinical features of the study population were consistent with a moderately to severely ill patient group, with significant symptomatic and functional morbidity due to their illness (Table 2).

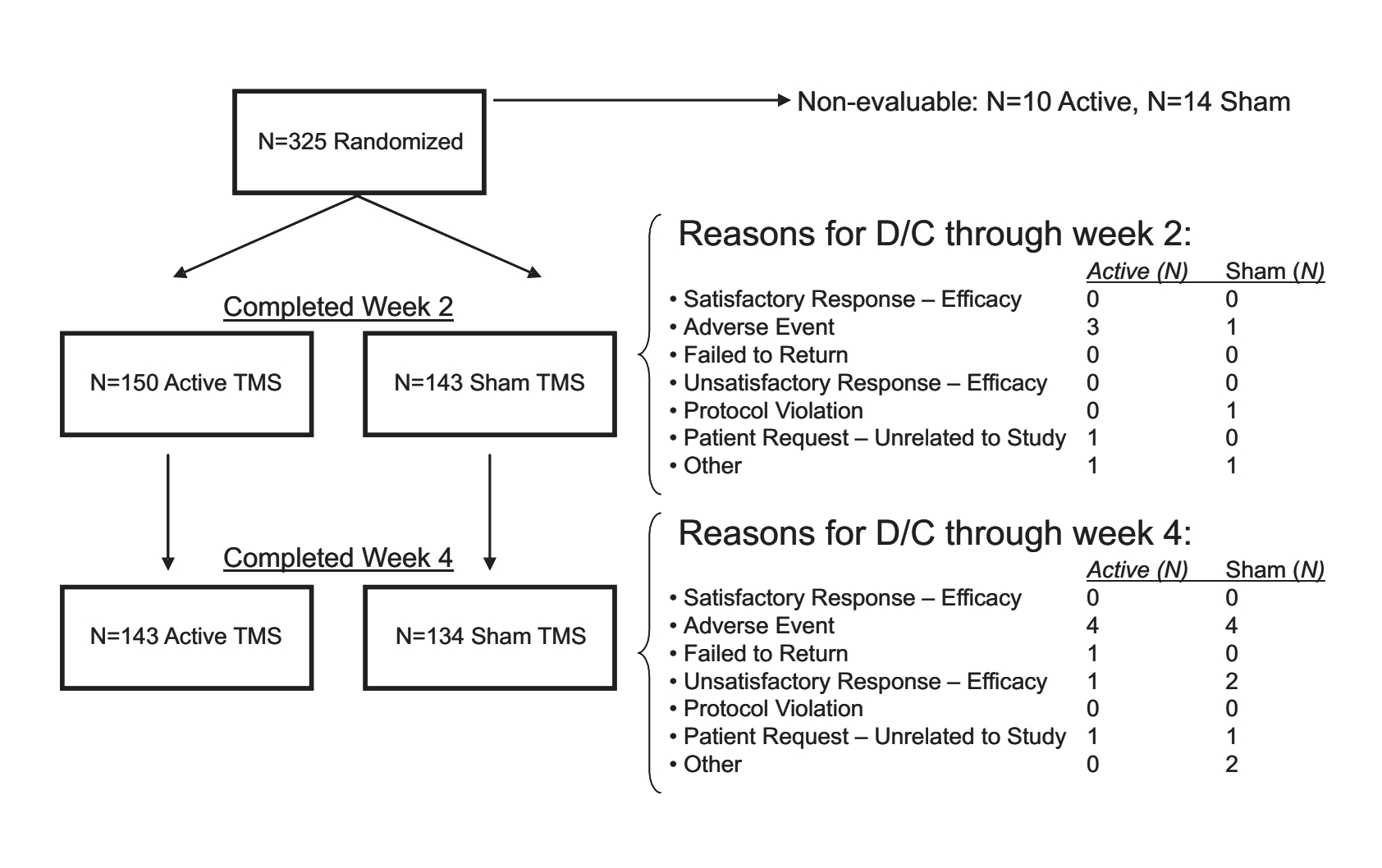
Table 2. Demographic and Clinical Features of the Study Population

	Active TMS (N=155)	Sham TMS (N=146)	P Value
Demographic Variables			
- N(%) Female	86 (55.5)	74 (50.7)	0.421
- Age (yr)	47.9 (11.0)	46.7 (10.6)	0.509
- Ethnic origin (N%)			
- Caucasian	146 (94.2)	131 (89.7)	
- Other	9 (5.8)	15 (10.3)	0.201
- Employment status (N%)			
- Full time	56 (35.6)	45 (28.3)	
- Part time	27 (16.6)	31 (19.3)	
- Unemployed	76 (47.9)	85 (52.2)	
- Receiving disability compensation	28 (32.9)	31 (34.1)	
Clinical Variables			
- Recurrent illness score (%)	149 (95.5)	136 (93.8)	0.611
- Duration of current episode in months (Mean (SD))	13.6 (8.9)	13.2 (9.3)	0.728
- N(%) of population with current episode > 2 years	36 (23.2)	21 (14.8)	0.112
- Number of fully adequate antidepressant treatments in current episode	1.6	1.6	0.816
Baseline Symptom Severity			
- MADRS total score (SD)	32.8 (6.0)	33.9 (5.7)	0.206
- HAMD 17 total score (SD)	22.6 (3.3)	22.9 (3.0)	0.508
- HAMD 24 total score (SD)	30.1 (6.0)	30.5 (4.9)	0.568
- CGI-Severity (SD)	4.7 (0.6)	4.7 (0.7)	0.964
- IDS-SR total score (SD)	42.0 (9.4)	43.4 (9.9)	0.197

Patient Disposition Through the Primary Efficacy Time Point (Week 4)

Adherence to the study protocol through the primary efficacy time point was excellent (Table 3). Through week 4, the overall discontinuation rate was low and was similar in the active TMS (7.7%) and sham TMS (8.2%) treatment groups. Discontinuation due to adverse events with TMS was rare, similar across treatment conditions (4.5% of active TMS vs. 3.4% of sham TMS patients). Beyond the primary efficacy time point, 47.7% patients in the active TMS group and 63.0% patients in the sham TMS treatment group elected to enter the open-label extension study.

Table 3. Reasons for Study Discontinuation Through Primary Efficacy Time Point (Week 4)



Efficacy Findings - Study 101

- Active TMS showed a significant benefit over sham TMS on continuous outcome measures at 4 and 6 week time points (MADRS total score: P = 0.057 and 0.058, HAMD24 total score: P=0.012 and 0.015, HAMD17 total score: P=0.006 and P=0.005), (Figures 1a, 1b and 1c)
- The clinical significance of these group differences are supported by significant outcomes for the contrasts between active and sham TMS that were observed on categorical responder rates at 4 and 6 weeks and on categorical remission rates for the MADRS and HAMD24 at 6 weeks, (Figures 2a, 2b and 2c)
- Analysis of HAMD Factor Scores confirmed a strong clinical effect of active TMS on core depression and anxiety symptom scores. (Table 4)
- The clinical effect of TMS was sustained as observed during the 3-week transition to medication monotherapy during the Taper Phase, with a continued improvement in clinical benefit observed in the active TMS group. (Figure 3)

Efficacy Findings - Study 102

- Patients crossing into Study 102 from prior treatment with sham TMS in Study 101 achieved response rates ~42-44% after 6 weeks of active TMS, providing confirmatory support for the evidence of efficacy observed in the controlled Study 101. (Figure 4)

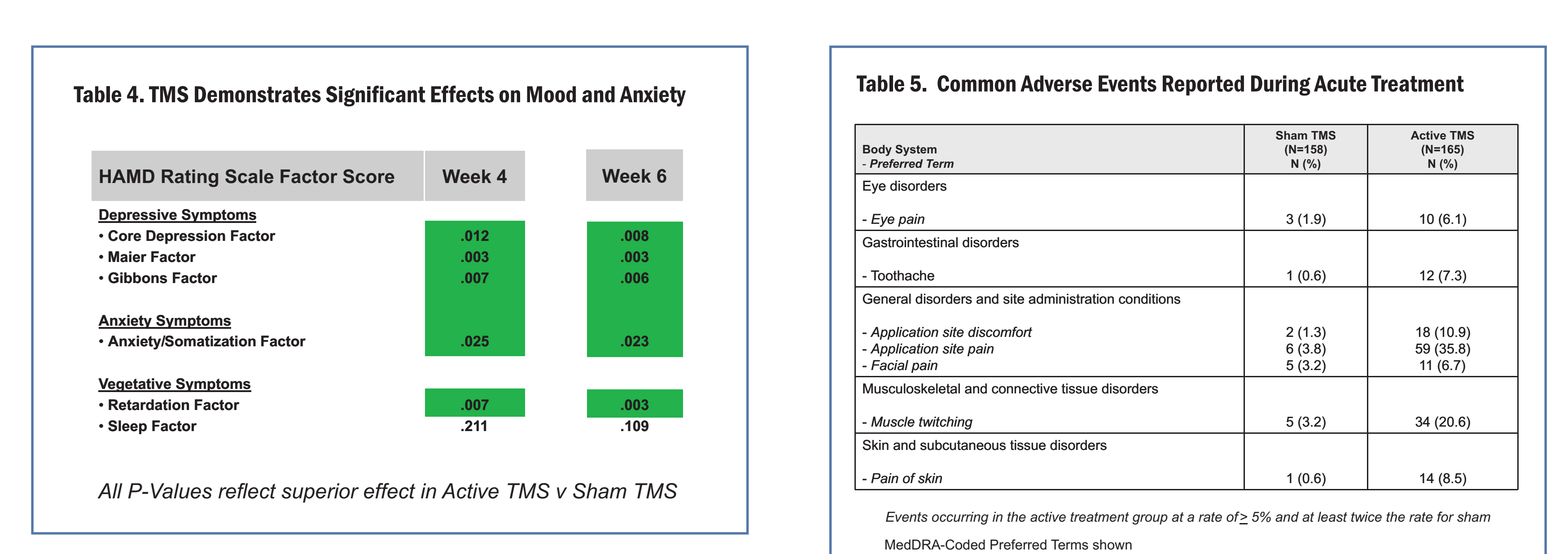
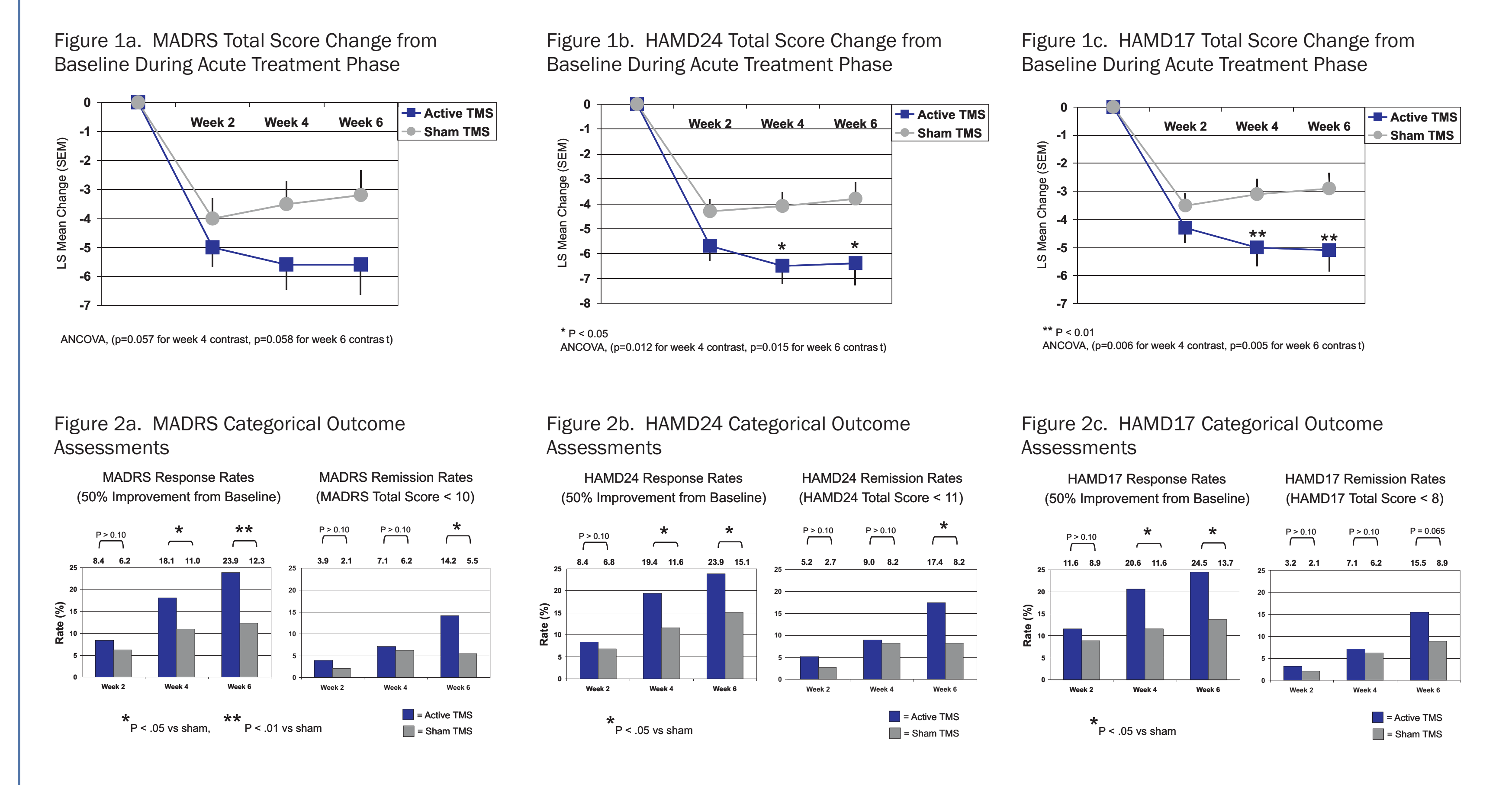
Safety Observations

- There were no seizures or deaths in this study. There were no changes in auditory threshold or cognitive function (data not shown).
- During the acute treatment phase, 16 serious adverse events were reported, 9 in the active TMS group and 7 in the sham TMS group. Events reflecting disease-related exacerbation were the most common serious adverse events.
- Spontaneously reported adverse events were as expected based on the prior literature experience, and were generally mild to moderate in reported severity, transient in nature, and did not lead to treatment discontinuation. (Table 5)
- A separate analysis showed no relationship between the experience of adverse events indicating treatment discomfort during week 1 and clinical outcome at week 4, indicating that the study blind was appropriately maintained (data not shown).

The TMS Therapy Study Group

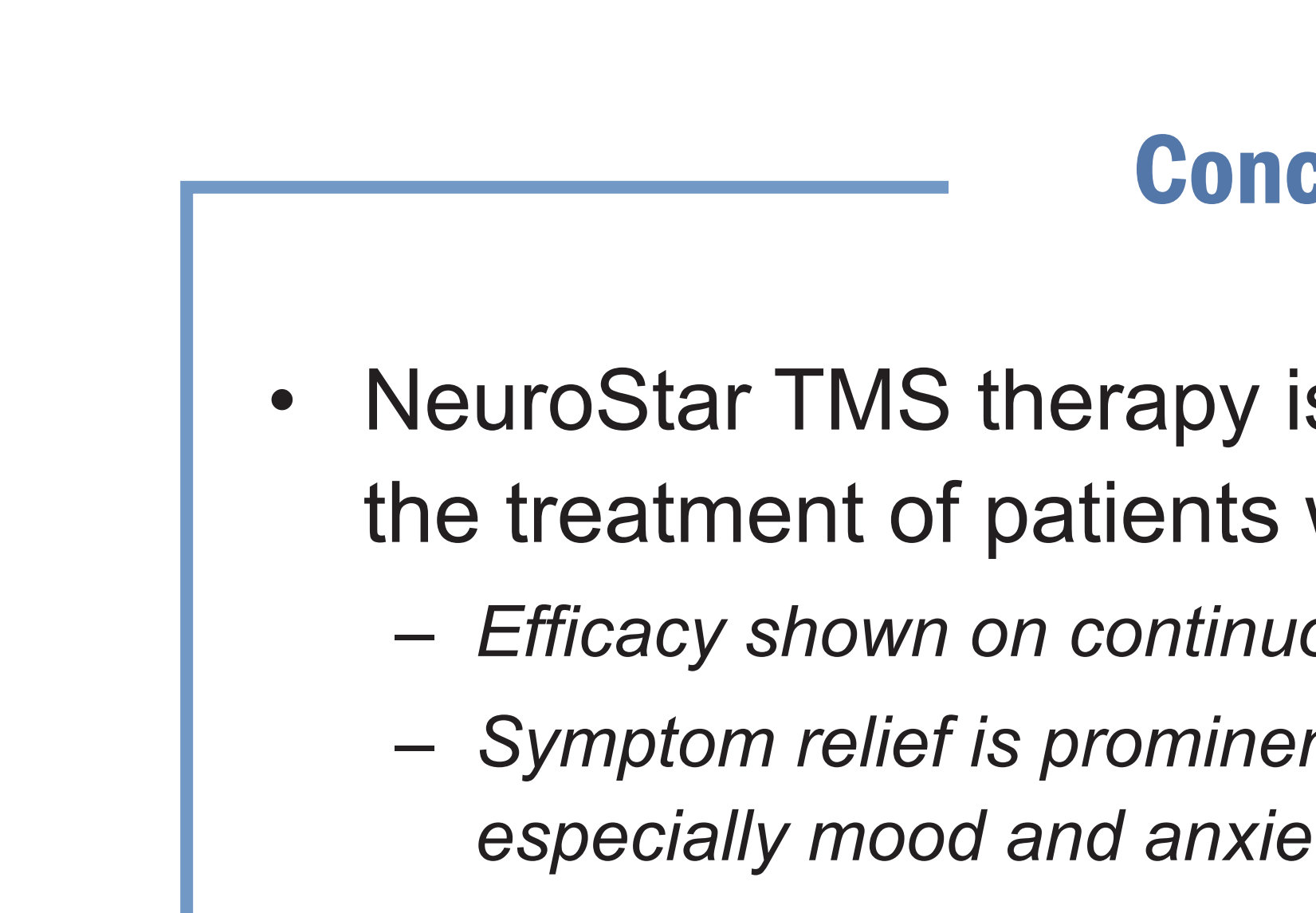
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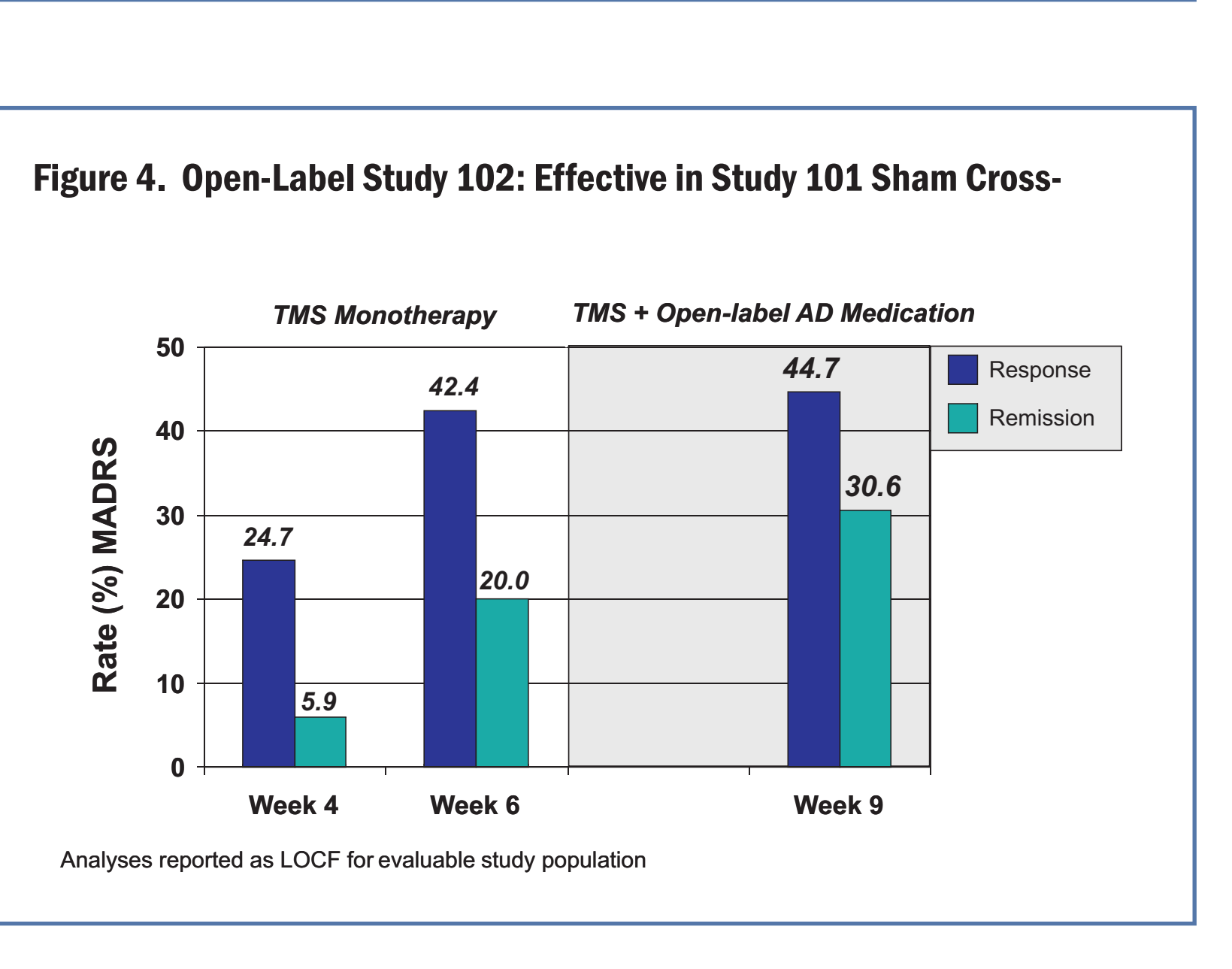
HAMD Rating Scale Factor Score	Week 4	Week 6
Depressive Symptoms		
- Core Depression Factor	.912	.368
- Males Factor	.063	.063
- Gibbons Factor	.007	.006
Anxiety Symptoms		
- Anxiety/Somatization Factor	.025	.023
Vegetative Symptoms		
- Retardation Factor	.007	.003
- Sleep Factor	.211	.109

All P-Values reflect superior effect in Active TMS v Sham TMS



Body System - Preferred Term	Sham TMS (N/155) N (%)	Active TMS (N/146) N (%)
Eye disorders		
- Eye pain	3 (1.9)	10 (6.1)
Gastrointestinal disorders		
- Toothache	1 (0.6)	12 (7.3)
General disorders and site administration conditions		
- Application site discomfort	2 (1.3)	18 (10.9)
- Application site pain	6 (3.8)	59 (35.8)
- Facial pain	5 (3.2)	11 (6.7)
Musculoskeletal and connective tissue disorders		
- Muscle twitching	5 (3.2)	34 (20.6)
Skin and subcutaneous tissue disorders		
- Pain of skin	1 (0.6)	14 (8.5)

Events occurring in the active treatment group at a rate of ≥ 5% and at least twice the rate for sham MedDRA-Coded Preferred Terms shown



Conclusions

- NeuroStar TMS therapy is an effective antidepressant for the treatment of patients with Major Depressive Disorder
 - Efficacy shown on continuous outcome measures
 - Symptom relief is prominent across a range of symptoms, especially mood and anxiety
 - Effect is clinically meaningful as shown by categorical response and remission rates
 - Open-label study provides consistent evidence confirming the results seen in the controlled trial
- Neurostar TMS therapy is safe and well tolerated with no evidence of adverse cognitive or auditory effects.