

Durability of Acute Response to TMS in the Treatment of Major Depression: Relapse During a Continuation Pharmacotherapy Extension Study

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Abstract

Objective: Transcranial magnetic stimulation has been shown to be effective in the acute treatment of major depression. Limited information exists regarding approaches to maintaining this acute response, or what the longer-term expectations may be for persistence of benefit from treatment with TMS. We present evidence from recently completed studies of the use of TMS in the acute treatment of major depression. The inclusion of a transitional phase at the conclusion of acute treatment, and enrollment in a separate, 24-week continuation treatment study permitted characterization of the overall persistence of the acute benefit from TMS.

Methods: The study program consisted of 3 separate clinical protocols (N=301 patients), a 6-week randomized controlled trial of active TMS with the NeuroStim Model 2100 System v sham TMS, a 6-week open-label extension study for non-responders in the first trial, and a 24-week continuation pharmacotherapy maintenance of effect study for responders in either the controlled or the open-label study. The latter study also permitted reintroduction of TMS as an add-on treatment for symptom worsening. Treatment parameters were optimized in a fixed, maximum feasible dose design. Persistence of benefit was examined in two study periods: 1) response rate during the 3-week period of transition from TMS to maintenance pharmacotherapy, and 2) Kaplan-Meier estimated relapse rate during the 24-week maintenance of effect continuation study. Outcomes were assessed with the MADRS, HAMD24, and HAMD17 rating scales.

Results: Response was successfully maintained during transition to continuation therapy. For active TMS patients continuing into the maintenance of effect study, Kaplan-Meier relapse rates at 24 weeks follow up ranged from 5.6% to 22.2% depending upon the relapse definition used.

Conclusions: Acute response to TMS shows a persistence of benefit in both short-term transition to continuation therapy, and after longer-term follow up.

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 treatment options 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 substance. 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 with electroconvulsive therapy. TMS can be administered as single or 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. Furthermore, these local effects may produce broader, indirect functional effects in brain areas distant from the site of direct stimulation.

We have recently reported the results of a large, multisite randomized controlled trial of TMS (O'Reardon, et al, *Biol Psychiatry*, in press) that demonstrated superior outcomes for active TMS compared to a sham TMS intervention in patients with pharmacoresistant unipolar major depression.

In this report, we separately examine the persistence of the acute response to TMS during follow up after successful treatment in the randomized controlled study. There are two questions of interest with regard to persistence of effect of TMS:

- 1) Does the clinical benefit of TMS dissipate immediately upon discontinuation of active treatment or during taper? (Short-term persistence)
- 2) Does the acute benefit of TMS persist over a clinically meaningful duration of follow-up, (eg, 24 weeks after resolution of acute symptoms)? (Long-term benefit)

Persistence of benefit was assessed by evaluation of:

Longitudinal symptom change (short-term and long-term outcomes)

Time to first rescue treatment with TMS (long-term outcome).

Relapse of illness despite medication maintenance and TMS rescue (long-term outcome).

Methods

Assessment of Short-Term Persistence of Effect

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 for clinically appropriate transition to maintenance treatment on a known active antidepressant medication. Choice of medication in this phase was restricted to antidepressant monotherapy only.

Assessment of Long-Term Persistence of Effect

All patients were followed in Study 103, an open-label, continuation of effect study (Study 103), for 24 weeks. Active open-label TMS was permitted in this study as a rescue add-on treatment for symptom breakthrough. The criterion for symptom breakthrough sufficient to require TMS rescue treatment was defined by deterioration in CGI-Severity score of at least 1 point, observed over a 2 week interval of time. If this criterion was established, TMS was initiated as an add-on to the current antidepressant medication regimen. Relapse was defined as recurrence of the full syndrome of major depression per DSM-IV criteria observed over at least 2 weeks at any time. Patients were discontinued from study if they met criteria for relapse, or if they received complete, 6 week reintroduction course of TMS rescue with symptom improvement, and referred for appropriate clinical management.

Efficacy Outcomes

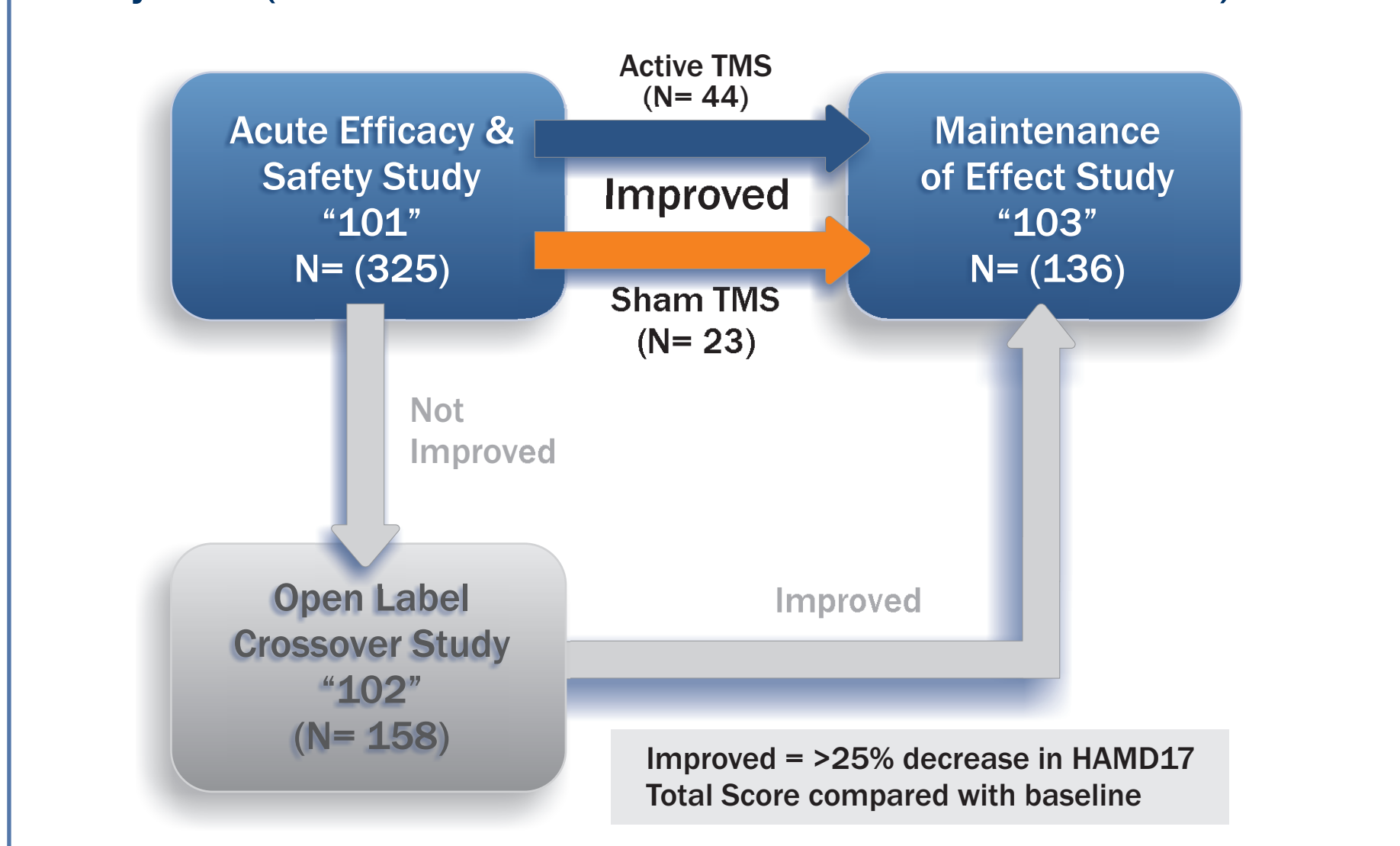
Depression symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and the 24-item and 17-item Hamilton Depression Rating Scales (HAMD24 and HAMD17). Data are summarized by continuous outcome defined as the change from baseline in mean score, and by categorical outcomes with response defined as a 25% reduction from baseline score, and remission defined as total score <10 for MADRS and <11 for HAMD24.

Relapse during long-term treatment was determined as described above.

Safety Outcomes

Adverse events were assessed at each treatment visit. Verbatim terms were coded by body system and preferred term using the MedDRA coding system.

Figure 1. NeuroStar TMS Therapy Clinical Development Program: Study 103 (Evaluation of 24 Week Maintenance of Effect)



Results

Subject Characteristics

Three hundred one patients comprised the evaluable study population at entry to the clinical development program in Study 101. (Data not shown)

Sixty-seven patients completed Study 101 in its entirety through both the Acute and Taper Phases and were subsequently enrolled in Study 103. Patients were not unblinded to their previously randomized treatment assignment at the conclusion of Study 101. Table 1 summarizes major clinical features of these two patient groups entering Study 103 based on their prior randomized treatment assignment in Study 101.

Comparison of these patient populations shows:

In general, patients enrolled in the NeuroStar TMS Therapy clinical development program were moderately to severely ill by symptom measures at baseline, and moderately to severely resistant to prior antidepressant treatment as measured by the Antidepressant Treatment History Form (ATHF).

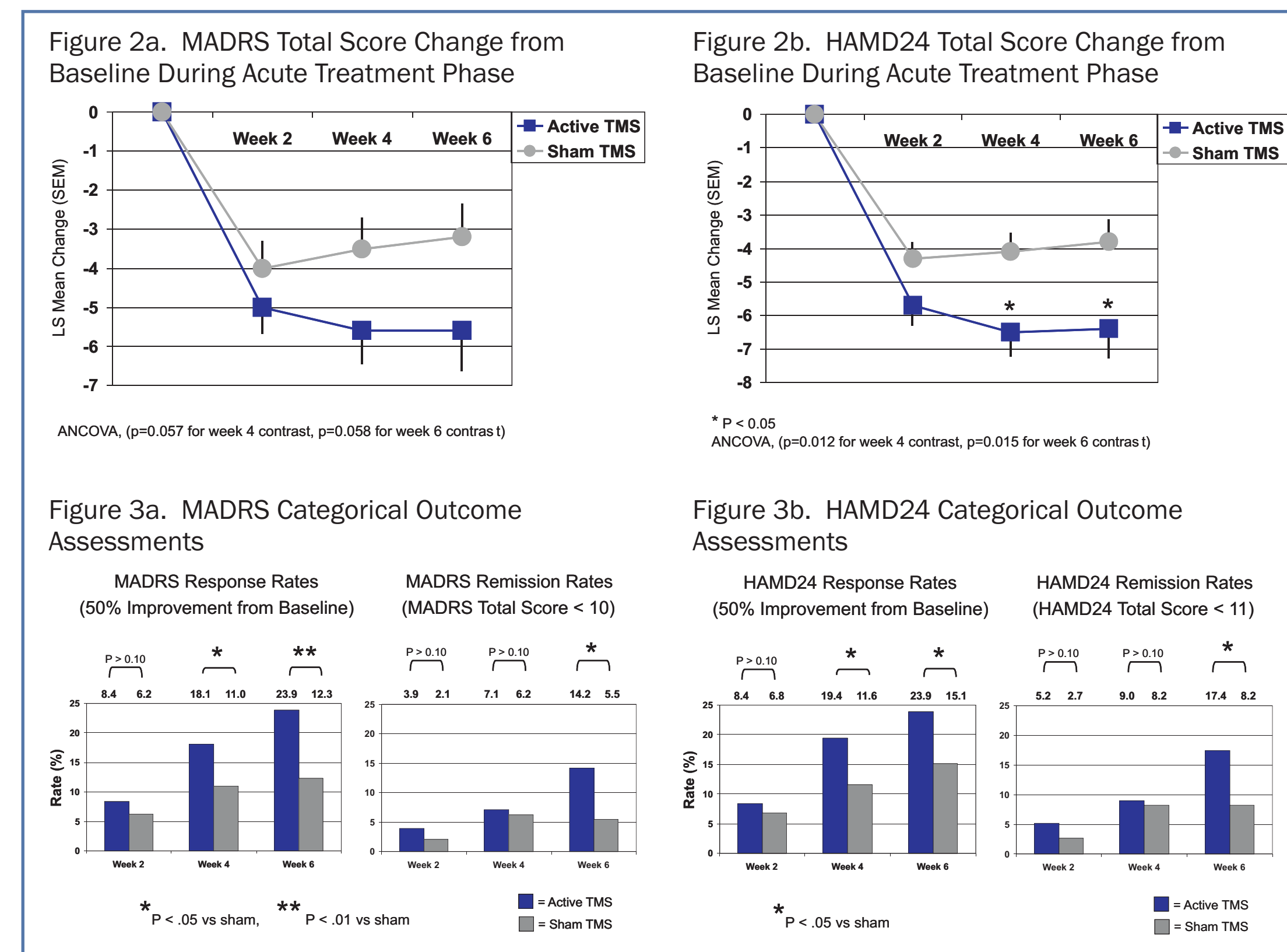
Upon enrollment into Study 103, patients who were previously randomized to active TMS in Study 101 had a slightly greater percentage of patients with a recurrent course of illness and a greater incidence of comorbid anxiety disorder compared to patients who were previously randomized to sham TMS prior to entry into Study 103.

Table 1. Subject Characteristics: Study 103 Enrolled Population (N=67)

Clinical Variables	Study 101 Active TMS (N=44)	Study 101 Sham TMS (N=23)
Demographic Variables		
• N (%) Female	24 (54.5)	11 (47.8)
• Age in years (SD)	48.2 (9.7)	48.8 (10.2)
• N (%) Caucasian	39 (88.6)	19 (82.6)
Illness History		
• N (%) Recurrent Illness	42 (95.5)	20 (87.0)
• Mean duration of current episode in mos (SD)	12.4 (8.8)	15.1 (9.4)
• N (%) with duration < 24 mos	37 (84.1)	19 (82.6)
• N (%) w/comorbid anxiety disorder	18 (40.9)	3 (13.0)
Treatment History		
• Avg # of Adequate Antidepressant Trials in Current Episode (ATHF-validated)	1.6	1.7
Symptom Severity		
• MADRS Total Score (SD)	9.0 (8.2)	10.9 (8.1)
• HAMD24 Total Score (SD)	8.8 (8.8)	9.9 (8.6)
• HAMD17 Total Score (SD)	6.5 (4.9)	7.5 (6.0)
• CGI-Severity Total Score (SD)	1.9 (1.2)	2.3 (1.0)
• IDS-SR Total Score (SD)	14.4 (9.8)	13.4 (9.4)

Acute Efficacy of TMS Demonstrated in 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). (Figures 2a, 2b)
- 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 3a, 3b).
- Analysis of HAMD Factor Scores confirmed a strong clinical effect of active TMS on core depression and anxiety symptom scores. (Data not shown).

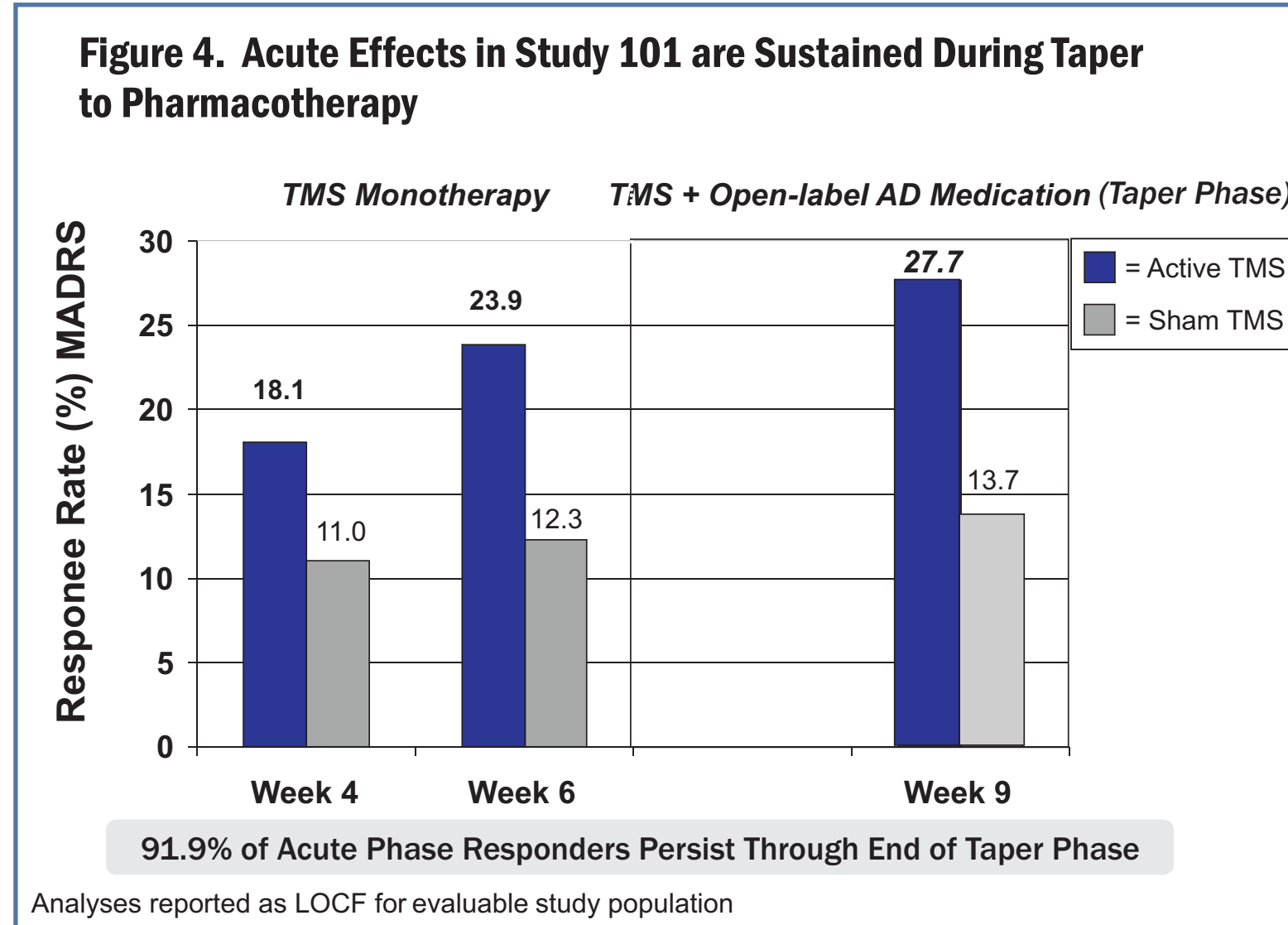


Durability of Acute Effect is Demonstrated During Taper Phase

The clinical effect of TMS was sustained as observed during the 3-week transition to medication monotherapy during the Taper Phase, with continued improvement in clinical benefit observed in the active TMS group. (Figure 4).

The sustained nature of this clinical effect is demonstrated by the observation that over 90% of patients treated with active TMS who met response criteria at the end of the Acute Phase still met response criteria at the end of the Taper Phase of Study 101.

Results

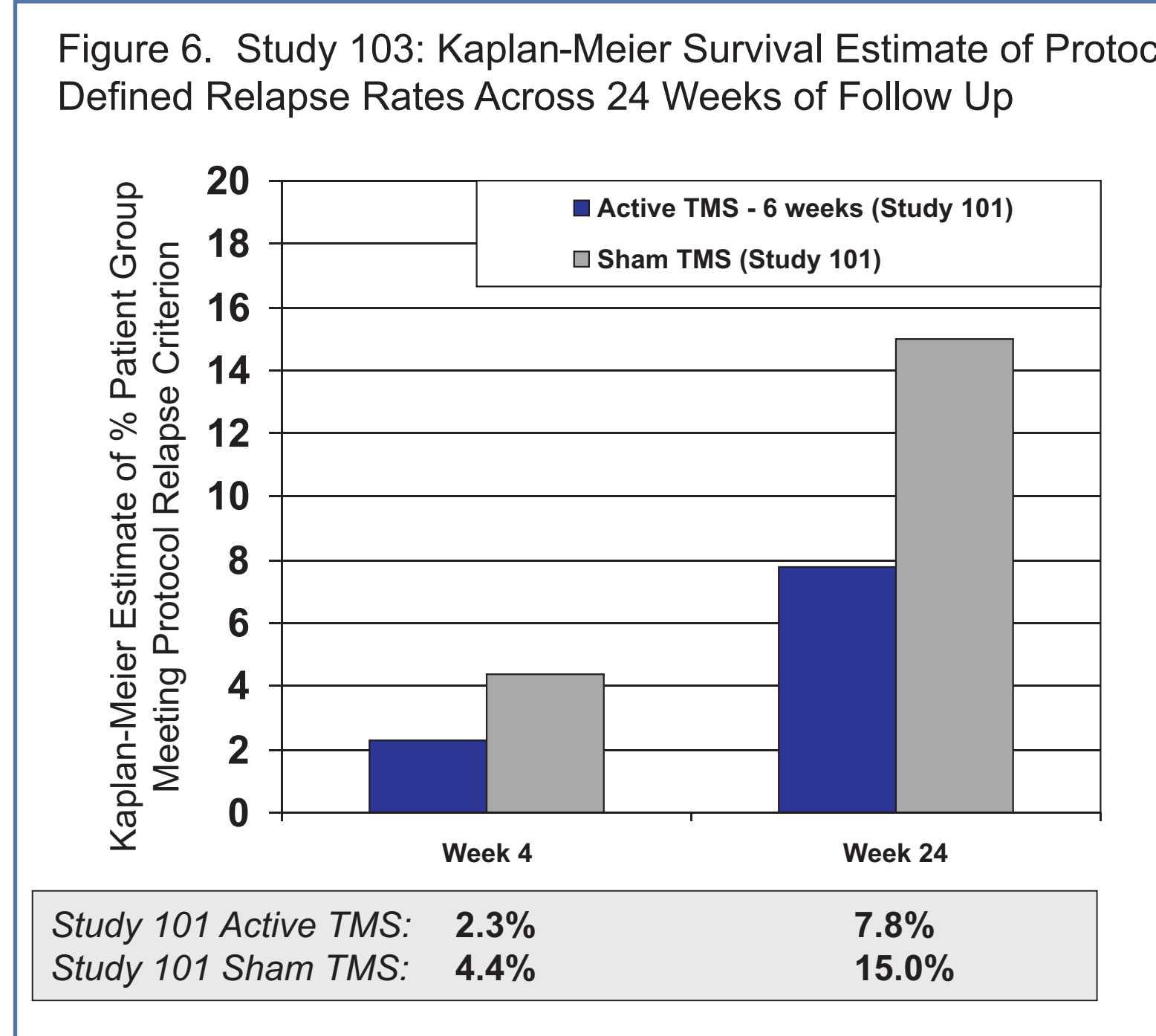
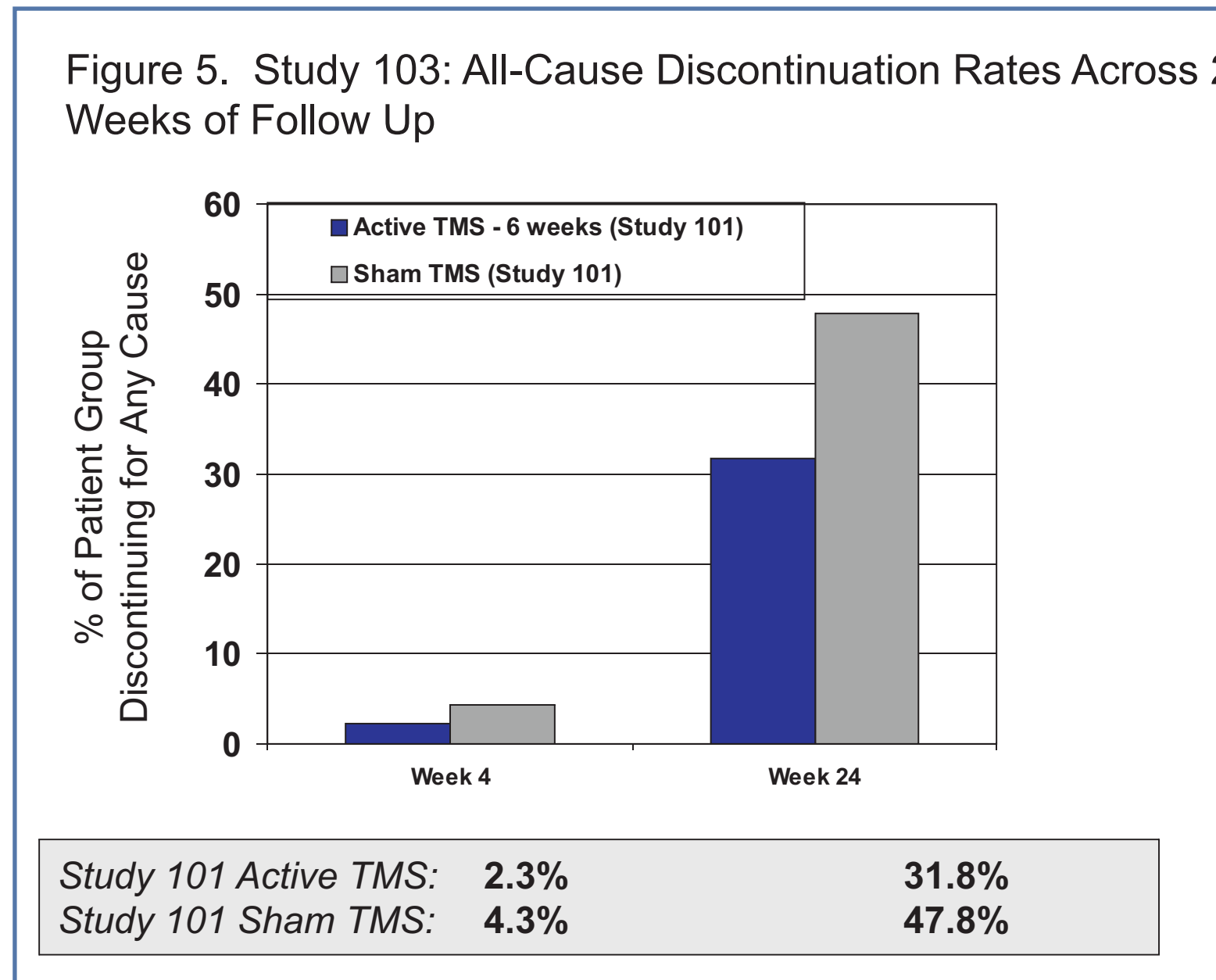


Durability of the Acute Response to TMS is Demonstrated During 24 Weeks of Open-Label Follow Up

After 24 weeks, for patients treated with active TMS prior to entry to Study 103, the all-cause discontinuation rate (31.8%) was lower than observed in patients treated with sham TMS prior to study entry (47.8%) [Figure 5].

After 24 weeks, for patients treated with active TMS prior to entry to Study 103, the Kaplan-Meier survival estimate of the protocol-defined relapse rate (7.8%) was lower than observed in patients treated with sham TMS prior to study entry (15.0%) [Figure 6].

Observation of longitudinal symptom change, as measured by both continuous and categorical outcomes demonstrated sustained evidence of clinical benefit for patients who completed the 24-week period of observation (Data not shown).



For patients treated with active TMS prior to entry into Study 103 and who completed 24 weeks of maintenance follow-up, 36.4% experienced symptomatic worsening and were provided with active TMS reintroduction (Table 2).

Over 2/3rds of these patients benefited from TMS reintroduction and continued in the study.

For patients treated only with sham TMS prior to entry into Study 103 and who completed 24 weeks of maintenance follow-up, 47.8% experienced symptomatic worsening and were provided with active TMS reintroduction (Table 2).

Less than half of these patients benefited from TMS reintroduction and continued in the study.

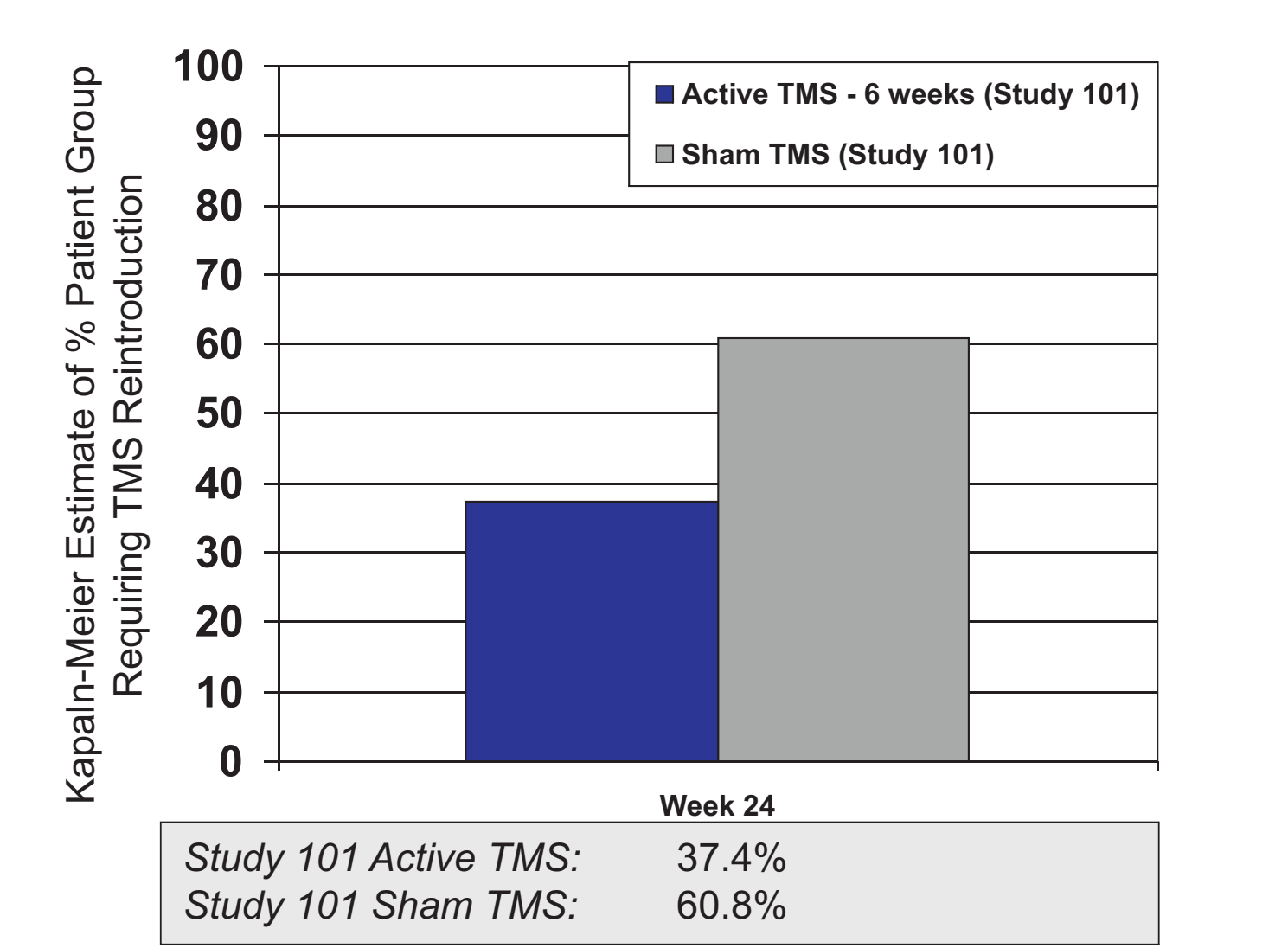
The Kaplan-Meier survival estimate of the percentage of patients experiencing symptomatic deterioration and requiring active TMS reintroduction was 37.4% in patients previously treated with active TMS and 60.8% in patients previously treated with sham TMS (Figure 7).

Results

Table 2. Overview of TMS Reintroduction – First Cycle Data

First TMS Reintroduction Cycle N(%)	Treatment Group	
	Study 101 Active TMS (N=44)	Study 101 Sham TMS (N=23)
• Number of sessions (median)	14.0	14.0
• Time to reintroduction in weeks (median)	11.0	10.0
• Population continuing past cycle (N)	11	5

Figure 7. Kaplan-Meier Survival Advantage at 6 Months: Previous active TMS exposure compared with previous sham TMS exposure



Results- Safety

- No seizures, suicides or deaths occurred in Study 103
- Six serious adverse events were reported, none were assessed by the study investigator as device-related
- Non-serious adverse events were consistent with those previously observed in the acute efficacy results in Study 101 [Table 3]
- The most commonly observed device-related adverse events were application site pain, muscle twitching, and headache
- Active TMS was safely reintroduced as an add-on rescue treatment with concurrently administered antidepressant pharmacotherapy
- Medications used in this study included SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (venlafaxine, duloxetine), and others (bupropion, mirtazapine, and trazodone)

Table 3

Body System (:) Preferred Term	Study 101 Active TMS (N=44)	Study 101 Sham TMS (N=23)
Gastrointestinal disorders		
• Constipation	0	0
• Dry Mouth	0	0
General disorders and site administration conditions		
• Application site pain	3 (6.8)	6 (26.1)
Musculoskeletal and connective tissue disorders		
• Arthralgia	1 (2.3)	0
• Muscle twitching	2 (4.5)	3 (13.0)
Nervous system disorders		
• Headache	3 (6.8)	2 (8.7)
Psychiatric disorders		
• Insomnia	0	0

Incidence of adverse events occurring at an overall rate of 5% or greater in either treatment group, and assessed by the investigator as probably or definitely related to the study device

Conclusions

- Active TMS is an effective acute treatment in patients with major depression who have not received adequate benefit from prior treatment
- During continuation follow up for up to 24 weeks, patients previously treated with active TMS show greater clinical benefit compared with patients treated only with sham TMS prior to follow up
- Reintroduction of active TMS can be used safely and effectively as an add-on rescue treatment during a continuation course of antidepressant medications

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