NeuroStar TMS Therapy System

(Transcranial Magnetic Stimulation)

for the Treatment of Major Depression

FDA Neurological Devices Panel Meeting

Gaithersburg, MD

26 January 2007

Neuronetics Panel Presentation

NeuroStar TMS Therapy System Overview
Judy P. Ways, Ph.D., Vice President, Regulatory Affairs and Quality Assurance, Neuronetics

Clinical Study Design, NeuroStar Safety and Efficacy Results
Mark A. Demitrack, M.D., Vice President and Chief Medical Officer, Neuronetics

Major Depression: Clinical Considerations of Current Options
Alan F. Schatzberg, M.D., Professor and Chairman, Department of Psychiatry, Stanford University

Clinical Significance and Risk-Benefit
Michael E. Thase, M.D., Professor of Psychiatry, University of Pennsylvania

Closing Summary
Judy P. Ways, Ph.D., Vice President, Regulatory Affairs and Quality Assurance, Neuronetics

NeuroStar TMS Therapy System Overview

- Rationale for the Use of TMS as a Treatment for Depression
- Description of the Neuronetics NeuroStar TMS Therapy System
- Regulatory History
- 510(k) Requirements: Risk/Benefit

Evidence for TMS as an Antidepressant

- **Mechanism of Effect**
  - Non-convulsive neuronal depolarization
  - Target: Left prefrontal cortex
  - Monoamine neurotransmitter release
  - Active in animal behavioral models of depression
- **Proof of Concept in Depression Clinical Trials**
  - > 30 single-site controlled clinical trials (active > sham)
  - Recent studies[1] demonstrated statistically and clinically significant antidepressant effects (active > sham)
  - 6/8 published meta-analyses positive; most recent evaluated 33 TMS studies[2]: <u>active TMS > sham</u>

[1]Fitzgerald, 2003, 2005; Avery, 2005
[2]Herrman, 2006

Bringing Investigational TMS to Clinical Practice

- **A clinical study of safety and efficacy**
  - *Using optimized TMS treatment parameters*
  - *Rigorous sham-controlled study design*
  - *Adequately sized, blinded randomization*
  - *Multicenter trial to demonstrate generalizability in clinical use*
- **Use by prescription by a licensed psychiatrist**
- **User-friendly and reproducibly delivers safe and effective TMS Therapy in an office-based environment**

Regulatory History

- **Investigational Plan – conducted under approved IDE**
- **Premarket Notification: 510(k)**
  - Predicate: Electroconvulsive therapy (ECT) devices
- **Clinical study requirements determined with the FDA:**
  - Evidence of acute antidepressant safety and efficacy in a randomized, controlled multicenter trial comparing active TMS vs. sham TMS (20 tx's @ 4 weeks)
  - Evidence of persistence of clinical benefit following cessation of acute treatment (durability of effect in 1-month follow-up)

Intended Use
(Panel Question 10)

- **"Treatment of DSM-IV-defined Major Depressive Disorder"**
  - TMS used as monotherapy
  - Unipolar, non-psychotic Major Depressive Disorder (DSM-IV)
  - MDD patients who had failed to receive benefit from adequate treatment in current episode
  - Risk/benefit profile applies broadly to MDD (excluding treatment-refractory depression)
  - ECT also indicated for MDD without restriction for level of treatment resistance

510(k) Requirements: Risk/Benefit

- **Substantial Equivalence based on Risk/Benefit**
  - Does **not** require *EQUAL* RISK **AND** *EQUAL* BENEFIT
    - Device can be safer but less effective than predicate device
    - Device can be less safe but more effective than predicate device

- **Risk/Benefit Ratio**
  - Risk = Device SAFETY
  - Benefit = Device ACUTE EFFICACY and DURABLITY
  - NeuroStar Risk/Benefit Profile Compares Favorably to ECT
    - *NeuroStar safety is superior to ECT*
    - *NeuroStar is effective, but less than ECT*
    - *NeuroStar benefit is sustained and at least as durable as ECT*

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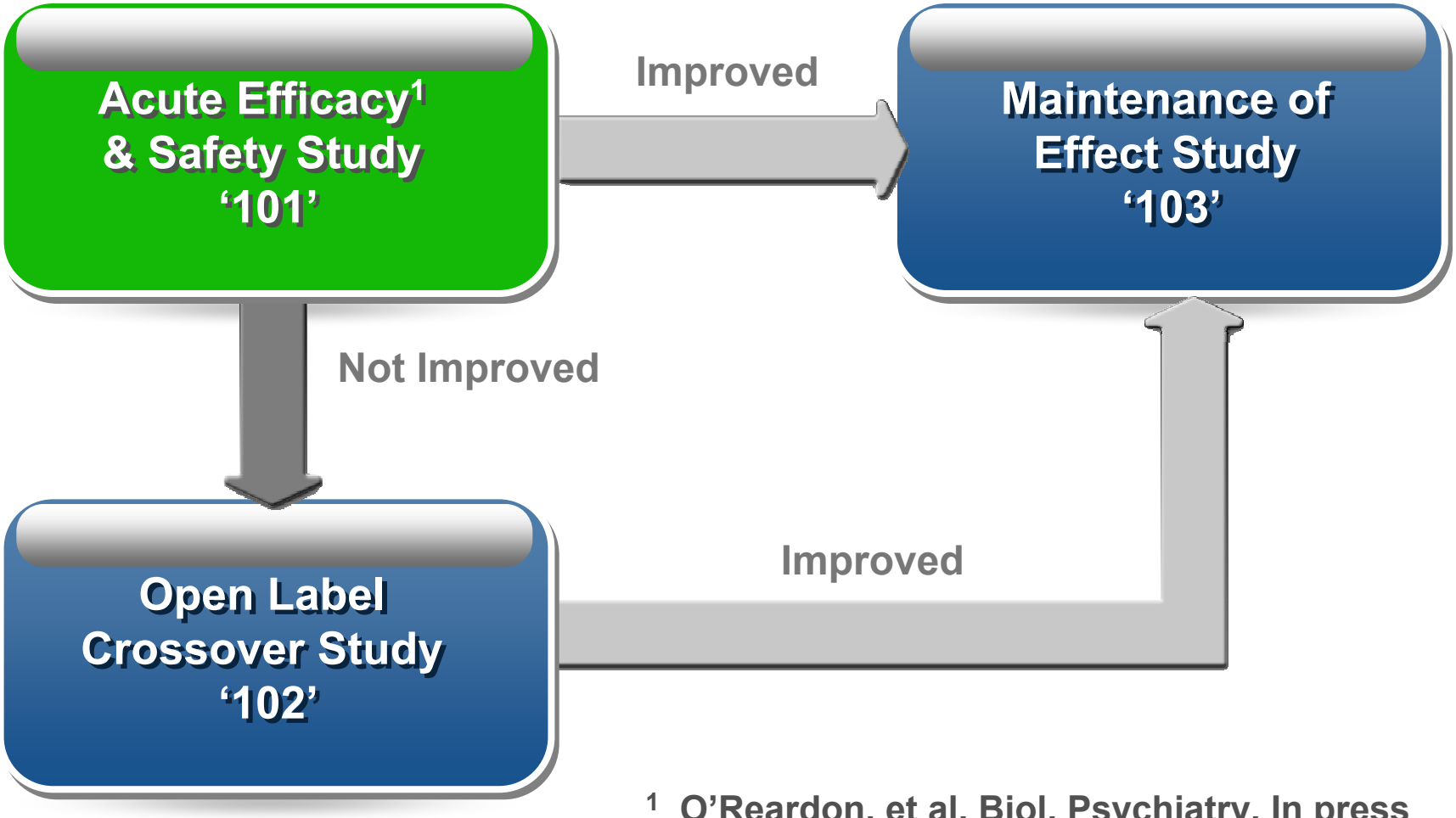
Key Points

- NeuroStar TMS Therapy is **EFFECTIVE**
- The clinical benefit of NeuroStar TMS Therapy is **DURABLE**
- NeuroStar TMS Therapy is **SAFE AND WELL-TOLERATED**
- NeuroStar TMS Therapy has a **FAVORABLE RISK/BENEFIT PROFILE**

NeuroStar Clinical Development Program

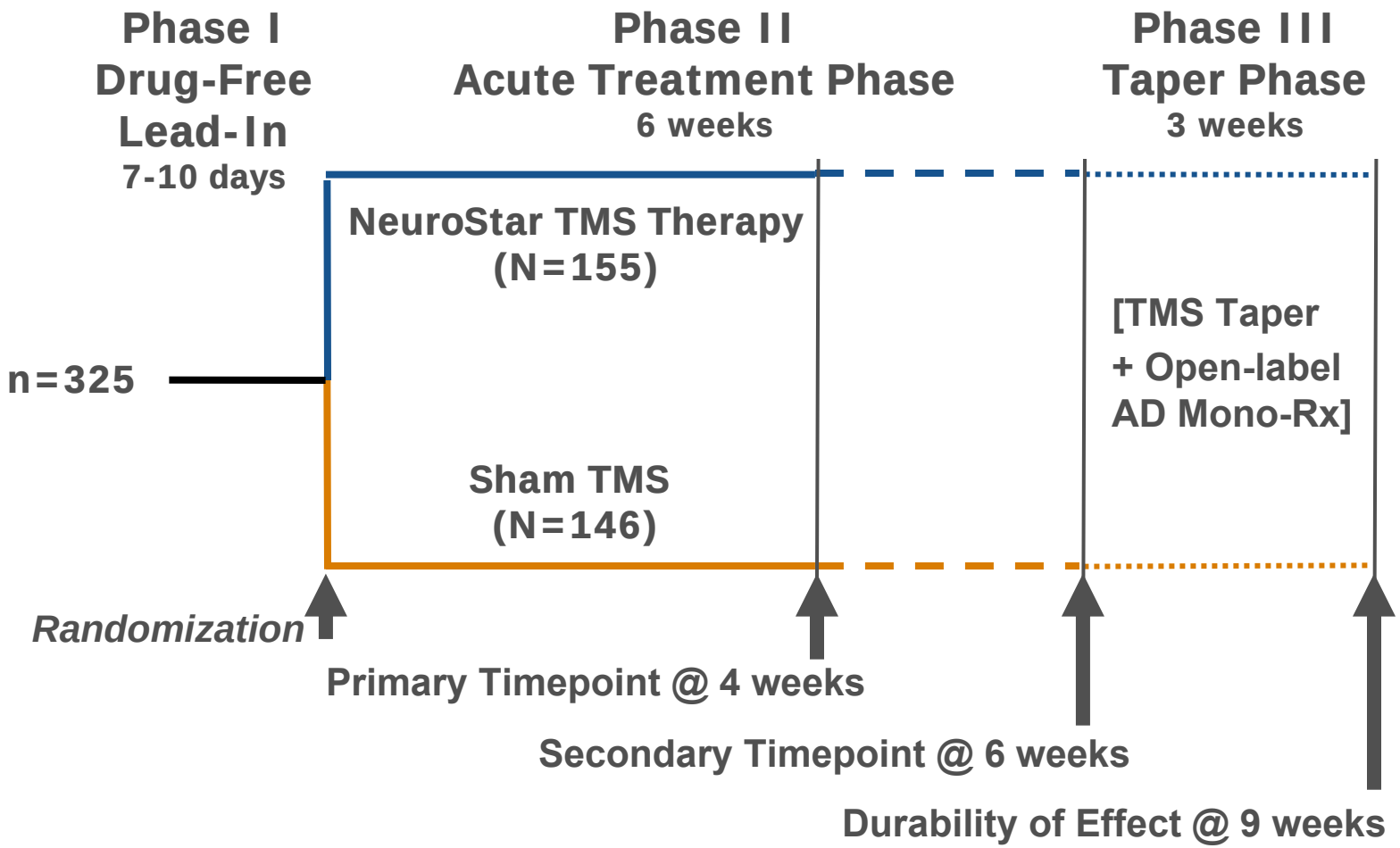


[1] O'Reardon, et al, Biol. Psychiatry, In press

Study 101 Trial Design

Randomized, Double-blind, Sham-Controlled

(Panel Question #3)



Assurance of Outcome Integrity

Study 101

Study Procedures

- **3 separate magnetic coils provided**
  - Coil MT: used for dose setting
  - Coils B & C: blinded active & sham treatment coils
- **Pre-specified randomization by electronic 'smart cards'**
- **Independent roles for Study Rater and TMS Treater**
- **Primary efficacy measure and timing of primary outcome concealed from investigator per protocol**
- **Study blind maintained through entire clinical program**

Training

- **Intensive training on device procedures (TMS Treater)**
- **Systematic reliability assessment (Efficacy Rater)**

Study 101 Patient Population
(Panel Question 8)

- **Diagnosis, Disease Severity & Illness Course**
  - DSM-IV Diagnosis: Major Depressive Disorder
  - Largely (~95%) recurrent illness course
  - Approximately 50% unemployed due to illness
  - Moderate to severe symptom burden
    - Avg HAMD24 ~30, MADRS ~32 at study entry
- **Treatment Resistance**
  - Moderate to severe treatment resistance in current episode
    - Nearly 50% failed to receive benefit from >2 adequate treatments (ie, dose/duration)
    - Nearly all received multiple (avg $\geq$ 4), ineffective treatments in current episode

TMS Study Population Is Similar to Patients Treated with ECT
(Panel Question #9)

- **Comparison to two large reference ECT datasets:**
  - OPT-ECT Study JAMA (2001): Research study sample, (N=290)
  - Community ECT Study Biol Psychiatry (2004): Naturalistic study sample, (N=347)

- **FDA suggested a subset analysis**
  - Exclude psychotic & bipolar depression
  - Source data analyzed by Dr. Harold Sackeim

Comparison of TMS Study Population to ECT Reference Population

	Neuronetics Active TMS (N=155)	OPT-ECT Study (N=139)*	Community ECT Study (N=129)*
Demographic Variables			
● N(%) Female	86 (55.5)	95 (68.3)	82 (63.6)
● Age in years (SD)	47.9 (11.0)	46.8 (13.2)	48.2 (11.7)
Clinical Variables			
● Recurrent illness course N (%)	149 (95.5)	110 (79.1)	84 (65.1)
● Duration of current episode in mos (median)	10.0	11.0	8.3
● N (%) with current episode > 2 years	36 (23.2)	21 (15.1)	10 (7.8)
Treatment History			
● # Adequate in Current Episode	1.6	1.4	1.5
Baseline Symptom Severity			
● HAMD 24 total score (Mean [SD])	30.1 (5.0)	33.9 (6.7)	30.7 (6.6)

*Subset analysis provided by H. Sackeim

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Pre-Specified Analysis Plan and Rank Order of Importance of Study Outcomes: Study 101

Primary Outcome

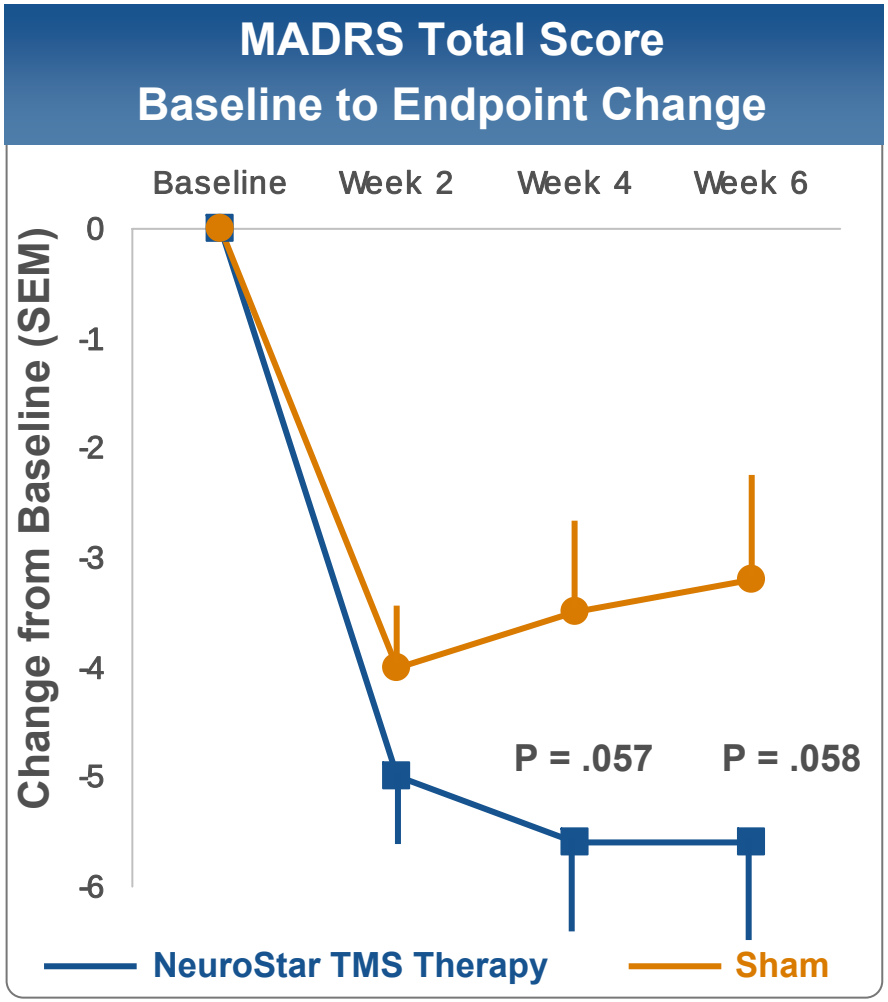
1. MADRS Total Score Change from Baseline

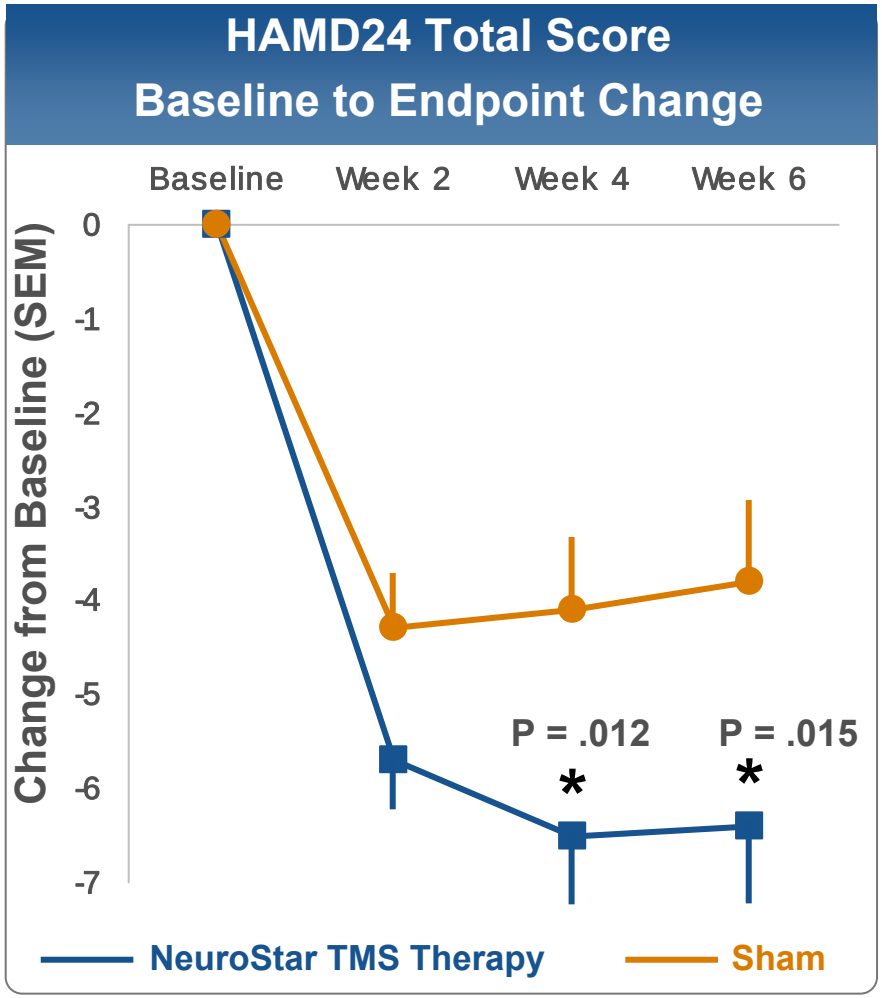
Secondary Outcomes

1. HAMD24 Total Score Change from Baseline
2. HAMD17 Total Score Change from Baseline
3. Response Rate (≥50% reduction: MADRS, HAMD24, HAMD17)
4. SF-36 and Q-LES-Q (Functional Status and Quality of Life Outcomes)
5. Remission Rate (MADRS <10, HAMD24 <11, HAMD17 <8)
6. HAMD Scale Factor Scores Change from Baseline
7. IDS-SR Total Score Change from Baseline
8. CGI-Severity Change from Baseline
9. PGI-Improvement Change from Baseline

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

Study 101 Efficacy Outcomes Continuous Measures





Pre-specified LOCF analysis of evaluable study population

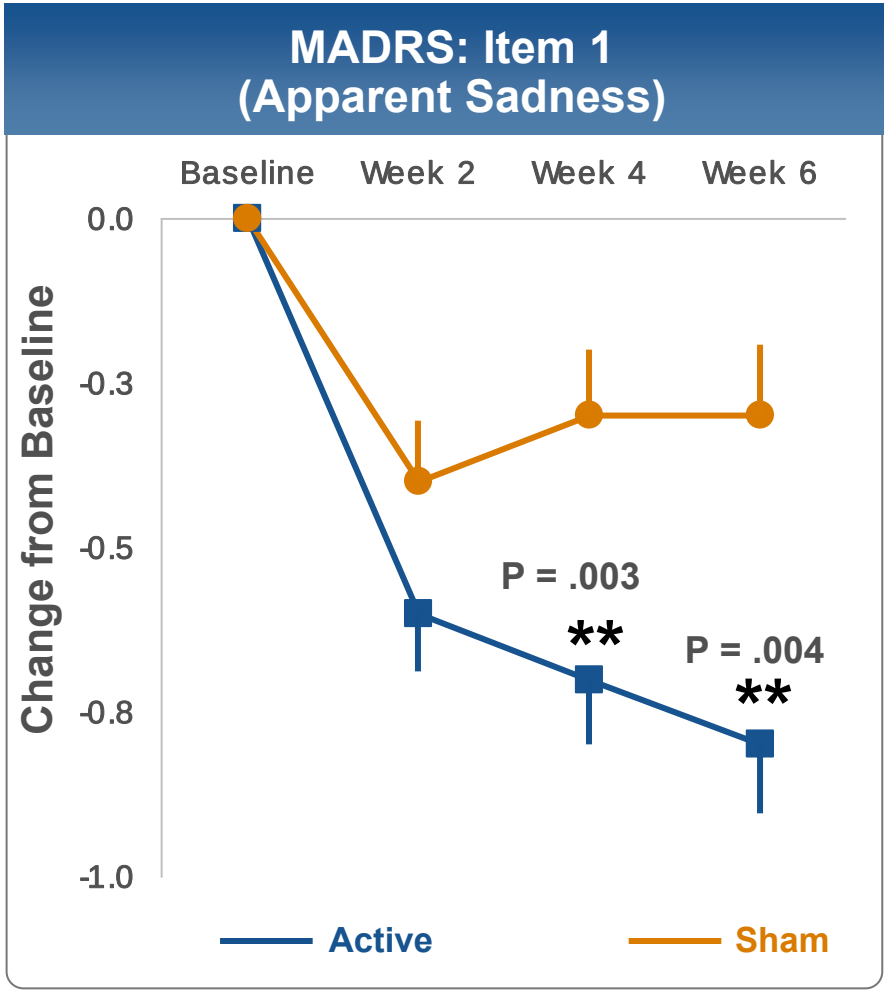
Primary Outcome Measure
Statistical Significance (Panel Question #1)

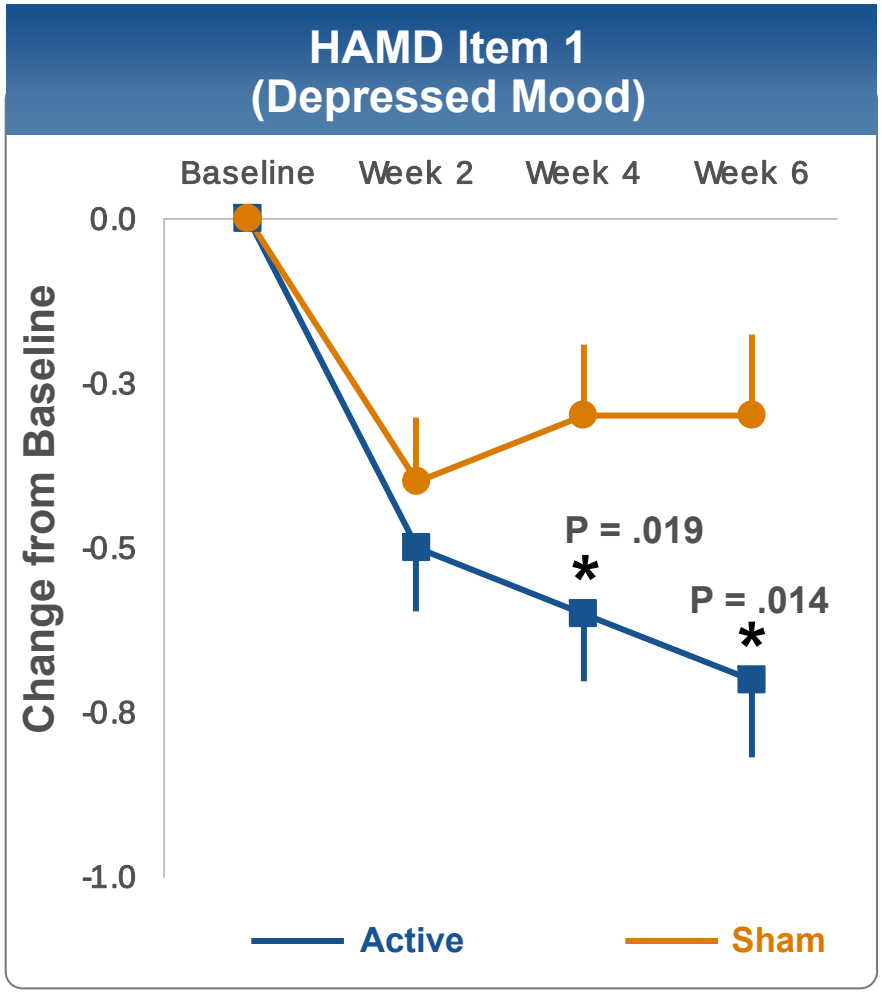
- **MADRS variance > HAMD variance**
  - Week 4 MADRS SD=11.1, HAMD SD=8.9
- **Entry threshold for HAMD but not MADRS**
  - Statistically significant baseline imbalance in MADRS Total Scores (active < sham)
  - Amplified difference in variance
  - Post-hoc subset analysis using MADRS threshold consistent with this hypothesis (p=0.038)

Primary Outcome Measure
Clinical Significance of MADRS Outcomes (Panel Question #1)

- **MADRS shows statistical significance on**
  - Core depression symptom
  - Categorical outcomes (response & remission)
- **MADRS effect size (0.39) is clinically meaningful by literature standards**
  - Varies with treatment resistance as expected
- **MADRS results consistent with HAMD (24 & 17)**

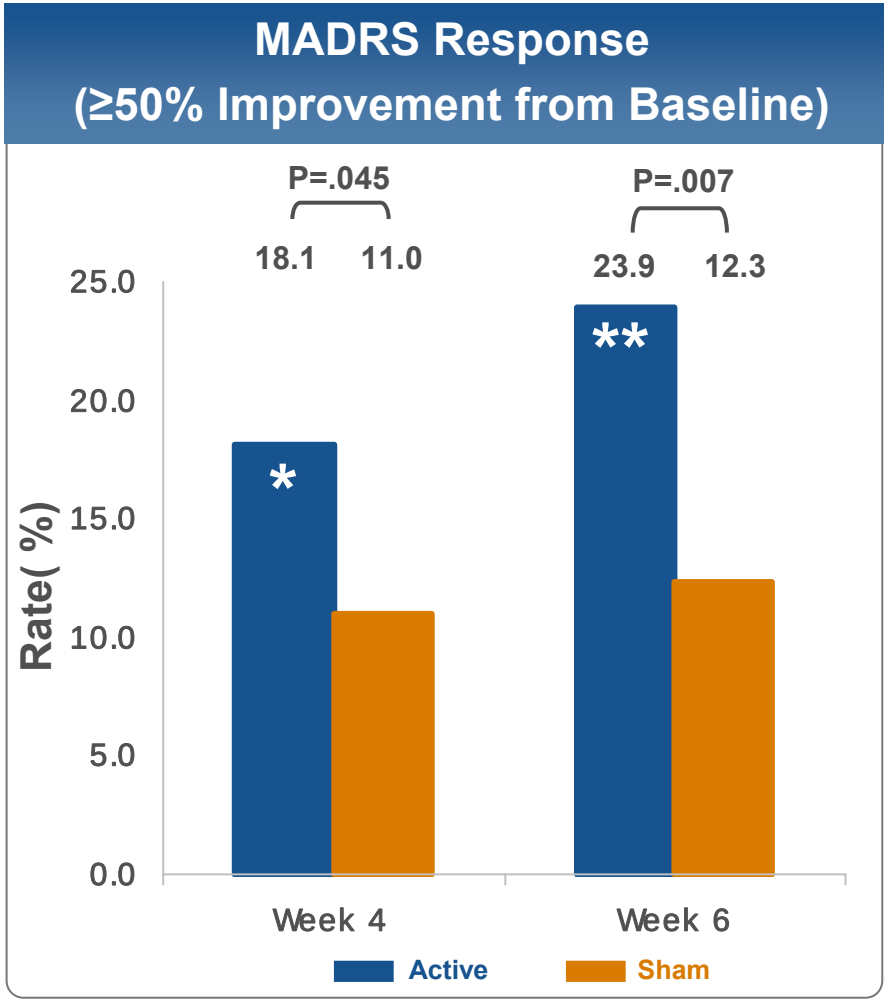
Study 101: Significant Clinical Effect on MADRS and HAMD Core Mood Item

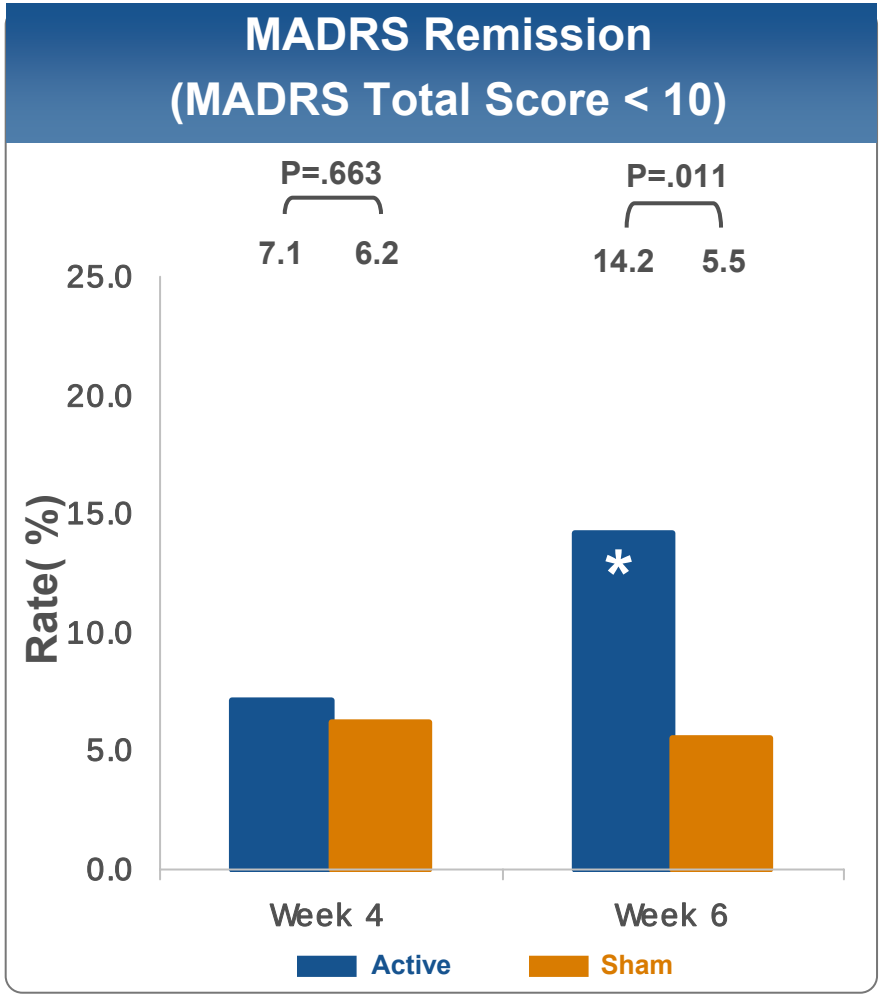




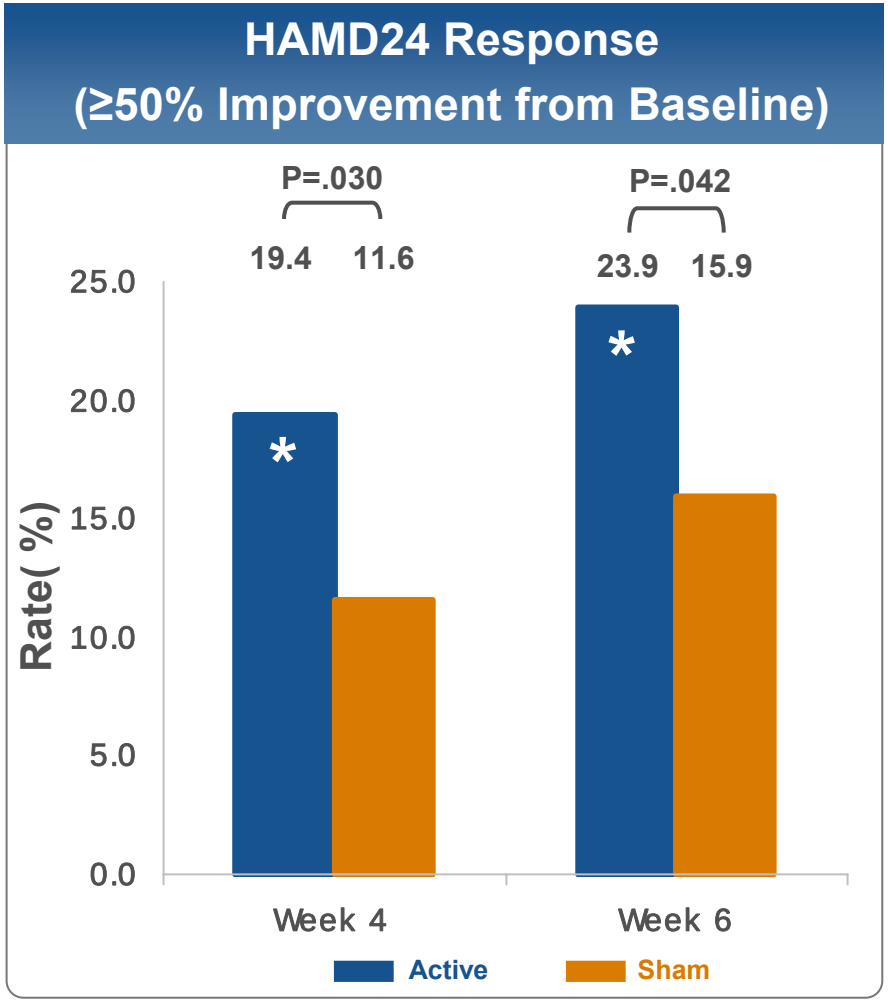
LOCF analysis of evaluable study population

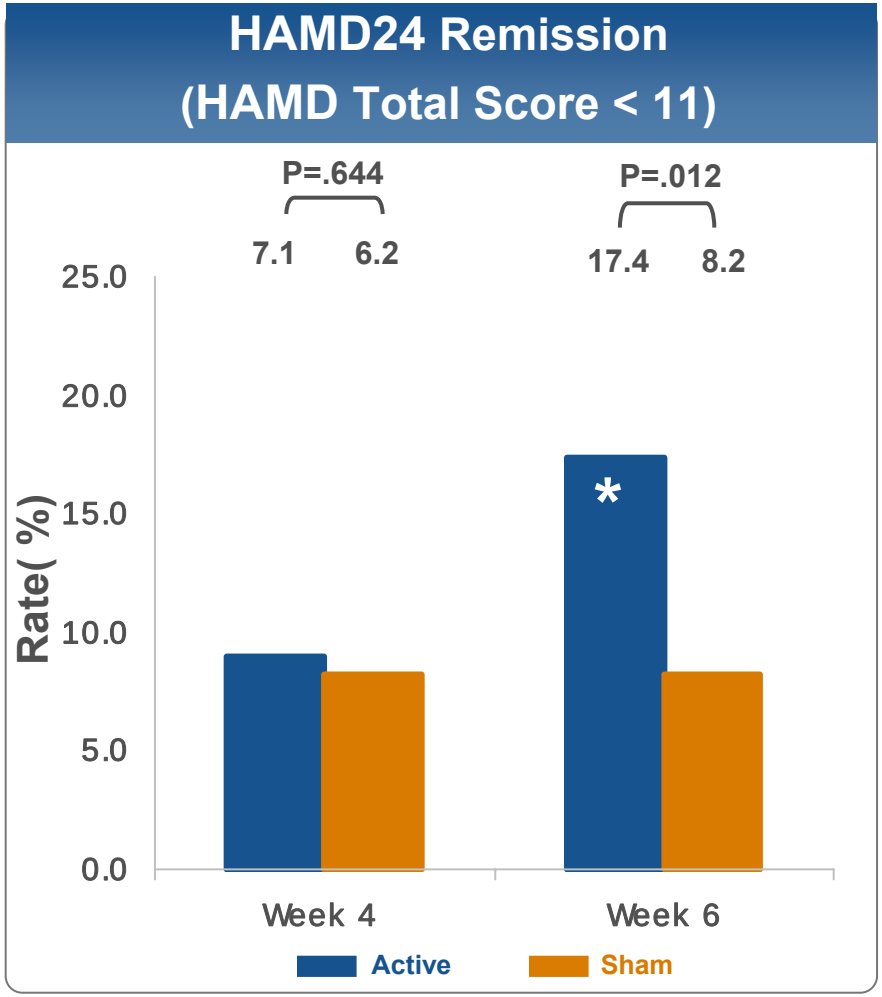
Study 101: Significant Clinical Effects on MADRS Categorical Measures





Study 101: Significant Clinical Effects on HAMD Categorical Measures





Standardized Effect Sizes (95%CI) by Treatment Resistance

Outcome Measure at Week 4	Overall Group (N=155 Active TMS) (N=146 Sham TMS)	1 Adequate Treatment (N=88 Active TMS) (N=76 Sham TMS)	2-4 Adequate Treatments (N=67 Active TMS) (N=70 Sham TMS)
MADRS	0.39 (-0.04 – 0.82)	0.94 (0.22 – 1.68)	-0.01 (-0.65 – 0.63)
HAMD24	0.48 (0.07 – 0.90)	0.83 (0.23 – 1.45)	0.26 (-0.37 – 0.90)
HAMD17	0.55 (0.10 – 1.00)	0.83 (0.20 – 1.48)	0.42 (-0.30 – 1.15)

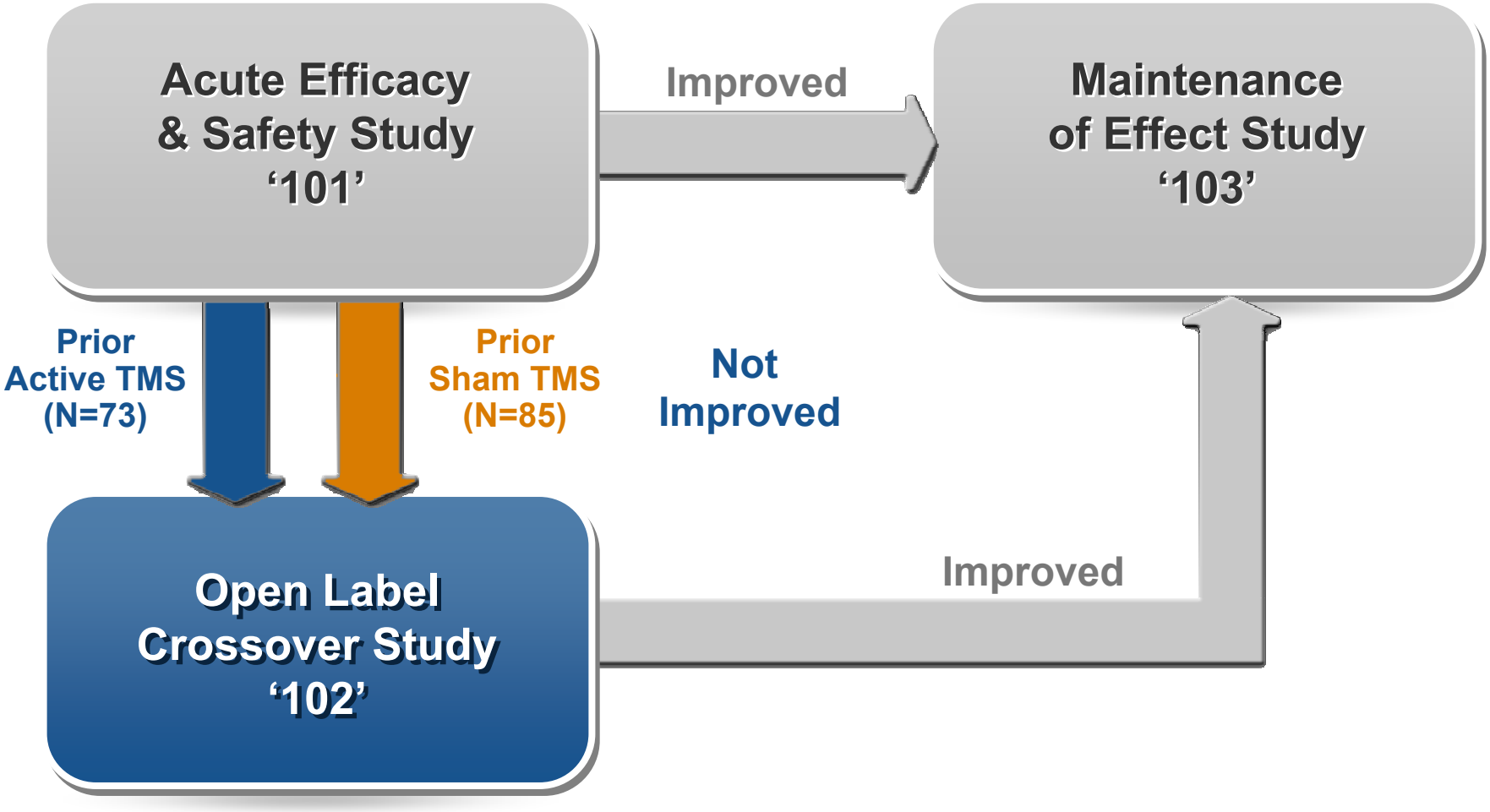
Effect size varies by treatment resistance as predicted from literature

Secondary Outcome Measures
Support Efficacy (Panel Question 2)

- **Statistical significance in clinician rated outcomes:**
  - HAMD24 & HAMD17 continuous measures (wks 4 & 6)
  - HAMD24 , HAMD17 & MADRS response (wks 4 & 6)
  - HAMD24 & MADRS remission (wk 6)
  - HAMD factor scores (wks 4 & 6)
  - CGI scores (wks 2, 4 and 6)
- **Statistical significance in patient rated outcomes**
  - SF-36 (wks 4 & 6) & Q-LES-Q (wk 6)
- **Expert statistical opinion (P. Lavori, PhD)**
  - Benjamini-Hochberg (multiplicity analysis) supports rejection of null hypothesis

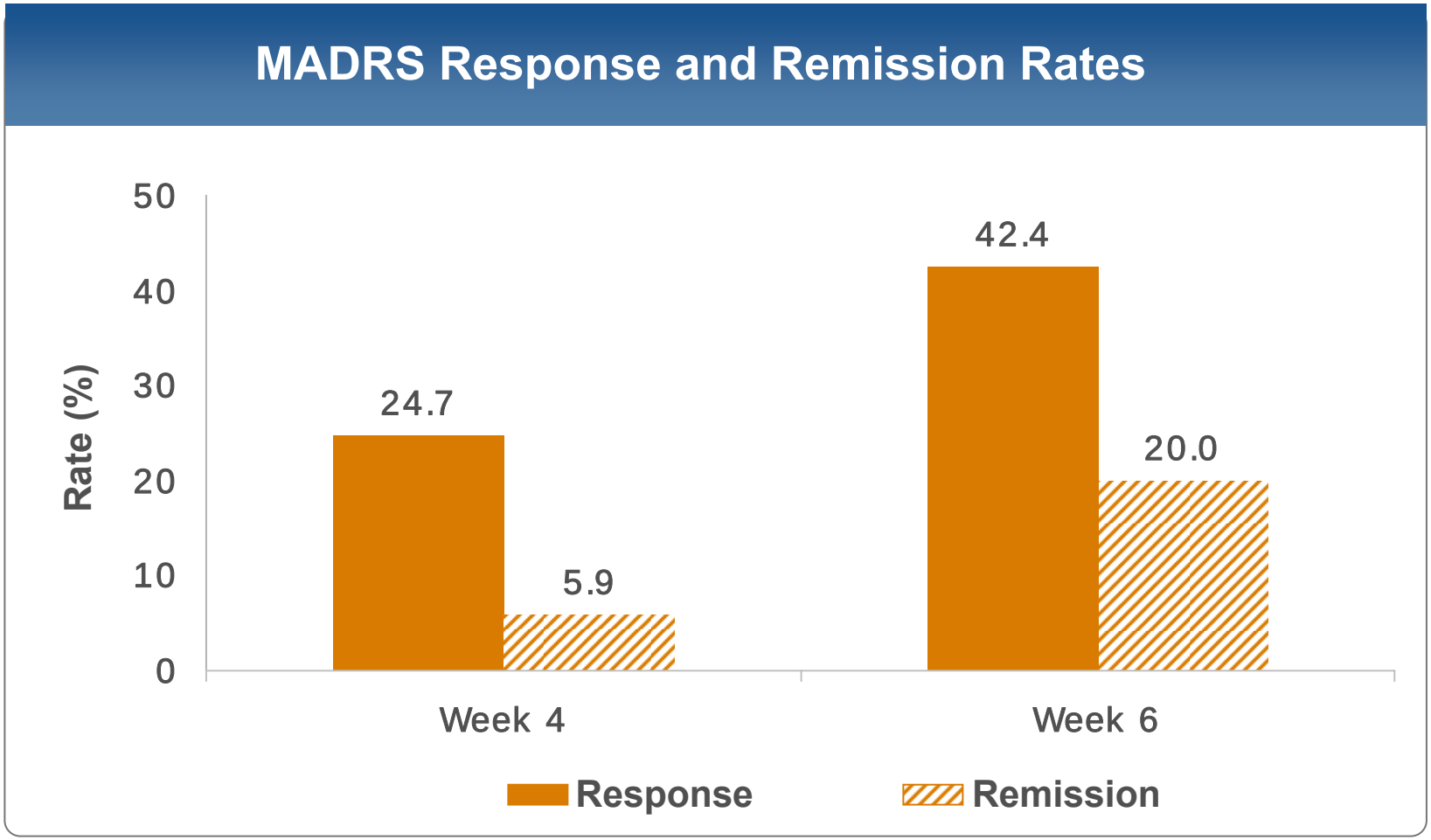
Study 102: Open Label Treatment Confirmatory Evidence of Effectiveness

(Panel Question 5)



Open-Label Study 102

Effective in Study 101 Sham Cross-Over Cohort



LOCF analysis of evaluable study population

Key Points

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- The clinical benefit of NeuroStar TMS Therapy is **DURABLE**
- NeuroStar TMS Therapy is **SAFE AND WELL-TOLERATED**
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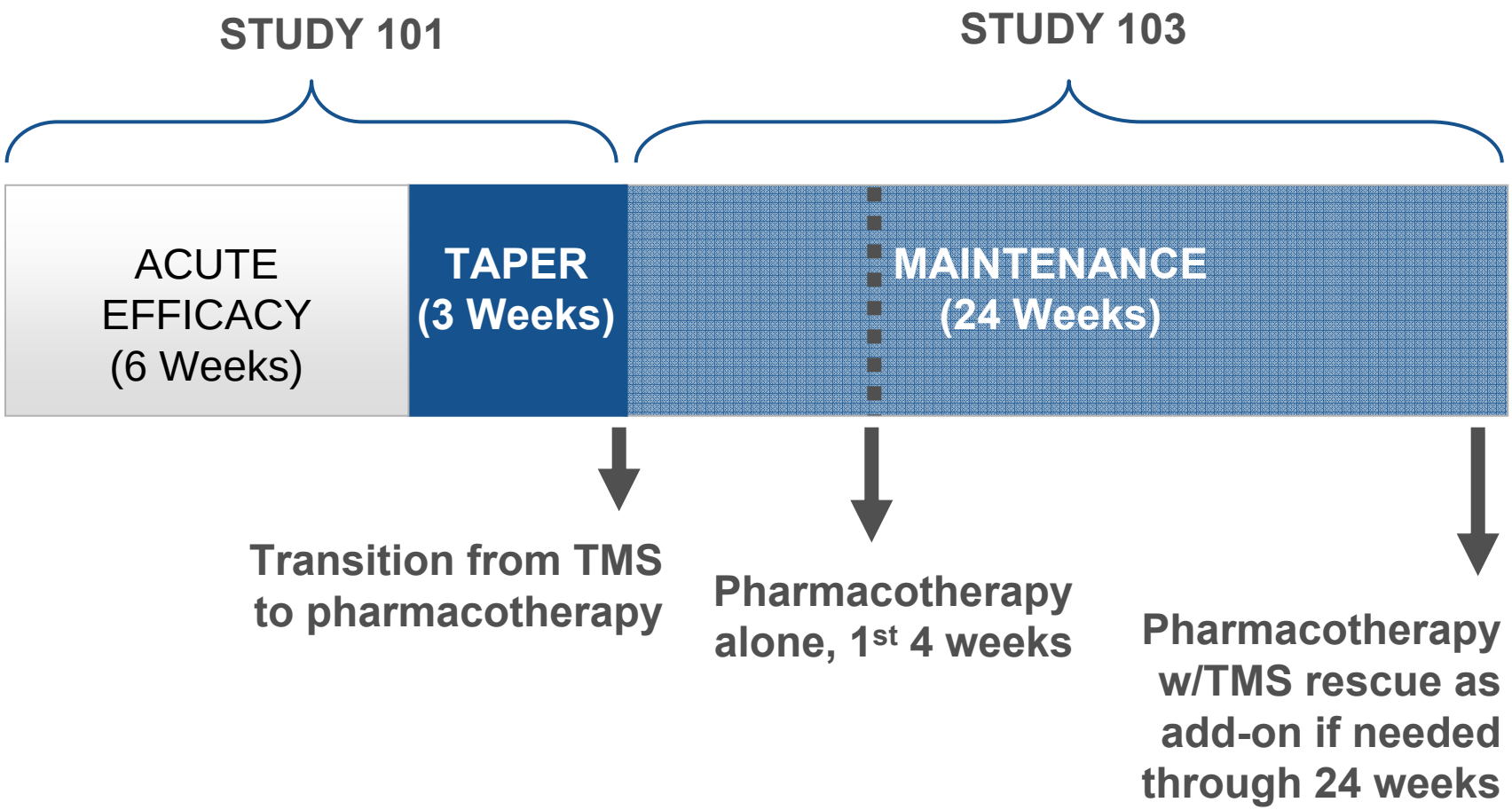
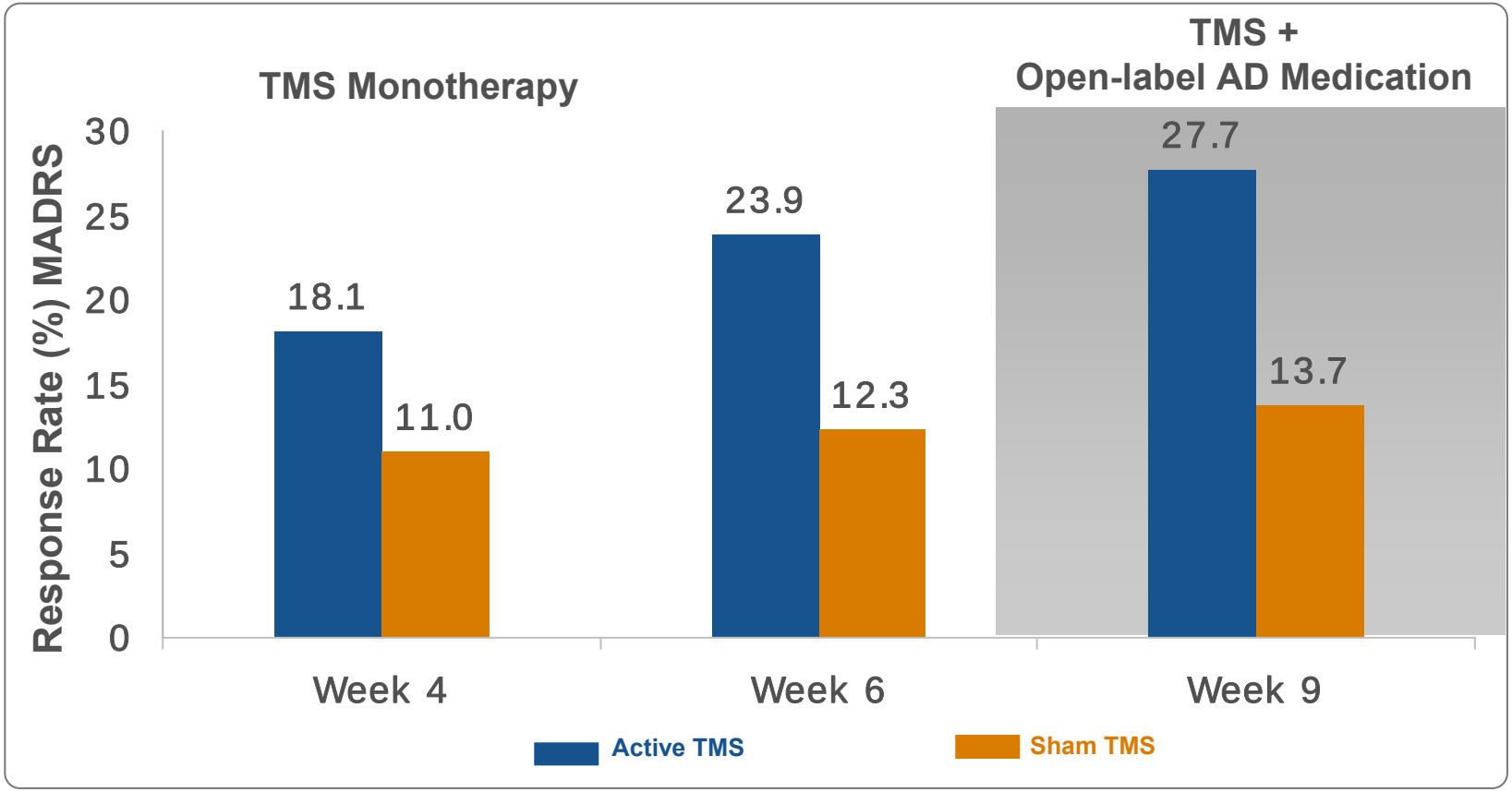
Durability of Effect Demonstrated at Three Points in Time



Acute Effects in Study 101 are Sustained

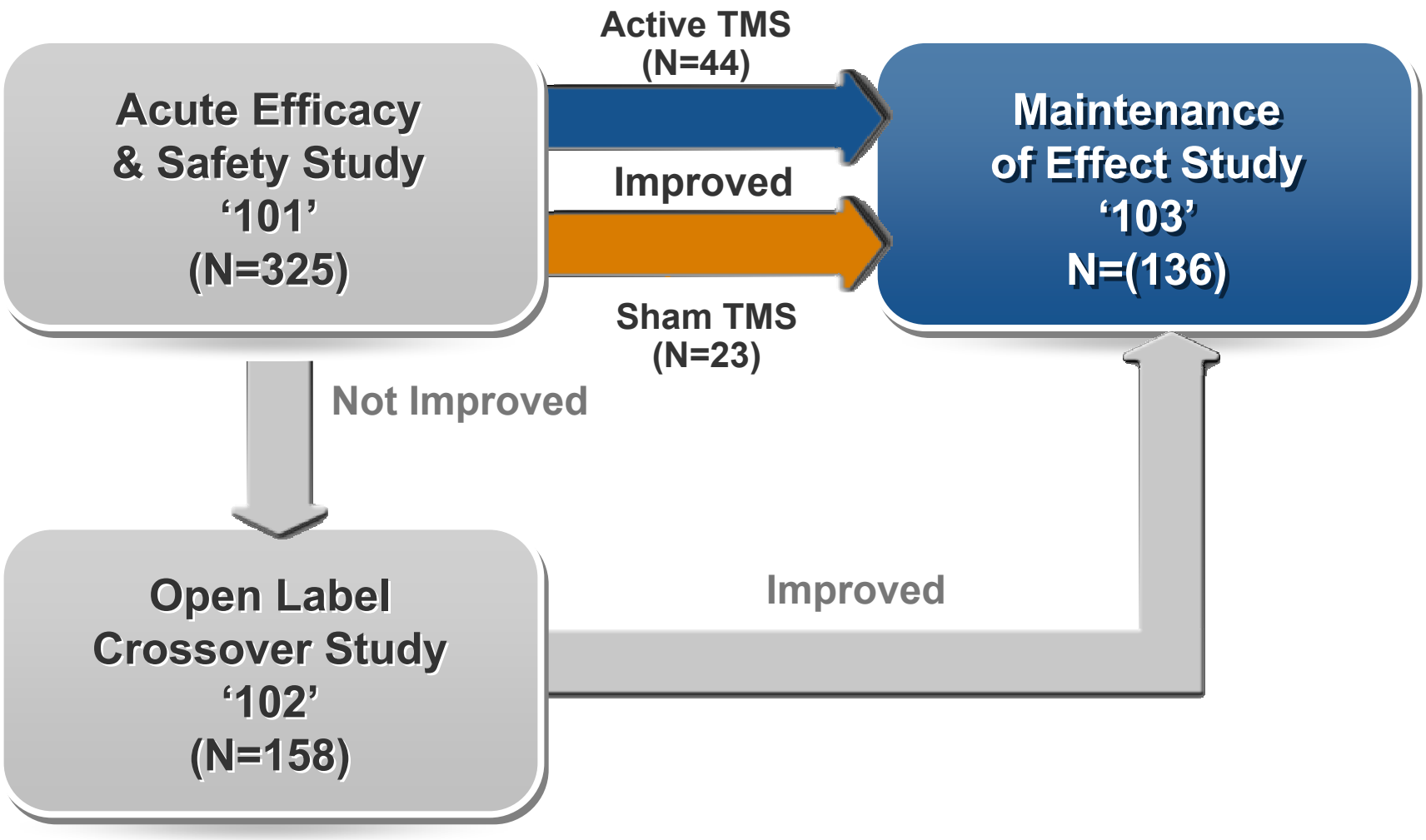
Maintained Effect in Taper From TMS to Pharmacotherapy



91.9% of Acute Phase Responders Persist Through End of Taper Phase

LOCF analysis of evaluable study population

Study 103: Assessing 6 Month Durability of Effect *(Panel Question 5)*

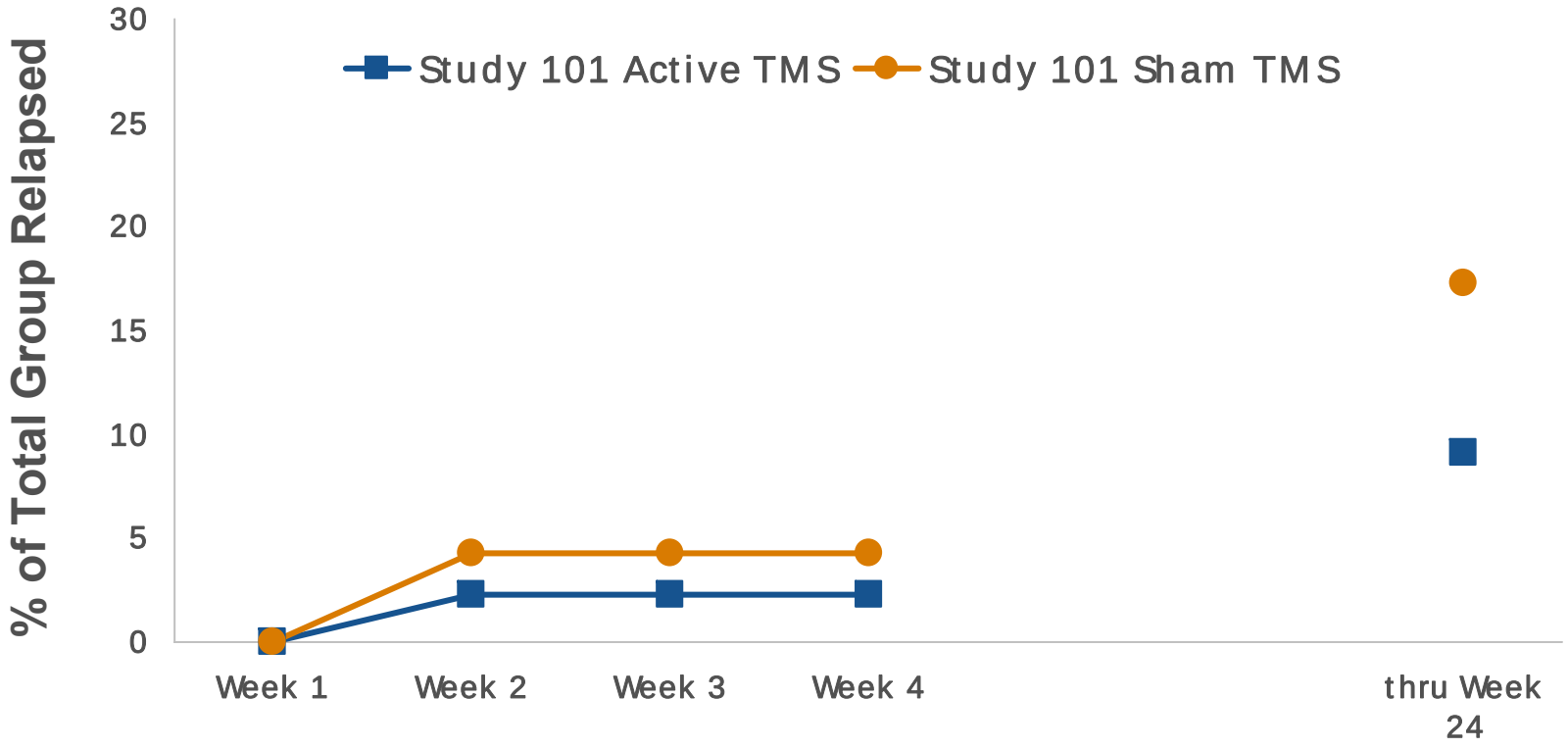


Study 103
Design of the Maintenance of Effect Study

- **24 weeks of open-label medication monotherapy**
  - Follows ECT clinical practice
  - TMS rescue permitted for symptom worsening
- **Main outcome of interest: Incidence of Illness Relapse**
  - Pre-specified definition: All-cause D/C through week 4 and D/C due to lack of efficacy through week 24
  - ECT Literature definition: HAMD24 > 16 and increase of >10 points in HAMD24 from entry score

Low Incidence of Illness Relapse

Study 103 Open-Label Maintenance of Effect



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

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NeuroStar Safety Summary
(Panel Question 6)

- **Safety population (N=325)**
  - Nearly 10,000 active treatments across all studies
- **No seizures, no suicides, no deaths**
  - Disease-related deterioration more frequently reported in sham group
- **Common adverse events (headache, application site pain) were consistent with expectations**
  - Transient and mild to moderate in severity
- **No adverse effect on cognitive function or auditory threshold**

Patient Adherence to Protocol

Reasons for Discontinuation through Primary Efficacy Timepoint (Week 4)

	Active TMS (N=155)*	Sham TMS (N=146)*
Satisfactory Response – Efficacy	0 (0)	0 (0)
Adverse Event	7 (4.5)	5 (3.4)
Failed to Return	1 (0.6)	0 (0)
Unsatisfactory Response – Efficacy	1 (0.6)	2 (1.4)
Protocol Violation	0 (0)	1 (0.7)
Patient Request – Unrelated to Study	2 (1.3)	1 (0.7)
Other	1 (0.6)	3 (2.1)

*Number of patients

All-cause drop-out <8% across entire study population

Serious Adverse Events and Device Malfunctions

Study 101 Acute Treatment Phase

Serious Adverse Event	Sham (N=158) N (%)*	Active (N=165) N (%)*
• Application site pain	0	1 (0.6)
• Facial pain	0	1 (0.6)
• Depression	3 (1.9)	1 (0.6)
• Intentional self injury	1 (0.6)	0
• Suicidal ideation	3 (1.9)	1 (0.6)

Device Malfunction Event	Sham (N=158) N (%)*	Active (N=165) N (%)*
• Burns, first degree	0	2 (1.2)
• Overdose (Operator error/asymptomatic)	0	4 (2.4)

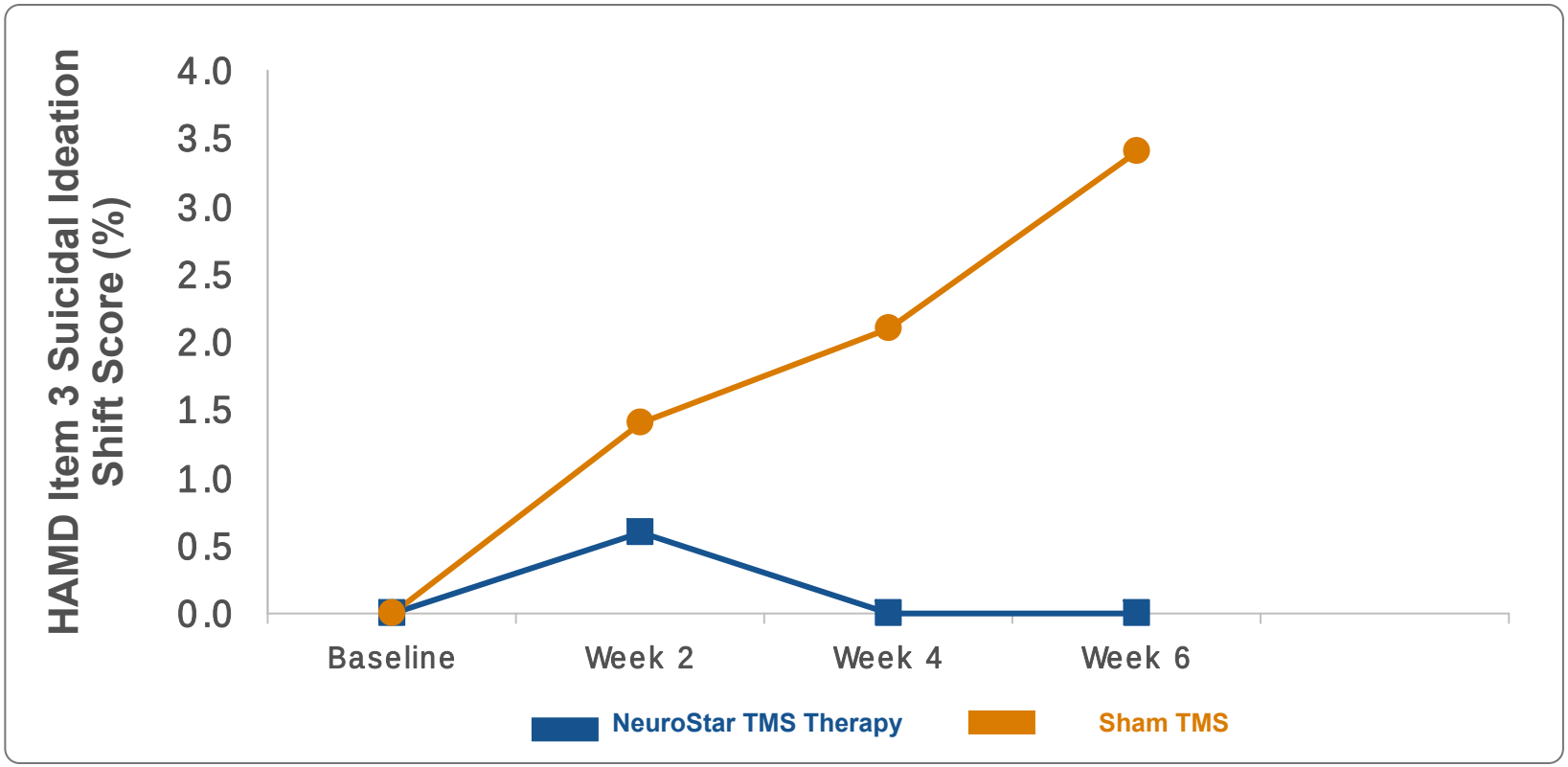
* Number of unique events reported

Well Tolerated w/ Absence of Systemic AEs MedDRA-Coded Common Adverse Events

Body System Preferred Term	Sham (N=158) N (%)	Active (N=165) 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

No Evidence of Emergent Suicidal Ideation With Active TMS



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

No Adverse Effect on Cognitive Function

Measures used are sensitive indicators of cognitive change with ECT:

Cognitive Function Outcome Measure	Domain of Function
Modified Mini Mental Status Examination	Global Cognitive Function
Buschke Selective Reminding Test	Short term recall Delayed recall
Autobiographical Memory Interview – Short Form	Long-term memory

Key Findings Supporting Safety and Efficacy

- **Efficacy shown on continuous outcome measures**
- **Effect is most prominent on core mood symptom (MADRS & HAMD)**
- **Effect is clinically meaningful as shown by categorical response and remission rates**
  - Effect sizes are comparable to literature benchmarks
- **Open-label Study 102 provides confirmatory evidence of Study 101 results**
- **Clinical relief is sustained and durable following cessation of acute treatment**
- **NeuroStar TMS Therapy is safe and well tolerated**

Study 101 Blind Was Maintained
(Panel Question 4)

- **Most common AE (headache) equally represented in active & sham arms**
- **Post-hoc analysis of discomfort AEs and outcome:**
  - Week 1 AE's & Week 4 categorical outcome
  - Week 1 AE's & Severity to Week 4 mean change
  - ANCOVA with AE terms included in model
- **Overwhelming weight of evidence supports maintenance of the study blind**

Risk of Antidepressant Discontinuation
(Panel Question 7)

- **Study 101 was conducted medication-free**
  - TMS studied as a monotherapy
  - Meds D/C'ed only if no benefit observed
- **TMS and antidepressant pharmacotherapy have been co-administered safely**
  - Neuronetics data
    - Taper phases of Study 101, Study 102
    - Study 103 reintroduction TMS
  - Extensive TMS literature

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Major Depression:
Current Treatment Reality

- **Significant unmet needs exist**
  - Partial or non-response to 1st treatment is norm
  - About 25% of patients remain refractory to all treatments (TRD)
  - Likelihood of benefit diminishes with increasing levels of treatment resistance
- **ACNP Task Force Report (2006)**
  - The goal in the treatment of depression
    - Acceptable categorical outcomes (response and remission)
    - Sustained relief over time
- ***Adverse events and treatment compliance are significant issues***

Discontinuation Rate with Pharmacotherapy During Acute Rx

% All-Cause Discontinuation Rate in RCTs

Duration of Study	Placebo Control	Investigational Treatment	Active Comparator
4 Weeks	37%	25%	43%
5 Weeks	38%	38%	--
6 Weeks	41%	38%	36%
8 Weeks	36%	36%	38%

45 RCTs | N > 19,000 patients | mean: 37%

Acute treatment discontinuation influenced by adverse events and lack of efficacy

Khan, Arch Gen Psychiatry, 2000

Discontinuation Rate with ECT During Acute Treatment and Long-Term Follow Up

% All-Cause Discontinuation Rate

Study	Acute Treatment	Long-Term Follow Up (24 Weeks)
OPT-ECT Study (N=290)	8%	67%
CORE Study (N=531)	26%	57%
Community ECT Study (N=347)	30%	70%

- Acute discontinuations substantially due to withdrawal of consent and adverse events,
- Long-term discontinuation primarily driven by relapse

Sackeim, JAMA, 2000; Prudic, Biol Psychiatry, 2004; Kellner, Arch Gen Psychiatry, 2006

Discontinuation Rate with TMS During Acute Treatment and Long-Term Follow Up

% All-Cause Discontinuation Rate

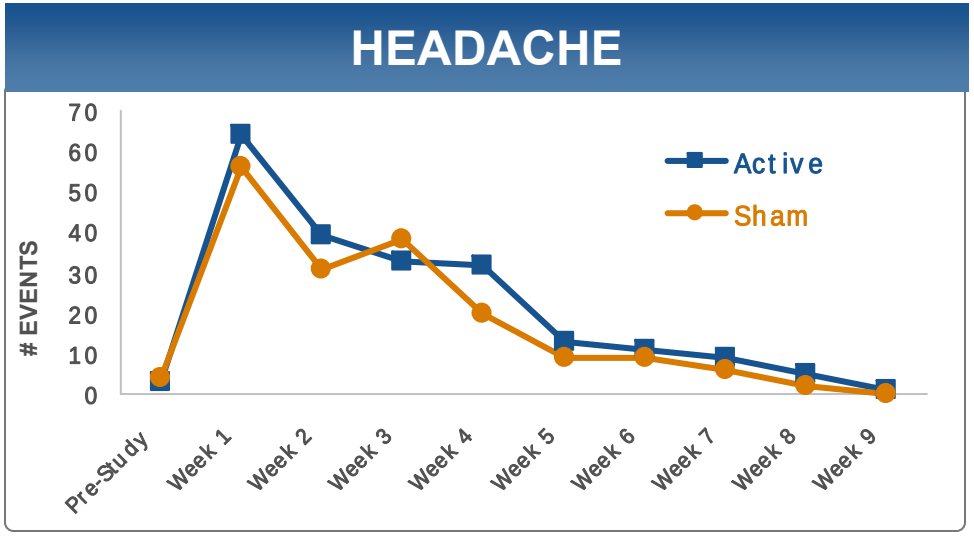
Study	Acute Treatment	Long-Term Treatment (24 Weeks)
Study 101 – Acute Efficacy Controlled Study (4 weeks)	8%	–
Study 102 – Acute Efficacy Open Label Study (4 weeks)	9%	–
Study 103 – Maintenance of Effect (24 weeks, interim report)	–	38%

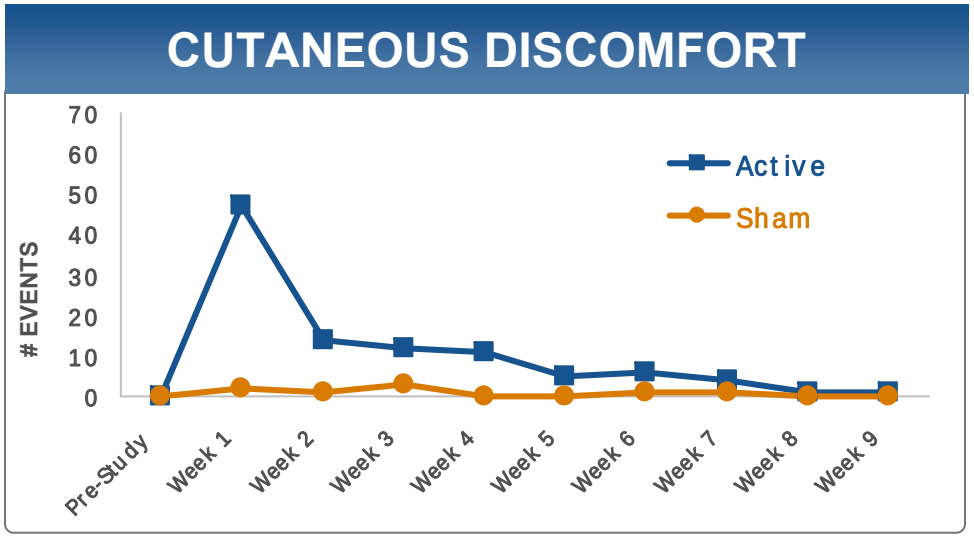
- TMS shows a considerably lower discontinuation during acute and long-term treatment than either medications or ECT
- TMS shows a favorable long-term benefit

Summary of AE Profile with TMS

Overall tolerability with TMS was good, w/ an absence of systemic AEs

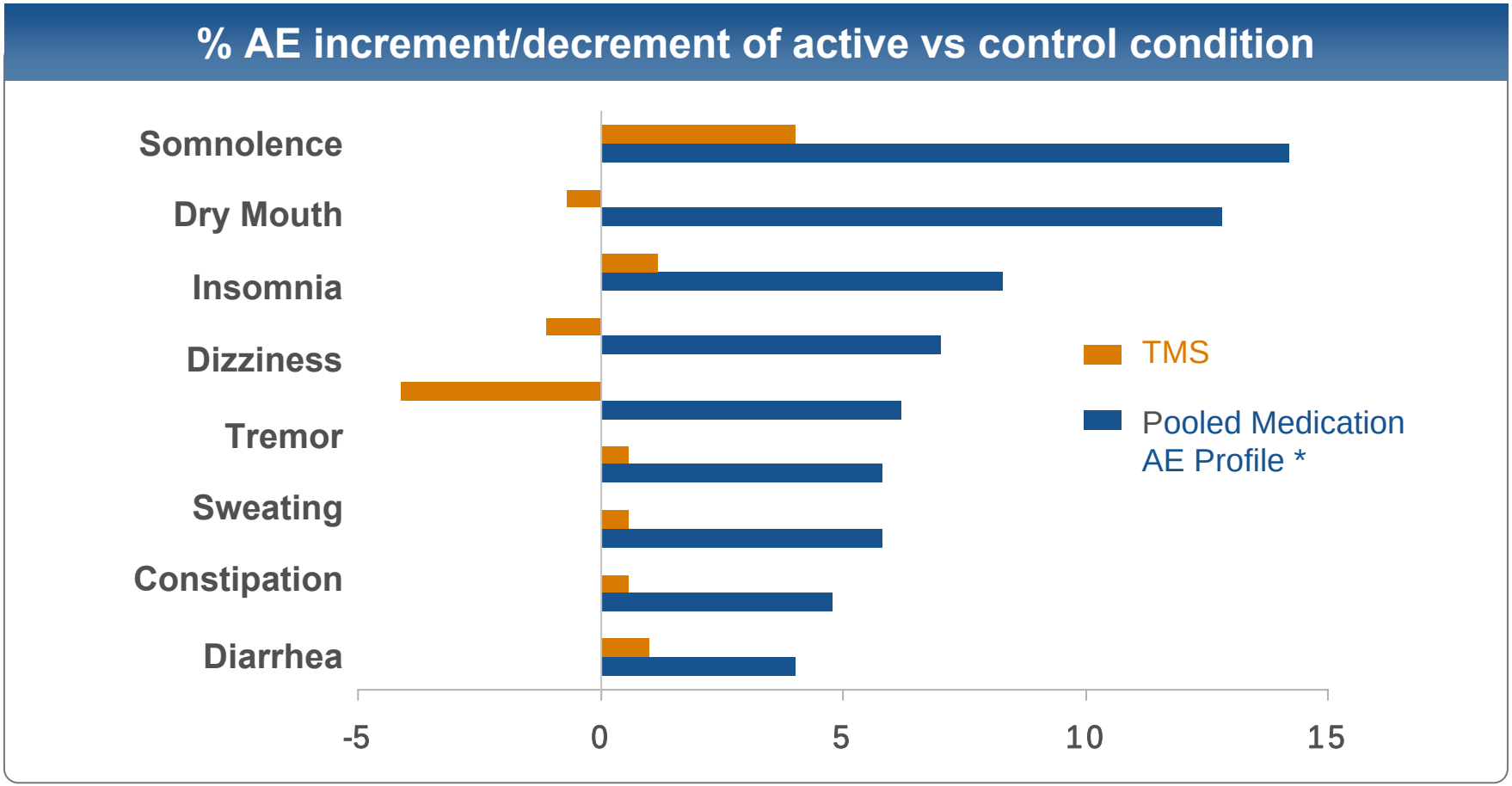
- Low discontinuation rate due to AEs (<5%)
- Profile consistent with prior literature
- Most common AE was headache, ~50% in both active and sham groups
- Mild/moderate severity
- Transient (< 1 wk) with rapid accommodation





Comparison of Common Adverse Events

TMS vs Medication Rx



Adverse events summarized from approved product labels for:
fluoxetine, sertraline, paroxetine, venlafaxine, duloxetine, bupropion, mirtazapine

Medical Complications and Adverse Events Experienced With ECT

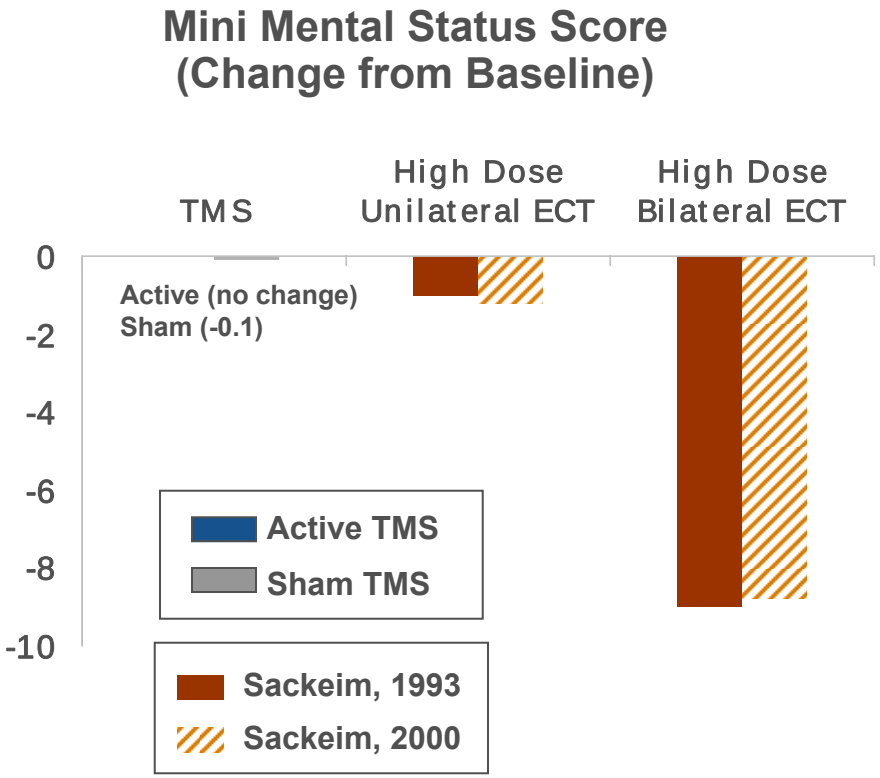
Adverse Events	Medically Important or Serious Adverse Events
Frequent • Headache • Myalgia • Nausea • Disorientation • Anterograde amnesia • Retrograde amnesia • Concentration difficulties	**Infrequent** • Cardiovascular complications (hypertension, hypotension) • Pulmonary complications (prolonged apnea) • Cardiac arrhythmias • Postictal delirium
Infrequent • Vomiting	**Rare** • Death • Cerebrovascular complications • Prolonged szs, status epilepticus, tardive szs • Mania • Severe retrograde amnesia • Dental complications • Orthopedic complications (bone fxs, disloc'ns)

from: APA Committee on ECT Report on the Practice of ECT, 2nd Edition (2001)

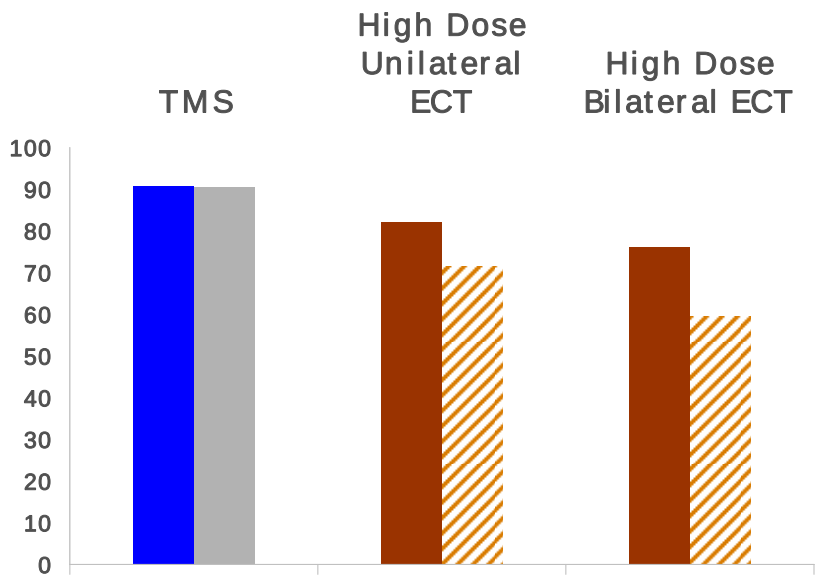
Cognitive Function Outcomes

Comparison of ECT to TMS

Global Cognitive Function



Long-Term Memory Function



The cognitive function profile of TMS is superior to ECT

Summary

- **Major depressive disorder is a disabling illness with highly recurrent disease course**
- **There are significant limitations with currently available treatment options**
  - A significant portion of patients fail to obtain an adequate level of acute benefit or do not achieve persistence of acute effect (relapse)
  - Tolerability of current treatments is frequently unsatisfactory, further exacerbating adherence to treatment
- **TMS shows a favorable tolerability and safety profile with comparable efficacy to other available antidepressant treatments**

Neuronetics Panel Presentation

NeuroStar TMS Therapy System Overview
Judy P. Ways, Ph.D., Vice President, Regulatory Affairs and Quality Assurance, Neuronetics

Clinical Study Design, NeuroStar Safety and Efficacy Results
Mark A. Demitrack, M.D., Vice President and Chief Medical Officer, Neuronetics

Major Depression: Clinical Considerations of Current Options
Alan F. Schatzberg, M.D., Professor and Chairman, Department of Psychiatry, Stanford University

Clinical Significance and Risk-Benefit
Michael E. Thase, M.D., Professor of Psychiatry, University of Pennsylvania

Closing Summary
Judy P. Ways, Ph.D., Vice President, Regulatory Affairs and Quality Assurance, Neuronetics

Risk/Benefit Profile of TMS as an Antidepressant
(Panel Question 11)

- **Magnitude of effect for TMS is consistent with other FDA approved antidepressant therapies**
  - Comparable to other well-established efficacy benchmarks in the literature
  - Consistent with literature expectations vis-à-vis treatment resistance and outcome
- **Risk/benefit ratio associated with TMS compares favorably to therapeutic alternatives, including ECT**

Clinical Significance of TMS Treatment Benefit

Comparison with Established Benchmarks

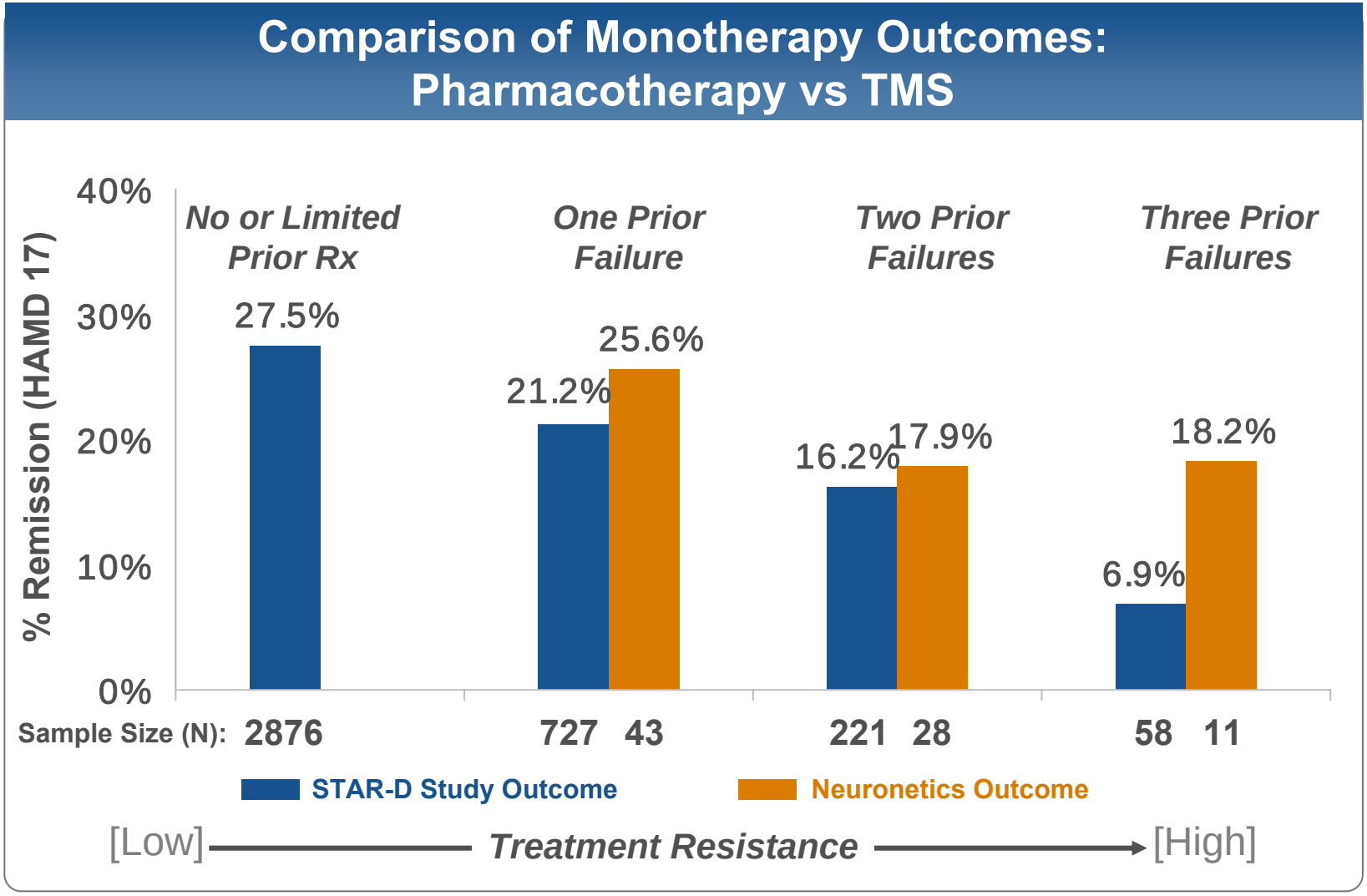
Pharmacotherapy	ECT devices
• Open-label trials – STAR-D Study • Double-blind, placebo-controlled trials – FDA registration database SBA review (Khan) – Literature-reported positive trials review (Walsh) – Meta-analysis of NDA published & unpublished trials (Thase)	• Open-label trials – OPT-ECT Study (Columbia University) – Community ECT Study (Columbia University) – CORE Report (Consortium study) • Double-blind, placebo-controlled trials – UK ECT Review Group Report

STAR-D Study Design Overview

LEVEL 1	**INITIAL TREATMENT:** Citalopram
LEVEL 2	**SWITCH TO:** Bupropion SR, Sertraline, Venlafaxine XR **OR AUGMENT WITH:** Bupropion SR, Buspirone
LEVEL 3	**SWITCH TO:** Mirtazapine or Nortriptyline **OR AUGMENT WITH:** Lithium or Triiodothyronine
LEVEL 4	**SWITCH TO:** Tranylcypromine or Mirtazapine combined with Venlafaxine XR

Rush, 2006.

Clinical Benefit Varies by Prior Treatment Failure in Both STAR-D and TMS Study 102



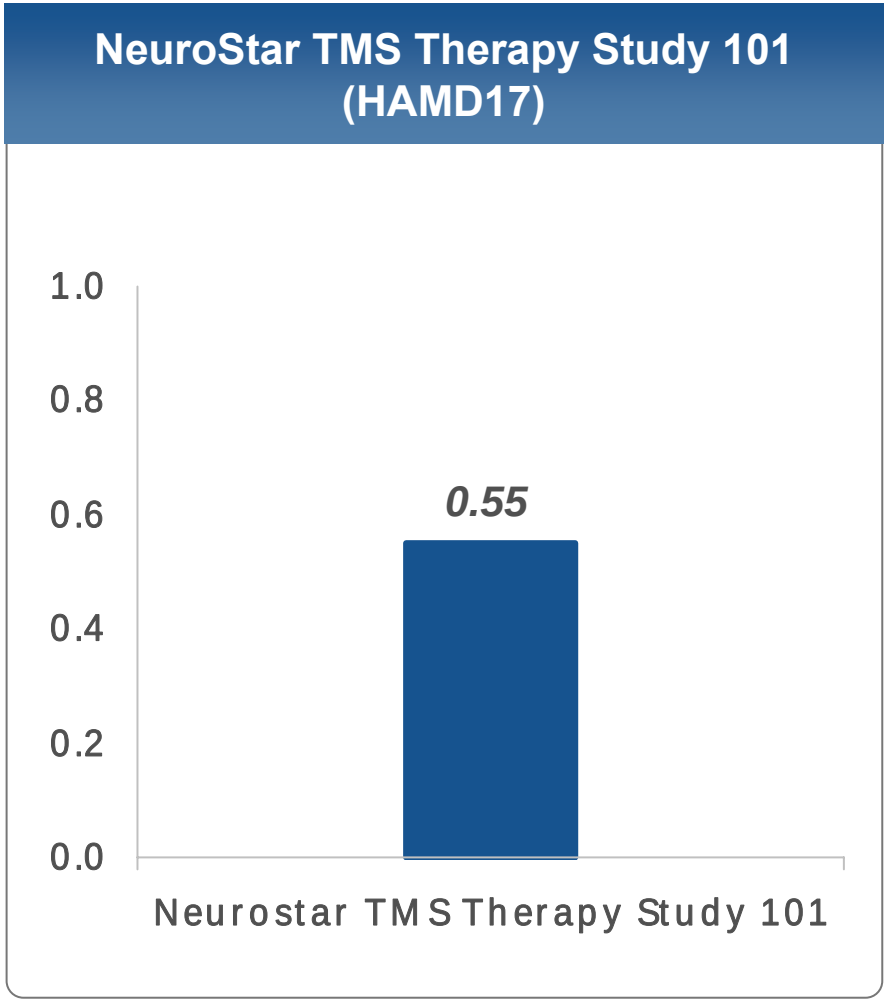
Acute and Long-Term Outcomes

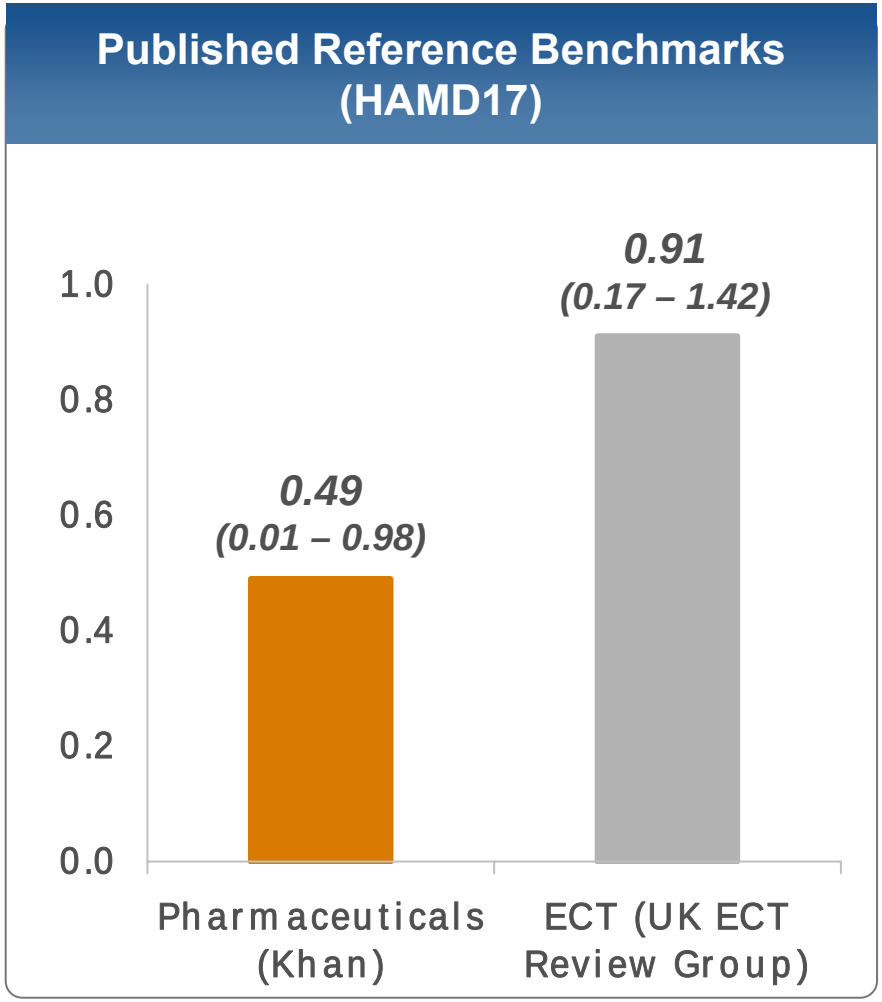
Comparison of Open-Label ECT and TMS

Study	Acute *Remission* Rate (HAMD24)	Long-Term *Relapse* Rate (HAMD24)
NeuroStar TMS Therapy		
• Study 102 Open-Label Acute	27.1% (6 week) 36.5% (9 week)	
• Study 103 Maintenance of Effect		20.5% (Med Mono + TMS)
OPT-ECT Study (N=290)	54.8%	60% (Mono Meds) 39% (Comb'n Meds)
CORE Study (N=531)	64.2%	37.1% (Cont-ECT) 31.6% (Comb'n Meds)
Community ECT Study (N=347)	46.7%	64.3% (Ad hoc)

Sackeim, JAMA, 2000; Prudic, Biol Psychiatry, 2004; Kellner, Arch Gen Psychiatry, 2006.

Comparative Analysis of Effect Size TMS (Study 101: Week 4) vs Meds vs ECT





Khan, 2000; UK ECT Review Group; 2003.

Risk-Benefit Profile of ECT

- **ECT is the most effective short-term treatment option for patients with MDD**
  - Large effect sizes, substantial acute response and remission rates, shortest time to illness recovery
- **ECT has substantial and clinically significant risks that limit its broader use**
  - Medical complications due to anesthesia and seizure induction
  - Acute and long-term cognitive dysfunction (amnesia)
  - Lack of persistence of clinical benefit
    - High rate of early relapse
    - Six month relapse rates ~50-70% without complex pharmacotherapy

Risk-Benefit Profile of TMS Compares Favorably to ECT

	ECT	TMS
Efficacy	♦Most effective short-term treatment	♦Substantial evidence of efficacy; positioned between pharmacotherapy and ECT
Durability	♦High rates of relapse <u>without complex pharmacotherapy as maintenance</u>	♦Low rates of early relapse (one month) with med monotherapy alone ♦Longer-term (24 week) persistence of benefit at least as good as ECT (with med monotherapy and TMS rescue)
Safety	♦Medical complications due to anesthesia and seizure induction ♦Acute and long-term cognitive dysfunction (amnesia)	♦Benign, transient adverse effects ♦Absence of systemic adverse effects

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Closing Summary
Judy P. Ways, Ph.D., Vice President, Regulatory Affairs and Quality Assurance, Neuronetics

Key Points

- NeuroStar TMS Therapy is **EFFECTIVE**
- The clinical benefit of NeuroStar TMS Therapy is **DURABLE**
- NeuroStar TMS Therapy is **SAFE AND WELL-TOLERATED**
- NeuroStar TMS Therapy has a **FAVORABLE RISK/BENEFIT PROFILE**