

FDA Presentation

Neuronetics, Inc.

NeuroStar™ System

K061053

FDA Review Team

- **Kristen A. Bowsher, Ph.D.** – Lead Reviewer
- **Victor Krauthamer, Ph.D.** – Neurophysiologist
- **Ann Costello, Ph.D., D.M.D.** – Medical Officer
- **Pablo Bonangelino, Ph.D.** – Statistician
- **Robert De Luca, M.S.** – Electrical Engineer
- **Gregory Dubitsky, M.D.** – Medical Officer
- **Joseph Jorgens, III** – Software Engineer
- **Donald Witters** – EMC Engineer

Presentation Outline

- Kristen A. Bowsher, Ph.D. – *Device Overview*
- Victor Krauthamer, Ph.D. – *ECT Overview*
- Ann Costello, Ph.D., D.M.D. – *Clinical Summary*
- Pablo Bonangelino, Ph.D. – *Statistical Summary*
- Ann Costello, D.M.D., Ph.D. – *Summary*

Proposed Indications for Use

“The NeuroStar™ System is indicated for the treatment of major depressive disorder (MDD).”

Device Description



Trial Device (*Model 2100*) vs. Proposed Commercial System (*NeuroStarTM System*)

- Variations in coil output levels between trial and commercial models are minimal.
- Sponsor has provided measurement data showing experimental confirmation of magnetic field similarity, as a function of output level.
- The minimal differences in output magnitude are inconsequential because the treatment level is set based on the patient's own motor threshold as determined at each treatment session.

Electroconvulsive Therapy (ECT) Overview

Victor Krauthamer, Ph.D.
Neurophysiologist, Group Lab Leader

Division of Physics
Office of Science and Engineering Labs

510(k) Process - Substantial Equivalence

- Same intended use as predicate device (ECT)
- Same technological characteristics; when technological characteristics differ:
 - No new types of questions regarding safety and effectiveness, and
 - Clinical evidence of a **comparable risk to benefit profile**

Historical Perspective of ECT

- 1937 – came into use for reliable production of convulsion, Ugo Cerletti
- Modern ECT
 - Anesthesia, oxygenation, respiratory support and muscle relaxation
 - Less charge/energy with pulsed current instead of sine wave
 - Right unilateral (RUL) and bifrontal electrode placement to improve safety
- National and international consensus for the treatment of the most severe forms of depression
- Main safety concern is long-term changes in memory

History of TMS

- Marketed under 510(k) for peripheral nerve stimulation for diagnostic purposes
- Literature for depression treatment:
 - Meta-analyses calculate treatment effect of -0.35 (Martin et al., Br. J. Psych. 182:480-491, 2003, Couturier, J. Psych. Neurosci 30:83-90, 2005), but question reliability of studies because of patient number, quality of sham, masking of subjects and investigators
 - Neuronetics' multicenter study was larger than any previous, employed a new type of **sham**, and triple blinding

ECT Indications For Use

1. From 21 CFR § 882.5940 – “Severe psychiatric disturbances, e.g., severe depression”
2. Cleared indications for use
 - a) “Severe depression or major depression with melancholia” (1985)
 - b) “Disorders when rapid response needed, pharmacoresistant, previous response to ECT, valid patient preference for ECT” (1984)
3. Present practice – modern ECT
 - a) Recommended for **severe forms of major depression** by UK ECT Review Group (Lancet 2003, 361:799-808)
 - Rapid response needed -marked physical deterioration, catatonia, immediate suicide risk
 - resistance to other treatments – i.e., pharmaco- and psychotherapy
 - b) Actual community use (Prudic et al., Biol Psych 2004,55:301-312) for **depression** often with **comorbib psychotic features, bipolar disorder and/or substance abuse**

ECT Technological Characteristics

- applies electric current to brain to activate neurons
- biological mechanism is unknown – may relate to stimulation-induced changes in synaptic plasticity: long-term-potential and/or long-term depression
- treatments are performed in multiple sessions
- not implanted, not used at home
- **electric current spreads broadly in brain**
- **induces a generalized motor seizure**

ECT Safety Issues

- Convulsion
- Anesthesia with muscle relaxant, oxygen, respiratory support
- Transient hypertension
- Adverse events
 - **memory loss – retrograde and anterograde**
 - burns
 - residual twitching
 - mania
 - worsening depression
 - severe headache
 - bone fracture
 - death fewer than 1/10,000

ECT Effectiveness

- Significant reduction in depression achieved in randomized studies⁺
- Treatment HAMD₁₇: -9.7 points lower than sham (95% CI = -5.7 to -13.5) at 2 weeks¹
- Standardized treatment effect = -0.91 (95% CI = -1.27 to -0.54)²
- Remission rate of 85% for non-psychotic depression (>60% decrease in HAMD)³
- Short durability of effectiveness – lasts weeks

¹UK ECT Review Group (2003 Lancet); ²Table 12.11, K061053; ³Petrides (2001 J ECT)

Clinical Summary

Ann H. Costello Ph.D., D.M.D.

Biochemist, Oral and Maxillofacial Surgeon

Division of General, Restorative, and Neurological Devices

Office of Device Evaluation

NeuroStar™ System

- Regulatory Path
- Clinical Data

510(k) Premarket Notification Pathway

- Predicate Device: ECT
- Determine whether the NeuroStar™ System has a comparable risk to benefit profile to the risk to benefit profile of ECT devices for the treatment of MDD

Proposed Indications for Use

“The NeuroStar™ System is indicated for the treatment of major depressive disorder (MDD).”

Clinical Study Overview

Three phases of the clinical trial:

- Study 01: Triple blind randomized controlled phase for safety and effectiveness (RCT/no ADDs)
- Study 02: Open label rTMS of 01 non-responders (Open Label rTMS/no ADDs)
- Study 03: 6 month follow-up of 01 and 02 responders on ADD monotherapy to demonstrate durability of rTMS (ADD/no rTMS)

Study 01: Design

RCT/no ADDs

- Multicenter randomized triple blind
- 325 subjects at 23 sites
- Duration 9 weeks
- **Washout ADDs**
- Screening phase: 1 week
- Treatment phase: rTMS 5 days/week (30 sessions max) for up to 6 weeks
- **Primary efficacy endpoint assessed at 4 weeks**
- Taper phase: taper rTMS plus ADD monotherapy over 3 weeks

Stimulation Protocol

- Treatment over left prefrontal cortex
- Output stimulus strength: 120% motor threshold
- Session 37.5 min
- **Operator blinded**
- **Sham coil with acoustic artifact**

Inclusion Criteria

- DSM-IV criteria for MDE, single or recurrent
- Current MDE duration: ≥ 4 wks and ≤ 3 yrs
- Screening HAM-D 17 ≥ 20
- Baseline HAM-D 17 ≥ 18
- ATHF 1 to 4
- No current ADD
- 30% of subjects on anxiolytics

Exclusion Criteria

- Significant acute suicide risk
- History of psychosis, bipolar disease, OCD
- History of substance abuse or dependence
- Active history of PTSD or eating disorder
- Failure to respond to ECT or ECT treatment within 3 mos
- Recently entered or changed psychotherapy
- History of seizure disorder
- Ferromagnetic material in area of head
- Pregnancy

Study 01: Evaluation Schedule

- Pretreatment: Screening and baseline
- Treatment: 2, 4 and 6 weeks
- **Primary effectiveness at 4 weeks**
- Taper: 7, 8 and 9 weeks

Efficacy Endpoints

- **Primary Endpoint:**
MADRS at 4 weeks
- **Secondary Endpoints:**
HAM-D 17 and 24
Responders/Remitters
CGI-S
SF-36
QLES-Q
IDS-SR
PGI-I

Rating Scales

Scale	# Items	Rater
MADRS	10	Clinician
HAM-D	17 or 24	Clinician
IDS-SR	30	Patient

Effect Size

- The sample size was based on a standardized effect size (d) of 0.4 which was the “minimally clinically interesting difference between the treatment groups.”
- $d=0.79$ SE 0.13 (Burt et al. Int. J. Neuropsych 2002: 5: 73-103)
- The effect size is the ratio of the size of the treatment effect to the standard deviation of the measuring instrument. Thus, it serves as a means of standardizing the effect size.

Cohen's Standard*	Effect Size
	2.0
	1.9
	1.8
	1.7
	1.6
	1.5
	1.4
	1.3
	1.2
	1.1
	1.0
	0.9

Cohen's Standard*	Effect Size
Large	0.8
	0.7
	0.6
Medium	0.5
<i>Sponsor's Goal</i>	<i>0.4</i>
	0.3
Small	0.2
	0.1
	0.0

*Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Patient Accounting

	Active	Sham	Total (%)
Randomized	165	160	325
Modified ITT	155	146	301 (92.6%)
Week 2	150	143	293 (90.2%)
Week 4	143	134	277 (85.2%)
Week 6	86	59	145 (44.6%)
Taper week 1	64	40	104 (32.0%)
Taper week 2	59	38	97 (29.8%)
Taper week 3	54	35	89 (27.4%)

Demographics

Variable	Sham N=146	Active N=155	P-value
Age (SD)	48.7 (10.6)	47.9 (11.0)	0.509
Gender:			
Male	72 (49.3)	69 (44.5)	0.421
Female	74 (50.7)	86 (55.5)	
Depression History:			
Single episode	9 (6.2)	7 (4.5)	0.611
Recurrent	136 (93.8)	149 (95.5)	
Duration of Current Episode:			
Mean	13.2 (9.5)	13.6 (9.9)	0.728
< 24 mos	123 (84.2)	119 (76.8)	
≥ 24 mos	23 (15.8)	36 (23.2)	
Secondary Diagnosis:			
None	104 (71.2)	96 (61.9)	0.112
Other anxiety disorder	42 (28.8)	59 (38.1)	

Demographics (Cont'd)

Variable	Sham N=146	Active N=155	P-value
ATHF:			
1	76 (52.1)	88 (56.8)	ND*
2	50 (34.2)	45 (29.0)	
3	15 (10.3)	15 (9.7)	
4	5 (3.4)	6 (3.9)	
>4	0	1 (0.6)	

*ND = Not Determined

Mean # ATHF Level 3 Exposures = 1.6

Screening Assessments

	Sham N=160	Active N=165	P-Value
MADRS	32.9 (5.6)	32.6 (5.3)	0.476
HAM-D 24	30.6 (4.3)	30.7 (3.9)	0.803
HAM-D 17	22.9 (3.1)	22.6 (2.3)	0.325
CGI	4.7 (0.7)	4.7 (0.6)	0.871
IDS-SR	43.4 (9.9)	42.0 (9.4)	0.197

Study 01: Safety

RCT/no ADDs

Adverse Events*	Active (N=165) N (%)	Sham (N=158) N (%)
Headache	96 (58.2)	87 (55.1)
Application site pain	59 (35.8)	6 (3.8)
Muscle twitching	34 (20.6)	5 (3.2)
Anxiety	19 (11.5)	18 (11.4)
Application site discomfort	18 (10.9)	2 (1.3)
Nausea	17 (10.3)	10 (6.3)

*AEs that occurred with an incidence of $\geq 10\%$

Study 01: Serious Adverse Events

RCT/no ADDs

SAE	Active (N=165)	Sham (N=158)
Worsening major depression	1	2
Suicidal ideation	1	3
Suicide attempt	0	1
Overdose of rTMS ¹	5	0
First degree burn	1	1
Severe pain at treatment site	1	0
Lower lobe pneumonia	0	1
Bowel obstruction	0	1
Total ²	9	9

¹Refers to treatment of >75 trains of active TMS to subject on a single day

²5 SAEs were reported prior to randomization, including worsening depression (2), Suicidal ideation (2), SOB and increased HR (1)

Study 01: Primary Efficacy Endpoint

RCT/no ADDs

Outcome	Change from BL	Difference (90% CI)	P-Value	Effect Size
MADRS	-5.6 Active -3.5 Sham	-2.1 (-3.9, -0.3)	0.057	-0.355

The sample size was based on a standardized effect size (d) of 0.4 which was the “**minimally clinically interesting difference between the treatment groups.**”

Adjusted Primary Efficacy Endpoint

Outcome	Change from BL	Difference (90% CI)	P-Value	Effect Size
MADRS	-5.6 Active -3.5 Sham	-2.1 (-3.9, -0/3)	0.057	-0.355
Adjusted MADRS	ND*	ND*	0.038	ND*

* ND = Not Determined

Subjects with MADRS Scores < 20

Score	Sham N	Active N
14	0	1
15	0	1
18	0	1
19	2	1
Total	2	4

Study 01: Secondary Efficacy Endpoints

RCT/no ADDs

Outcome	Change from BL	Difference (90% CI)	P-Value
HAM-D 24	-6.5 Active	-2.4 (-4.0, -0.8)	0.012
	-4.1 Sham		
HAM-D 17	-5.0 Active	-1.9 (-3.1, -0.7)	0.006
	-3.1 Sham		
Responders			
MADRS	18.1% Active	7.1% (0.2%, 13.9%)	0.045
	11.0% Sham		
HAM-D 24	19.4% Active	7.7% (0.7%, 14.7%)	0.030
	11.6% Sham		
HAM-D 17	20.6% Active	9.0% (1.7%, 16.1%)	0.018
	11.6% Sham		

Outcome SF-36 Subscores	Change from BL	Difference (90% CI)	P-Value
Physical Functioning	1.3 Active 0.4 Sham	0.9 (-.05, 2.3)	0.299
Role Physical	1.0 Active -0.2 Sham	1.2 (-1.4, 3.8)	0.361
Bodily Pain	1.4 Active 1.0 Sham	0.4 (-1.0, 1.8)	0.520
General Health	1.3 Active -0.3 Sham	1.6 (0.2, 3.0)	0.049
Vitality	3.3 Active 2.1 Sham	1.2 (-0.3, 2.7)	0.179
Social Functioning	3.2 Active 1.8 Sham	1.4 (-0.5, 3.3)	0.183
Role Emotional	3.6 Active 1.9 Sham	1.7 (-0.1, 3.5)	0.105
Mental Health	3.7 Active 0.6 Sham	3.1 (1.2, 5.0)	0.006

Outcome	Change from BL	Difference (90% CI)	P-Value
Q-LES-Q	3.5 Active 2.0 Sham	1.5 (-0.2, 3.2)	0.124
Remitters			
MADRS	7.1% Active 6.2% Sham	0.9% (-4.2%, 5.9%)	0.633
HAM-D 24	9.0% Active 8.2% Sham	0.8% (-4.7%, 6.4%)	0.644
HAM-D 17	7.1% Active 6.2% Sham	0.9% (-4.2%, 5.9%)	0.705

Outcome HAM-D Factor Scores	Change from BL	Difference (90% CI)	P-Value
Anxiety/ Somatization	-1.6 Active -1 Sham	-0.6 (-1.1, -0.1)	0.025
Core Depression	-1.9 Active -1 Sham	-0.9 (-1.5, -0.3)	0.012
Maier	-2.5 Active -1.4 Sham	-1.1 (-1.5, -0.5)	0.003
Gibbons	-3.0 Active -1.8 Sham	-1.2 (-2.0, -0.4)	0.007
Retardation	-1.6 Active -0.9 Sham	-0.7 (-1.2, -0.2)	0.007
Sleep	-0.9 Active -0.6 Sham	-0.3 (-0.7, 0.1)	0.211

Outcome	Change from BL	Difference (90% CI)	P-Value
IDS-SR	-7.7 Active -5.2 Sham	-2.5 (-4.8, -0.2)	0.058
CGI-S	-0.6 Active -0.2 Sham	-0.4 (-0.6, -0.2)	0.009
PGI-I	-0.6 Active -0.3 Sham	-0.3 (-0.6, 0.02)	0.181

Study 01: Summary of Secondary Endpoints

RCT/no ADDs

Secondary Endpoints	P-Value ≤ 0.05	Rater
HAM-D 17 and 24	Yes	Clinician
CGI-S	Yes	Clinician
Responders	Yes	Clinician
Remitters	No	Clinician
QLES-Q	No	Patient
IDS-SR	No	Patient
PGI-I	No	Patient

Depression-Specific Rating Assessments

Outcome	P-Value
MADRS	0.057
HAM-D 24	0.012
IDS-SR	0.058

Study 01: Response by ATHF Level

Outcome	N	P-Value
MADRS:	301	0.057
ATHF 1	164	0.001
ATHF 2	95	0.710
ATHF 3	30	0.588
ATHF 4	12	0.022
HAM-D 24:	301	0.012
ATHF 1	164	0.001
ATHF 2	95	0.933
ATHF 3	30	0.577
ATHF 4	12	0.077
IDS-SR:	301	0.059
ATHF 1	164	0.002
ATHF 2	95	0.710
ATHF 3	30	0.706
ATHF 4	12	0.269

Mean # ATHF Level 3 Exposures = 1.6

Questions 7, 8,
9 and 10

Study 01: Reasons for Week 4 to 6 Discontinuation

Week 6: N=145 of 301 patients (48%)
(86 active, 59 sham)

Reason	Active	Sham	Total
Unsatisfactory Efficacy	51	70	121
Patient Request	2	3	5
Adverse Event	2	0	2
Failed to Return	1	1	2
Satisfactory Efficacy	1	0	1
Other	0	1	1
Total	57	75	132

Study 01: Week 6

RCT/no ADDs

Variable	LOCF P-Value	Completers Only P-Value
MADRS	0.058	0.881
HAM-D 24	0.015	0.984
IDS-SR	0.053	ND*

*ND = Not determined

N=145 of 301 patients (48%)
(86 active, 59 sham)

Study 02

Open Label rTMS/No ADDs

- Open label rTMS
- No ADDs
- rTMS therapy 6 weeks followed by 3 week taper
- Non-responders (Study 01) as defined by reduction in HAM-D 17 \leq 25%
- 158 subjects (52.5%) at 22 sites
- 30% of subjects had some anxiolytic use

Study 02: Safety

Open Label rTMS/no ADDs

Adverse Events	A (N=73) n (%) Active in 01	B (N=85) n (%) Sham in 01
Headache	35 (47.9)	39 (45.9)
Application site pain	8 (11.0)	27 (31.8)
Insomnia	22 (30.1)	22 (25.9)
Muscle twitching	15 (20.5)	18 (21.2)
Anxiety	11 (15.1)	12 (14.1)
Nausea	10 (13.7)	6 (7.1)

Study 02: Results

Open Label rTMS/no ADDS

Study 02 Open label rTMS/no ADDs N=158 (52.5%)	LS Mean Change from BL	
	Group A (N=73) Active in 01	Group B (N=85) Sham in 01
Active rTMS wks (# sessions)	12 weeks (60)	6 weeks (30)
MADRS	-12.5	-17.0
HAM-D 24	-11.1	-14.5
IDS-SR	-9.9	-16.8

Study 02: Open Label rTMS/no ADDs N=158 (52.5%)	LS Mean Change from BL	
	Group A (N=73) Active in 01	Group B (N=85) Sham in 01
Active rTMS wks (# sessions)	12 weeks (60)	6 weeks (30)
MADRS	-12.5	-17.0
HAM-D 24	-11.1	-14.5
IDS-SR	-9.9	-16.8

Study 01: RCT/no ADDs N=301	LS Mean Change from BL	
	Active N=155	Sham N=146
Active rTMS wks (# sessions)	6 weeks (30)	0 weeks (0)
MADRS	-5.6	-3.2
HAM-D 24	-6.4	-3.8
IDS-SR	-7.7	-4.7

Study 03

ADD/no rTMS

- Open label monotherapy
- Open label rTMS for symptom recurrence:
CGI-S change on two sequential visits
- Discontinued if recurrence of MDD or fail to receive benefit from open label rTMS
- Duration: 24 weeks
- Responders (Studies 01 and/or 02):
Ham-D 17 \geq 25%
- 136 subjects (45.2%) at 22 sites
- Interim data analyses

Study 03: Groups

ADD/no rTMS

Group	N = 136	Population	Active rTMS (wks)	% FU
1	44	Active 01 → 03	6	28.4% (44/155)
2	27	Active 01 → 02 → 03	12	37.0% (27/73)
3	42	Sham 01 → 02 → 03	6	49.4% (42/85)
4	23	Sham 01 → 03	0	15.8% (23/146)

Study 01 RCT	Active N = 155	Sham N = 146
Study 02 Open Label/no ADDs	Group A N = 73	Group B N = 85

Study 03: Results

ADD/no rTMS

	Group			
	1	2	3	4
rTMS (wks)	6	12	6	0
rTMS Retreatment at 24 wks	36.4%	33.3%	38.1%	47.8%

Study 03: Relapse Rates

ADD/no rTMS

		Group			
		1	2	3	4
rTMS (wks)		6	12	6	0
Protocol ¹	4 wks	2.3%	0%	7.2%	4.3%
	24 wks	9.1%	14.8%	14.4%	17.3%
Literature ²	4 wks	9.1%	11.1%	9.6%	12.9%
	24 wks	20.5%	22.2%	26.3%	25.8%

¹Protocol defined relapse rate: Discontinuation for all cause during time interval

²Literature defined relapse rate: HAM-D >16 on two consecutive visits and an absolute increase of 10 points; based on 03 entry.

Statistical Summary

Pablo Bonangelino, Ph.D.
Biostatistician

Office of Science and Biometrics

Statistical Issues

- Effectiveness
- Integrity of blinding
- Missing data
- Center effects

Mean Change in MADRS

Baseline Scores:

Active 32.8

Sham 33.9

Mean Change at Week 4:

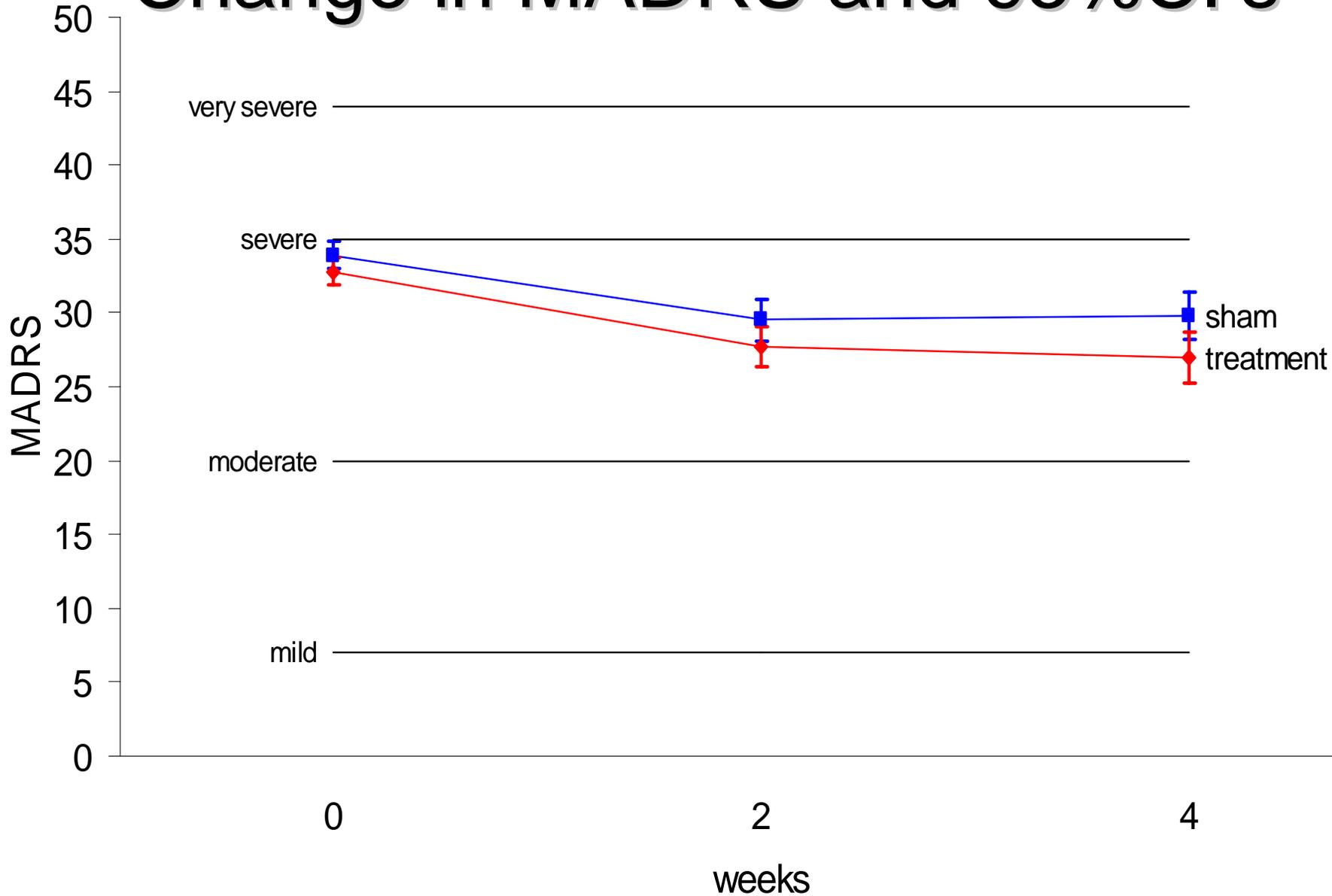
Active -5.6

Sham -3.5

Mean Difference:

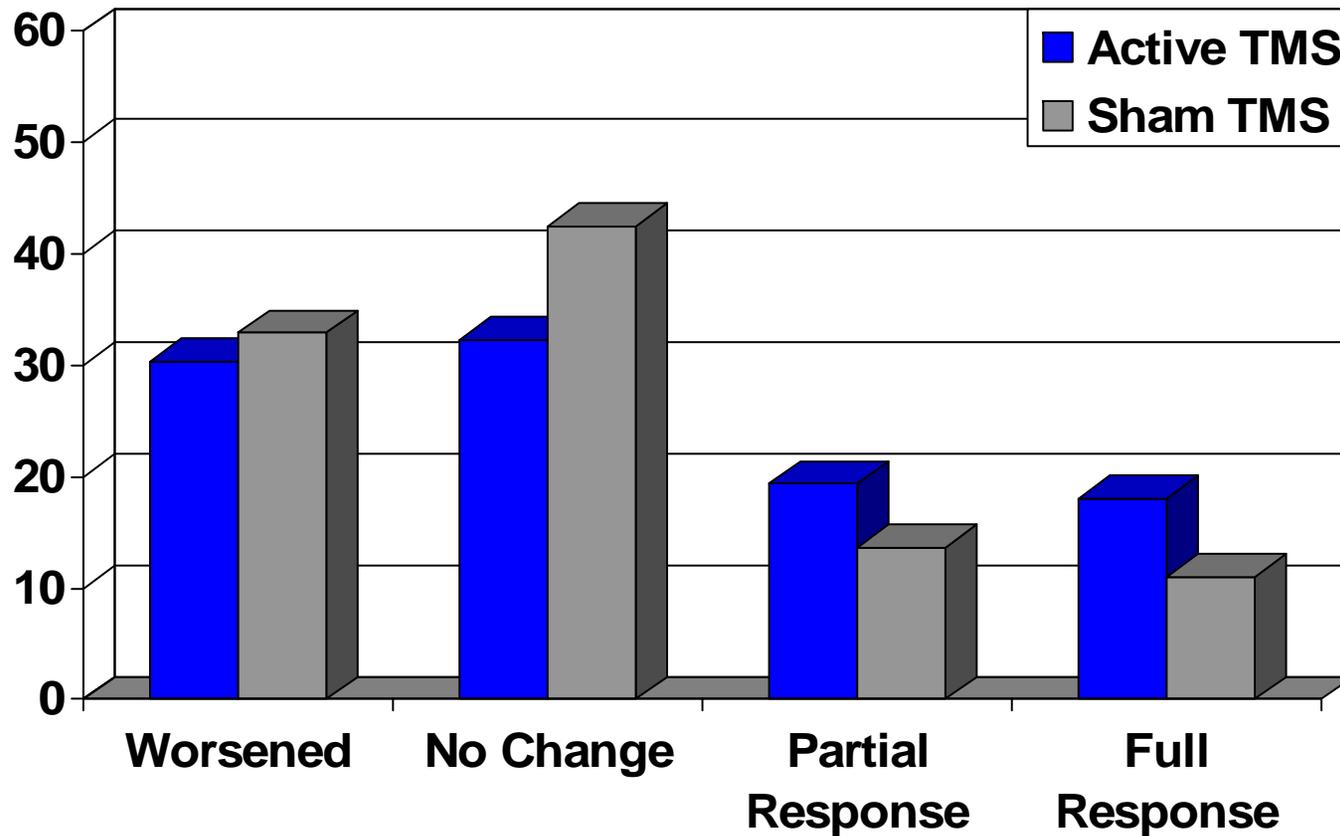
- -2.1 (-4.3, 0.08) p-value= 0.057
- Mean improvement of about 6% of baseline score.
- Effect size of -0.36 (FDA) or
-0.39 (Sponsor)

Change in MADRS and 95%CI's



Distribution of Categorical Outcome

MADRS Week 4



P = 0.058 Cochran-Mantel-Haenszel (non-zero correlation)

Statistical Multiplicity

- In general, claims should only be made based on secondary endpoints after the primary endpoint has been met.
- In addition, multiple secondary endpoints require an adjustment for multiplicity.
- The sponsor has 26 secondary endpoints at the Week 4 time point.
- No adjustment for multiplicity was specified in the protocol.

Sponsor's Approach

- The sponsor's statistical consultant found between one and nine secondary endpoints significant after a multiplicity adjustment
- This analysis suffers from the post-hoc selection of the 13 endpoints which were included.

Additional Considerations

- Under the most conservative adjustment, a Bonferroni correction, none of the 26 secondary endpoints would be statistically significant.
- However, note that 13 of 26 secondary endpoints were significant at the 0.05 level without an adjustment for multiplicity.

Caveat to Study 01 Results

- The primary endpoint was at 4 weeks and there was a maximum of 9 weeks of follow-up in Study 01. Therefore, these results speak primarily to short term effectiveness.
- Note that Study 03, which was designed to examine maintenance of effect, was incomplete at the time of this 510(k) submission.

Blinding

Steps taken to assure blinding:

- Sham coil with an “acoustic artifact”
- Separation of “treating staff” and “rating staff”
- It was not planned for patients and investigators to guess the treatment assignment

Possible Unblinding

- Application site pain in:
35.8% of Active vs. 3.8% of Sham
- There was a significant correlation between any pain/discomfort and change in MADRS score (p-value = 0.034)
- In covariate adjusted analysis with any/pain discomfort as a covariate:
 - p-value MADRS: 0.227
 - p-value HAMD24: 0.054
 - p-value HAMD17: 0.020
 - p-value IDS-SR: Not Reported

Caveats

- Headache was present to a similar degree in both Active and Sham groups.
- Application site pain and discomfort are post-treatment variables and as such may be confounded with effectiveness.

Missing Data

- 325 Enrolled – (24 non-evaluable + 24 withdrawn) = 277 complete Week 4 data
- 15% (48 patients) missing at Week 4
- Missing data were approximately balanced: 22 Active and 26 Sham missing.
- Imputation was by Last-Observation-Carried-Forward (LOCF)
- Week 6 data are not informative due to a large amount (156 out of 301) of imputed data.

Other Imputation Approaches

- Repeated measures modeling:
Results very similar to LOCF
- Multiple Imputation Week 4 p-values:
 - MADRS: 0.090
 - HAMD24: 0.008
 - HAMD17: 0.004
 - IDS-SR: Not Reported

Center Effects

- Study 01 was conducted at 23 centers
- There was a significant main effect for center (p-value = 0.0165)
- However, the center-by-treatment interaction was not significant (p-value = 0.7715)

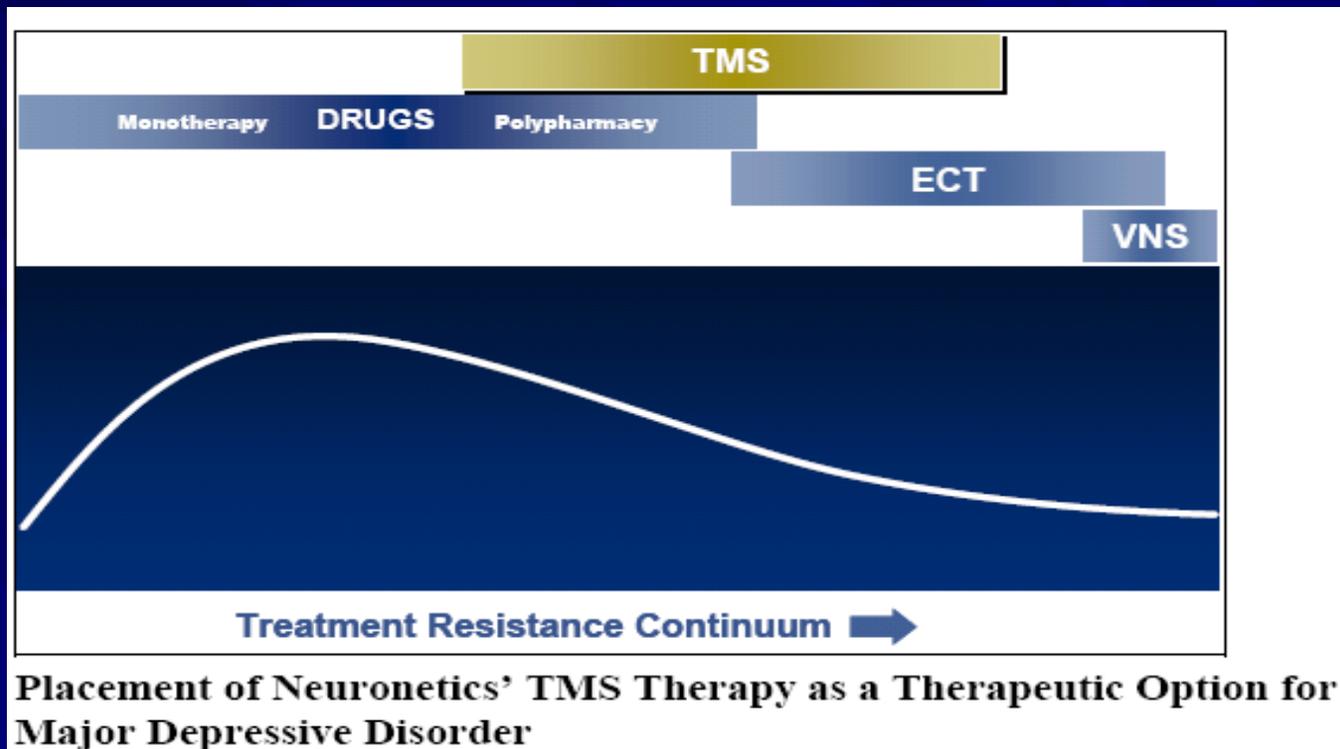
Statistical Issues

- The various study assessments provided mixed results, but multiplicity should be considered when interpreting secondary endpoints.
- Application site pain/discomfort could have led to partial unblinding.
- Primary missing data imputation was by Last-Observation-Carried-Forward, which may be problematic.
- There was no significant center-by-treatment interaction.

Summary

- Role of NeuroStar™ System in MDD
- Risk to Benefit Comparison of the NeuroStar™ System to ECT
- Study Issues

Sponsor's Proposed Role of rTMS in MDD



Proposed IFU: “The NeuroStar™ System is indicated for the treatment of major depressive disorder (MDD).”

Safety

- AEs include headache, application site pain and muscle twitching
- Cognitive function stable
- 1 report of worsening major depression and suicidal ideation in active group (Study 01)
- 2 reports of worsening major depression, 3 reports of suicidal ideation and 1 report of a suicide attempt in sham group (Study 01)

Effect Size

Variable	Effect Size
NeuroStar™ System	
MADRS	-0.355
HAM-D 24	-0.481
ECT ¹	
HAM-D 24	-0.91 (95% CI: -1.27 to -0.54)

¹Table 12.11 K061053

Cohen's Standard*	Effect Size
	1.0
ECT	0.9
Large	0.8
	0.7
	0.6
Medium	0.5
Sponsor	0.4
	0.3
Small	0.2
	0.1
	0.0

*Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Study Issues

- Primary Effectiveness/Secondary Effectiveness
- Multiplicity Testing
- Clinician Rated/Patient Rated
- Blinding
- Missing Data
- Concerns with Studies 02 and 03

Studies 02 and 03

Limitations

- Magnitude of mean change suggests placebo effect (Study 02).
- Relapse rate in sham only treated subjects was similar to that in subjects treated with 6 or 12 weeks of rTMS therapy (Study 03).

Is the risk to benefit profile of the NeuroStar™ System comparable to the risk to benefit profile of predicate ECT devices for the treatment of MDD?