

VNS Therapy™ System Postmarket Update

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Advisory Panel Recommendation

- Date: June 15, 2004
- Vote: 5 – 2 Approvable with Conditions
 - Patient should have four or more failed trials of traditional treatment
 - Appropriate physician training
 - Additional patient labeling and ID card
 - Physician labeling revised (12-month, open-label follow up, variable effect, patient selection, deletion of imaging claims)
 - **Patient registry to collect clinical data**

FDA Decisions

- **Approvable Date: February 2, 2005**
- **Conditions**
 - Submission of complete protocol for
 - 1-year randomized dose-ranging study (D-21 Study)
 - 5-year observational registry study (TRD Registry)
 - Revised Physician and Patient labeling
 - Resolution of GMP inspection issues
 - Resolution of Bioresearch Monitoring issues
- **Approval Date: July 15, 2005**
- **PAS Protocols Approval Date: November 8, 2005**

D-21 Study Overview

- Objective: To compare the safety and effectiveness of adjunctive VNS Therapy administered at different amounts of electrical charge among patients with TRD
- Study Design: Multicenter, double-blind, randomized comparison of adjunctive VNS Therapy using 3 different amounts of electrical charge among patients with TRD

D-21 Study Overview

- Number of Patients: 460
- Duration
 - Each patient: 54 weeks
 - Study: ~37 months
- Outcomes
 - QIDS-C change from baseline to week 22 (Primary)
 - Change in scores and categorical outcomes based on IDS-C, IDS-SR, MADRS, and CGI
 - Adverse events
 - Frequency, intensity, and burden of side effects rating

D-21 Study Status

- On schedule
- First patient enrolled in February 2006
- 89 patients enrolled through 12/31/2006
- Future enrollment outlook
 - Issue: Suboptimal payer coverage environment poses a threat to enrollment schedule
 - Action: Cyberonics will voluntarily roll out a Device Donation and Surgical Program to ensure timely completion of the study

No Unexpected Trends Observed in D-21 Serious Adverse Events

Event Description	Pre-implant	Post-implant
Worsening of depression	5	1
Suicide ideation	1	0
Urinary tract infection	1	0
Suicide attempt	0	1
Wound infection	0	1
Chest pain	0	1
Death (MV accident)	0	1
Carcinoma (thyroid)	0	1

*SAEs observed through 1/9/2007

TRD Registry Overview

- Primary Objective: To follow the course and outcomes for patients with TRD
 - Secondary Objective: To determine moderators of outcomes during adjunctive VNS Therapy
- Registry Design: Multicenter, prospective, observational patient registry
 - Enrolls patients with TRD treated with and without adjunctive VNS Therapy

TRD Registry Overview

- Number of Patients
 - 1000 patients with TRD receiving adjunctive VNS
 - 1000 patients with TRD not receiving VNS
- Duration
 - VNS Therapy patients: 60 months
 - Non-VNS Therapy patients: 24 months (65%) or 60 months (35%, randomly selected)
 - Total study duration: 9 years

TRD Registry Status

- On schedule
- First patient enrolled in January 2006
- 264 active patients as of 12/31/2006
 - VNS Therapy patients: 223
- Future enrollment outlook
 - No significant issues foreseen despite the suboptimal payer coverage environment

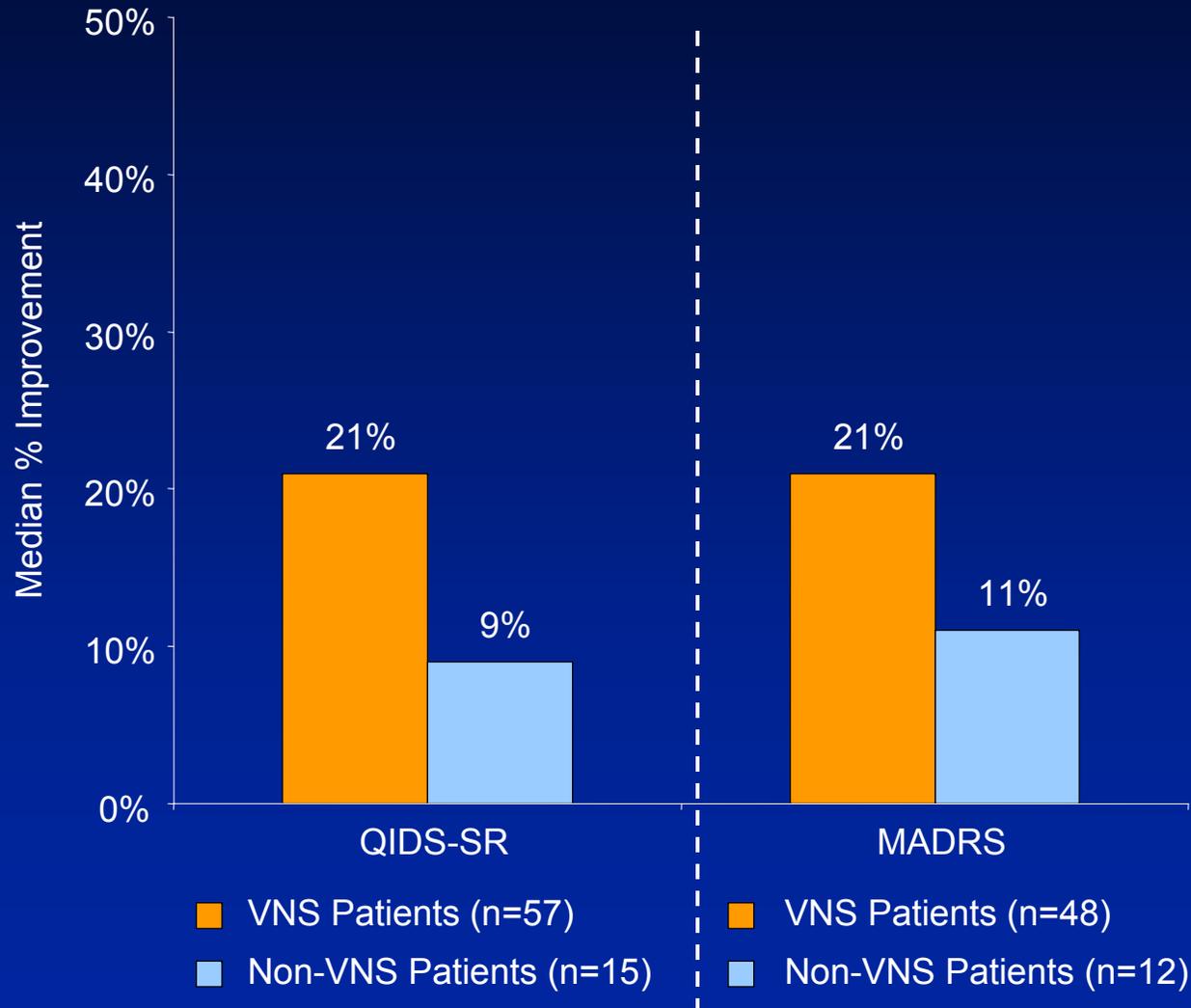
TRD Registry VNS Patients Have More Severe Illness Than Non-VNS Patients

Patient and Disease Characteristics	VNS Patients (n=216)*	Non-VNS Patients (n=35)*
Mean Age (yrs)	49	50
Mean Age at Onset of Illness (yrs)	21	21
% Female	67%	57%
Diagnosis: Unipolar / Bipolar	70% / 30%	77% / 23%
Mean # of Prior Psychiatric Hospitalizations	3.6	1.3
# of Prior Failed Antidepressant Treatments		
0-3	0	0
4-5	25%	21%
6-7	26%	41%
8-9	26%	18%
≥10	24%	20%
% Treated with ECT in Lifetime	56%	49%

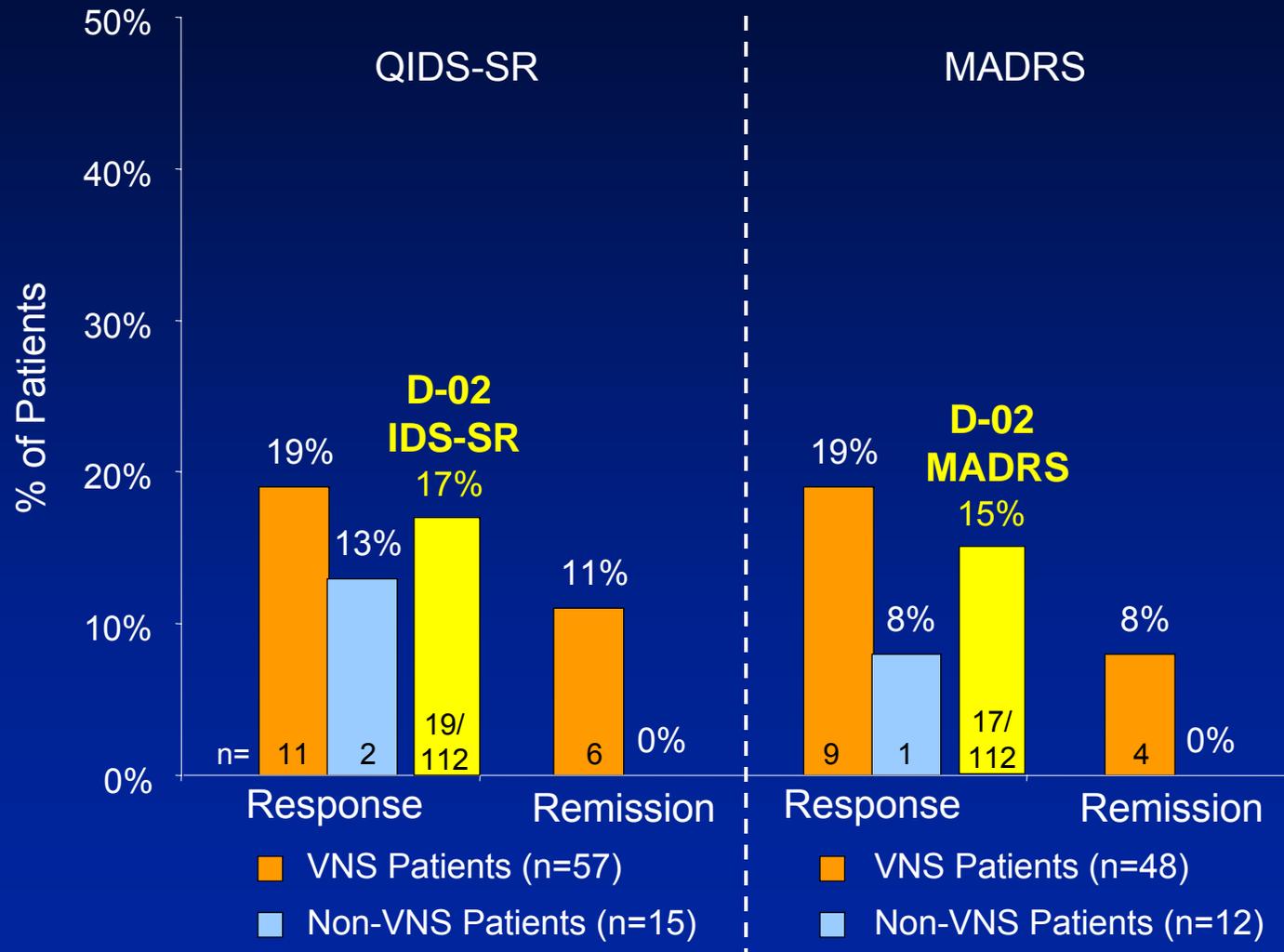
*Represents all data available as of data cutoff date of December 31, 2006

VNS Therapy Update to the Neurological Devices FDA Advisory Panel on 1/26/2007

TRD Registry Outcomes: Percent Improvement at 3 Months



TRD Registry Outcomes: Response and Remission Rates at 3 Months



Rush AJ, et al. *Biol Psychiatry* 2005;58:347-354.

VNS Therapy Update to the Neurological Devices FDA Advisory Panel on 1/26/2007

Summary

- Cyberonics is currently on schedule in meeting its PAS commitment to the FDA
- Cyberonics is working collaboratively with FDA to identify issues and solutions to fulfill its PAS commitment
 - Cyberonics will voluntarily roll out a Device Donation and Surgical Program to ensure that D-21 study enrollments remain on schedule in the present suboptimal payer coverage environment
- Early safety and effectiveness results from the PAS are consistent with the results of the PMA studies