

VNS Therapy™ System Postmarket Update

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Outline

- Background/ Post-Approval Authority
- PMA History
- Advisory Panel Summary
- Approval Summary
- Post-Approval Studies (PAS) Protocols
- PASs progress
- Areas of Concerns
- Evolving Strategies

Background: Post-Approval Authority

- Postapproval requirements can include “continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.” 21 CFR 814.82 (a) (2).

VNS Therapy™ System

PMA and General Information

- Premarket Approval Application (PMA) Number: P970003/S50
- Device Generic Name: Stimulator, Vagus Nerve
- Device Trade Name: VNS Therapy™ System

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 patent labeling and ID card
 - Patient registry to collect clinical data
 - Physician labeling revised (12 month open label follow-up, variable effect, patient selection, deletion of imaging claims)

FDA Approval Decision

- Date: July 15, 2005
- Conditions:
- Submission of complete protocol for
 - 1 year randomized dose ranging study
 - 5 year observational registry study
- Revised Physician and Patient labeling
- Resolution of GMP inspection issues
- Resolution of Bioresarch Monitoring issues

Indications for Use

- Adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more antidepressant treatments

Post-Approval Studies

- Date PAS Protocols approved by FDA
 - November 8, 2005
- P97003/S59 Randomization Comparison of Outcomes in Patients with Treatment-Resistant Depression who Receive VNS Therapy Administered at Different Amounts of Electrical Charge/D-21
- P97003/S60 Treatment-Resistant Depression (TRD) Registry

D - 21 Study: Objective

- To compare the safety and effectiveness of the VNS system administered at different amounts in patients with treatment resistant depression

D-21 Study : Design

- Multi-center, double-blind, randomized comparison of VNS therapy using three different amounts of electrical charge.

D-21 Study : Endpoints

■ Effectiveness:

- IDS – C
- MADRS
- CGI
- IDS – S

■ Safety:

- Adverse Event Record
- Frequency, Intensity and Burden of Side Effects Rating (FIBSR)

D-21 Study : Patients/Sites

- 460 patients
- 30 clinical sites
- Maximum 25 patients/per site

D-21 Study : Duration

- Each Patient: 54 weeks
- Study : Approximately 37 months

D-21 Study: Reporting Status

- Reporting status: On - time
- 18-month report submitted on January 9, 2007

D-21 Study : Progress

- Study: On- time
- Number of active sites 26
- Number of enrolled patients 89
- Number of implanted patients 51

D-21 Study - January 5, 2007 status

Sites/Patients	# Planned	# Actual
Initiated sites	30	26
Declining sites	-	21
Enrolled patients	85-115	89
Withdrawn patients	-	5
Active patients	85 - 115	84
Implanted Patients	-	51

D-21 Study - 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	-	1
Wound infection	0	1
Chest pain	0	1
Death (MV accident)	0	1
Carcinoma (thyroid)	0	1

TRD Registry : Objective

- To follow the clinical course and outcomes for patients with TRD, treated with and without adjunctive VNS therapy

TRD Registry : Design

- Long-term, prospective, observational, multi-center, patient outcome registry to collect data in patients with TRD.

TRD Registry : Patients/Sites

- Minimum 1000 TRD patients receiving VNS Therapy
- Approximately 1000 TRD patients not receiving the VNS Therapy

TRD Registry: Follow-up/Duration

- VNS Therapy patients: 60 months
- 35% randomly selected non-VNS therapy patients : 60 months
- 65% non – VNS patients: at least 24 months
- Potential registry duration: 9 years

TRD Registry : Reporting Status

- Reporting Status: On - time
- 18- month report submitted on January 9, 2007

TRD Registry: Progress

- Study : On-time
- Number of initiated sites 32
- Number of active patients 264
- Number of VNS implanted patients 223
- Number of non-VNS patients 41

TRD Registry Study: January 5, 2007 status

Sites/Patients	# Planned	# Actual
Initiated sites	35	32
Declining sites	-	87
Enrolled patients	200- 450	267
Withdrawn patients	-	3
Active patients	200-450	264
VNS		223
Non-VNS		41

Areas of Concern

- High cost of procedure
- Reimbursement difficulties
- Large number of declining sites
- Impact on sites/patients enrollment

Cyberonics' strategies to ensure timely enrollment

- Working with clinical sites on IRB applications
- Assisting in claim resolutions
- Listing the clinical study on www.clinicaltrials.gov
- Aggressively working with insurance companies
- Submitting the request to CMS for coverage with evidence development
- Providing reimbursement for the subset of patients
- Working closely with FDA

FDA's Strategies

General

- PAS Guidance issued (December 21, 2006)
- PAS Tracking System
- PAS Web-posting

Specific

- Working interactively with Cyberonics
- 6 – month review intervals
- 60 days FDA response commitment