

VNS Therapy™ System Post-Approval Studies Update

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Outline

- Approval Summary
- Post-approval Study Protocols
- Post-approval Study Progress
- Areas of Concern
- Evolving Strategies

FDA Decisions

- Approvable Date: February 2, 2005
 - Submission of complete protocols for:
 - 1 year randomized dose ranging study
 - 5 year observational registry study
 - Revised Physician and Patient labeling
 - Resolution of GMP inspection issues
 - Resolution of Bioresearch Monitoring issues
- Approval Date: July 15, 2005

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 of FDA PAS protocol approval
November 8, 2005
- P970003/S59 Randomization Comparison of Outcomes in Patients with Treatment-Resistant Depression who Receive VNS Therapy Administered at Different Amounts of Electrical Charge (**D-21 Study**)
- P970003/S60 Treatment-Resistant Depression (**TRD**) Registry

PAS Reporting Requirements

- Six – month reporting schedule
- General information
 - Sponsor, product, submission type
- Study information
 - Status
 - Changes
 - Interpretation

D - 21 Study: Objective

- To compare the safety and effectiveness of the VNS Therapy System administered at different amounts of electrical charge for the treatment of 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.
- Effectiveness and safety endpoints
- 460 patients
- 30 clinical sites
- Maximum 25 patients/per site
- Each Patient: 54 weeks
- Study : Approximately 37 months

D-21 Study - Period ending December 31, 2006

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Withdrawn patients	-	5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

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 registry
- 1000 TRD patients receiving VNS Therapy and 1000 TRD patients without the VNS
- 100 sites
- Follow-up :
 - VNS Therapy Patients: 60 months
 - 35% randomly selected non-VNS therapy patients : 60 months
 - 65% non – VNS patients: 24 months

TRD Registry Study: Period ending December 31, 2006

Sites/Patients	# Planned	# Actual
Initiated sites	35	46
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 issues
- Large number of declining sites
- Impact on sites/patients enrollment

Cyberonics' strategies to ensure timely enrollment

- Working with clinical sites on IRB applications
- Listed the D-21 study on www.clinicaltrials.gov
- Assisting in claim resolutions
- Working with insurance companies
- Submitted the request to CMS for a national coverage decision
- Covered the implantation cost and provided the device for up to 250 patients
- Working closely with FDA epidemiologists

FDA's General PAS Strategies

- PAS Guidance (December 21, 2006)
- PAS Tracking System
- PAS Web-posting
- Working interactively with sponsors
- 6 – month review intervals
- 60 days FDA response commitment
- Updates to the Advisory Panel