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# *Depression Physician's Manual*

**VNS Therapy™ Pulse**
**Model 102 Generator**

***and***

**VNS Therapy™ Pulse Duo**
**Model 102R Generator**

**July 2005**

**Caution:** U.S. federal law restricts this device to sale by or on the order of a physician.

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## 1-D. BRIEF DEVICE DESCRIPTION

Please refer to the Brief Device Description section in the 102/102R Epilepsy Physician's Manual for a brief description of the components of the VNS Therapy System, compatibility, and symbols and definitions used in this manual.

## 2-D. INTENDED USE / INDICATIONS

The VNS Therapy System is indicated for the 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 adequate antidepressant treatments*.

*See glossary for a definition of terms.

## 3-D. CONTRAINDICATIONS

⚠ The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.

⚠ Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (hereafter referred to as diathermy) on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

Energy delivered by diathermy may be concentrated into or reflected by implanted products such as the VNS Therapy System. This concentration or reflection of energy may cause heating.

Testing indicates that diathermy can cause heating of the VNS Therapy System well above temperatures required for tissue destruction. The heating of the VNS Therapy System resulting from diathermy can cause temporary or permanent nerve or tissue or vascular damage. This damage may result in pain or discomfort, loss of vocal cord function, or even possibly death if there is damage to blood vessels.

Because diathermy can concentrate or reflect its energy off any size-implanted object, the hazard of heating is possible when any portion of the VNS Therapy System remains implanted, including just a small portion of the Lead or electrode. Injury or damage can occur during diathermy treatment whether the VNS Therapy System is turned "ON" or "OFF".

Diathermy is further prohibited because it may also damage the VNS Therapy System components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. All risks associated with surgery or loss of therapy would then be applicable.

Advise your patients to inform all their health care professionals that they should not be exposed to diathermy treatment.

## 4-D. WARNINGS

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System physician's manuals.

⚠ This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

⚠ **Not curative**
Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression. Patients should be counseled to understand that individual results will likely vary. Beneficial results might not become evident for months. Most patients will continue to require antidepressant medications and/or electroconvulsive therapy (ECT) in addition to VNS Therapy.

⚠ **Unapproved uses**
The safety and efficacy of the VNS Therapy System have not been established for uses outside the "Intended Use/Indications" section of the physician's manuals (Depression and Epilepsy), including (but not limited to) patients with:

- Acute suicidal thinking or behavior
- History of schizophrenia, schizoaffective disorder or delusional disorders
- History of rapid cycling bipolar disorder
- History of previous therapeutic brain surgery or CNS injury
- Progressive neurological diseases other than epilepsy
- Cardiac arrhythmias or other abnormalities
- History of dysautonomias
- History of respiratory diseases or disorders, including dyspnea and asthma
- History of ulcers (gastric, duodenal, or other)
- History of vasovagal syncope
- Only one vagus nerve
- Other concurrent forms of brain stimulation
- Pre-existing hoarseness

⚠ **Worsening depression/suicidality**
Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes, including either increases or decreases in the stimulation parameters or concomitant treatments. Consideration should be given to changing the therapeutic regimen of VNS Therapy or concomitant treatments, including possibly discontinuing VNS Therapy or the concomitant therapy, in patients whose depression is

persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

⚠ **Dysfunctional cardiac conduction systems**
The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Evaluation by a cardiologist is recommended if the family history, patient history, or electrocardiogram suggests an abnormal cardiac conduction pathway. Serum electrolytes, magnesium, and calcium should be documented before implantation. Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

⚠ It is important to follow recommended implantation procedures and intraoperative product testing described in this manual. During the intraoperative Lead Test, infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a Lead Test or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac

arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm) or a clinically significant change in heart rate during a Lead Test at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during VNS Therapy System implantation.

⚠ **Swallowing difficulties**
Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Appropriate aspiration precautions should be taken for such patients.

⚠ **Dyspnea or shortness of breath**
Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea and should have their respiratory status evaluated prior to implantation and monitored following initiation of stimulation.

⚠ **Obstructive sleep apnea**
Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. It is

recommended that patients being considered for VNS Therapy who demonstrate signs or symptoms of OSA, or who are at increased risk for developing OSA, should undergo the appropriate evaluation(s) prior to implantation.

⚠ **Device malfunction**
Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

⚠ **MRI**
Patients with the VNS Therapy System or any part of the VNS Therapy System implanted should not have full body MRI. Additional surgery may be required to remove the VNS Therapy system if full body MRI is required. See "**Magnetic resonance imaging**" in this manual for details.

⚠ **Excessive stimulation**
**Note: Use of the Magnet to activate stimulation is not recommended for patients with depression. The Magnet Mode output current should remain at 0.0mA for patients with depression.**

Excessive stimulation at an excess duty cycle (that is, one that occurs when "ON" time is greater than "OFF" time) has resulted in degenerative nerve

damage in laboratory animals. An excess duty cycle can be produced by continuous or frequent magnet activation (> 8 hours), as determined by animal studies. Do not stimulate at these combinations of ranges.

⚠ **Device manipulation**
Patients who manipulate the Pulse Generator and Lead through the skin (Twiddler's Syndrome) may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve. Patients should be warned against manipulating the Pulse Generator and Lead.

## 5-D. PRECAUTIONS

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System physician's manuals.

⚠ **Appropriate physician training** is very important.

- **Prescribing physicians** should be experienced in the diagnosis and treatment of depression and should be familiar with the programming and use of the VNS Therapy System.
- **Physicians who implant the VNS Therapy System** should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System. (See the "Physician Training/Information" section of the Physician's Manual.)

⚠ **Use during pregnancy**
The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. There are no adequate and well-controlled studies of VNS Therapy in pregnant women. Reproduction studies have been performed using female rabbits stimulated with the commercially available VNS Therapy System at stimulation dose settings similar to those used for humans. These animal studies have revealed no evidence of impaired fertility or harm to the fetus due to VNS Therapy. Because animal reproduction studies are not always predictive of human

response and animal studies cannot address developmental abnormalities, VNS Therapy should be used during pregnancy only if clearly needed. Although the operating ranges of the VNS Therapy System and fetal monitors are dissimilar and no interaction would be expected, testing has not been performed. Therefore, the potential may exist for interaction between the VNS Therapy System and fetal monitoring systems.

⚠ The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating the **left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve.** The safety and efficacy of the VNS Therapy System have not been established for stimulation of the right vagus nerve or of any other nerve, muscle, or tissue.

⚠ It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the operation.

Frequent irrigation of both incision sites with generous amounts of bacitracin or equivalent solution should be performed prior to closure. To minimize scarring, these incisions should be closed with cosmetic closure techniques. Also, antibiotics should be administered postoperatively at the discretion of the physician.

⚠ **Effects on other medical devices**
The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillator therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device. Furthermore, when the VNS Therapy System and another stimulator are implanted in the same patient, the two stimulators should be placed at least four inches (10 centimeters) apart to avoid communication interference. Users should refer to the product labeling for the concurrent device to determine if there are additional precautions that should be observed.

⚠ **Reversal of Lead polarity has been associated with an increased chance of bradycardia** in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that leads with dual connector pins are correctly inserted (white marker band/serial number to + connection) into the lead receptacle(s).

⚠ The patient can use a neck brace for the first week to help ensure proper lead stabilization.

⚠ **Do not program the VNS Therapy System to an ON or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.** Failure to observe this precaution may result in patient discomfort or adverse events.

⚠ Do not use frequencies of 5 Hz or below for long-term stimulation. Because these frequencies generate an electromagnetic trigger signal, their use results in excessive battery depletion of the implanted Pulse Generator and, therefore, should be used for short periods of time only.

⚠ Resetting the Pulse Generator turns the device OFF (output current = 0.0 mA), and all device history information is lost. The device history information should be printed out before resetting.

⚠ Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.

### *5.1-D. Sterilization, Storage, and Handling*

Please refer to the Sterilization, Storage, and Handling section in the 102/102R Epilepsy Physician's Manual for information on sterilization, storage, and handling of the VNS Therapy System.

### *5.2-D. Lead Evaluation and Connection*

Please refer to the Lead Evaluation and Connection section in the 102/102R Epilepsy Physician's Manual for information on evaluating and connecting the Lead component of the VNS Therapy System.

## *5.3-D. Environmental and Medical Therapy Hazards*

⚠ Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. (For examples, see the "Other Environmental Hazards" below.) If a Pulse Generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

### 5.3.1-D. Hospital and Medical Environments

⚠ VNS Therapy System operation **should always** be **checked** by performing device diagnostics after any of the procedures mentioned in this manual. Additional precautions for these procedures are described below.

⚠ **For clear imaging, patients may need to be specially positioned for mammography procedures** because of the location of the Pulse Generator in the chest. (Most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation.)

⚠ **Therapeutic radiation** may damage the Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage

determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately.

⚠ **External defibrillation** may damage the Pulse Generator. Attempt to minimize current flowing through the Pulse Generator and Lead system by following these precautions:

- Position defibrillation paddles perpendicular to the Pulse Generator and Lead system and as far from the Pulse Generator as possible.
- Use the lowest clinically appropriate energy output (watt-seconds).
- Confirm Pulse Generator function after any internal or external defibrillation.

⚠ Use of electrosurgery (electrocautery or radio frequency (RF) ablation devices) may damage the Pulse Generator. Attempt to minimize the current flowing through the Pulse Generator and Lead system by following these precautions:

- Position the electrosurgery electrodes as far as possible from the Pulse Generator and Lead.
- Avoid electrode placement that puts the Pulse Generator or Lead in the direct path of current flow or within the part of the body being treated.
- Confirm that the Pulse Generator functions as programmed after electrosurgery.

⚠ **Magnetic resonance imaging** (MRI) should not be performed with a magnetic resonance body coil in the transmit mode. The heat induced in the Lead by an MRI body scan can cause injury.

If an MRI should be done, use only a transmit and receive type of head coil. Magnetic and RF fields produced by MRI may change the Pulse Generator settings (change to reset parameters) or activate the device. Stimulation has been shown to cause the adverse events reported in the "Adverse Events" section of this manual. MRI compatibility was demonstrated using a 1.5T General Electric Signa Imager with a Model 100 only. The Model 102 and Model 102R are functionally equivalent to the Model 100. Testing on this imager as performed on **a phantom[1] indicated that the following Pulse Generator and MRI procedures can be used safely without adverse events:**

- Pulse Generator output programmed to 0 mA for the MRI procedure, and afterward, retested by performing the Lead Test diagnostics and reprogrammed to the original settings
- Head coil type: transmit and receive only
- Static magnetic field strength: ≤ 2.0 tesla
- Specific absorption rate (SAR): < 1.3 W/kg for a 154.5-lb (70-kg) patient
- Time-varying intensity: < 10 tesla/sec

[1] A phantom is a material resembling a body in mass, composition, and dimensions that is used to measure absorption of radiation.

Use caution when other MRI systems are used, since adverse events may occur because of different magnetic field distributions. Consider other imaging modalities when appropriate.

⚠ Procedures in which the RF is transmitted by a body coil should not be done on a patient who has the VNS Therapy System. Thus, protocols must not be used that utilize local coils that are RF-receive only, with RF-transmit performed by the body coil. Note that some RF head coils are receive-only, and that most other local coils, such as knee and spinal coils, are also RF receive-only. **These coils must not be used in patients with the VNS Therapy System.**

⚠ **Extracorporeal shockwave lithotripsy** may damage the Pulse Generator. If therapeutic ultrasound is required, avoid positioning the area of the body where the Pulse Generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the Pulse Generator output to 0 mA for the treatment, and then after therapy, reprogram the Pulse Generator to the original parameters.

⚠ If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit) either the Pulse Generator output should be set to 0 mA or function of the Pulse Generator should be monitored during initial stages of treatment.

⚠ **Therapeutic ultrasound.** Routine therapeutic ultrasound could damage the Pulse Generator and may be inadvertently concentrated by the device, causing harm to the patient.

### 5.3.2-D. Home Occupational Environments

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft-prevention devices, and metal detectors are not expected to affect the Pulse Generator. Similarly, most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation. However, because of their higher energy levels, sources such as transmitting antennas may interfere with the VNS Therapy System. It is suggested that the Pulse Generator be moved away from equipment—typically at least six feet (1.8 meters)—that may be causing interference.

⚠ The patient should seek medical advice before entering environments that are protected by a warning notice preventing entry by patients implanted with a cardiac pacemaker or defibrillator.

### 5.3.3-D. Cellular Phones

Based on testing to date, cellular phones have no effect on Pulse Generator operation. Unlike an implanted pacemaker or defibrillator, the Pulse Generator does not sense physiologic signals.

### 5.3.4-D. Other Environmental Hazards

⚠ Strong magnets, hair clippers, vibrators, loudspeaker magnets, Electronic Article Surveillance (EAS) System tag deactivators, and other similar electrical or electro-mechanical devices, which may have a strong static or pulsing magnetic field, can cause accidental magnet activation. Patients should be cautioned to keep such devices away from the Pulse Generator, typically at least six inches (15 centimeters) away.

### 5.3.5-D. Programming Software

The Pulse Generator can be programmed using the Model 250 Software, Version 4.6, Version 6.1, Version 7.0 or higher. The Software should be used on a laptop or handheld computer dedicated only to programming the VNS Therapy System. (For more information, see the Model 250 Software Physician's Manual for Version 4.6, Version 6.1, Version 7.0, or higher, including a list of computers that have been qualified for use with this Software.)

### 5.3.6-D. Pulse Generator and EMI Effects on Other Devices

During stimulation, the Pulse Generator may interfere with devices operating in the 30 kHz to 100 kHz range, such as pocket transistor radios and hearing aids. This interference is a theoretical possibility, and no effects on hearing aids have yet been reported, although the Pulse Generator can interfere with a transistor radio when held directly over one. No specific testing has been done to date, and no definite information on effects is available.

The Pulse Generator should be moved—typically at least 6 feet (1.8 meters)—away from equipment with which it may be interfering.

Programming or interrogating the Pulse Generator may momentarily interfere with other sensitive electronic equipment nearby. The Pulse Generator is not expected to trigger airport metal detectors or theft-protection devices that are closer than about 6 feet (1.8 meters).

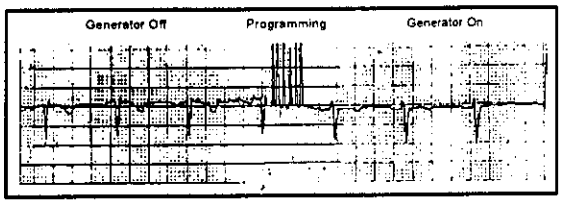
⚠ The Pulse Generator may affect the operation of **other implanted devices,** such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate Pulse Generator responses. If the Pulse Generator patient requires concurrent implantable pacemaker and/or defibrillator therapy, careful programming of each system is necessary to optimize the patient's benefit from each device.

⚠ The magnet provided for activation or inhibition of the Pulse Generator may damage **televisions, computer disks, credit cards, and other items** affected by strong magnetic fields.

### 5.3.7-D. Effects on ECG Monitors

Pulse Generator data communication produces an ECG artifact, an example of which is shown in the ECG tracings in Figure D-1.

**Figure D-1. ECG Artifact Produced by Pulse Generator Communication**




### 5.3.8-D. Pulse Generator Disposal

⚠ Do not incinerate the Pulse Generator, because it can explode if subjected to incineration or cremation temperatures.

⚠ Return all explanted Pulse Generators to Cyberonics for examination and safe disposal.

⚠ Do not implant an explanted Pulse Generator in another patient, because sterility, functionality, and reliability cannot be ensured.

## 6-D. CLINICAL STUDIES — SAFETY

Except where noted otherwise, the safety information presented in this section derives from the pivotal (D-02) study. The D-02 study of VNS Therapy consisted of both an acute and a long-term phase to collect data regarding the safety and efficacy of VNS Therapy as an adjunctive treatment for persons with chronic or recurrent treatment-resistant depression.

### *6.1-D. Adverse events*

The number (and percentage) of subjects reporting an adverse event during the 0-3 month period and during the 9-12 month period of the pivotal (D-02) study is depicted in Table D-1 for the most commonly reported adverse events. Adverse events were coded using the COSTART 5 dictionary. Note that some subjects may have reported multiple events.

**Table D-1. Adverse Events Reported During VNS Therapy at 0-3 Months and 9-12 Months (D-02)**

| Adverse Event | 0-3 Months (N=232) | 9-12 Months (N=209) |
|---|---|---|
| Voice Alteration | 135 (58.2%) | 113 (54.1%) |
| Increased Cough | 55 (23.7%) | 13 (6.2%) |
| Neck Pain | 38 (16.4%) | 27 (12.9%) |
| Dyspnea | 33 (14.2%) | 34 (16.3%) |
| Dysphagia | 31 (13.4%) | 9 (4.3%) |
| Paresthesia | 26 (11.2%) | 9 (4.3%) |
| Laryngismus | 23 (9.9%) | 10 (4.8%) |
| Pharyngitis | 14 (6.0%) | 11 (5.3%) |
| Nausea | 13 (5.6%) | 4 (1.9%) |
| Pain | 13 (5.6%) | 13 (6.2%) |
| Headache | 12 (5.2%) | 8 (3.8%) |
| Insomnia | 10 (4.3%) | 2 (1.0%) |
| Palpitation | 9 (3.9%) | 6 (2.9%) |
| Chest Pain | 9 (3.9%) | 4 (1.9%) |
| Dyspepsia | 8 (3.4%) | 4 (1.9%) |
| Hypertonia | 6 (2.6%) | 10 (4.8%) |
| Hypesthesia | 6 (2.6%) | 2 (1.0%) |
| Anxiety | 5 (2.2%) | 6 (2.9%) |
| Ear Pain | 5 (2.2%) | 6 (2.9%) |
| Eructation | 4 (1.7%) | 0 |
| Diarrhea | 4 (1.7%) | 2 (1.0%) |
| Dizziness | 4 (1.7%) | 3 (1.4%) |
| Incision Site Reaction | 4 (1.7%) | 2 (1.0%) |
| Asthma | 4 (1.7%) | 3 (1.4%) |
| Device Site Reaction | 4 (1.7%) | 0 |
| Device Site Pain | 4 (1.7%) | 2 (1.0%) |
| Migraine Headache | 4 (1.7%) | 2 (1.0%) |

It is important to note that subjects often had comorbid illnesses and almost all study subjects were also receiving antidepressant and other drugs that could have contributed to these events.

### 6.1.1-D. Discontinuation Due to Adverse Events

In the feasibility (D-01) study, no discontinuations were related to adverse events attributed to VNS Therapy or the implant procedure. By the time all continuing subjects in the pivotal (D-02) study had at least 1 year of VNS Therapy, 3% (8/235) of the subjects had discontinued VNS Therapy for an adverse event-related reason. The reasons for these eight discontinuations included one case each of suicide, implant-related infection necessitating device removal, hoarseness, lightheadedness, post-operative pain, chest and arm pain, sudden death (of unknown cause), and worsening depression (reported by the investigator as an adverse event rather than as lack of efficacy).

## *6.2-D. Serious Adverse Events (SAEs)*

### 6.2.1-D. Serious Adverse Events (SAEs)

The SAEs described in this section are based on investigator reports from the pivotal (D-02) study from study initiation through the data cutoff date for submission; the data cutoff date included the entire period of evaluation for subjects who did not complete 12 months of VNS Therapy and included a minimum of 12 months of evaluation during VNS Therapy for all subjects who continued the study for 12 months or longer.

During the pivotal (D-02) study, 12 SAEs were considered related to the implant procedure (wound infection, asystole, bradycardia, syncope, abnormal thinking, vocal cord paralysis , aspiration pneumonia, voice alteration, device site reaction [two reports], acute renal failure, and urinary retention). During the acute phase of the D-02 study, investigators did not report any

SAE to be related to stimulation. During the long-term phase of the D-02 study, eight SAEs were considered at least possibly related to stimulation (sudden death of unknown cause, syncope (two reports), dizziness, a manic depressive reaction in a subject with bipolar disorder, hemorrhage GI, paresthesia, and an incident of worsening depression. Table D-2 displays all the SAEs reported during the D-02 study prior to the data cutoff date, regardless of relationship to implantation or stimulation.

**Table D-2. Serious Adverse Events Reported in Study D-02, Regardless of Relationship to Implantation or Stimulation**

| Event | Acute (N=235) | | Long Term (N=233) | |
|---|---|---|---|---|
| | Number of Events Treatment (N=119) /Sham (N=116) | Number of Subjects | Number of Events | Number of Subjects |
| Worsening Depression | 5/7 | 11 | 62 | 31 |
| Suicide Attempt | 0 | 0 | 7 | 6 |
| Syncope | 0 | 0 | 4 | 3 |
| Dehydration | 1/1 | 2 | 1 | 1 |
| Wound Infection | 1/0 | 1 | 1 | 1 |
| Cholecystitis | 0/1 | 1 | 1 | 1 |
| Gastrointestinal Disorder | 0 | 0 | 2 | 2 |
| Abnormal Thinking | 1/0 | 1 | 1 | 1 |
| Convulsion | 0 | 0 | 2 | 2 |
| Device Site Reaction | 2/0 | 2 | 0 | 0 |
| Pneumonia | 0/1 | 1 | 0 | 0 |
| Abdominal Pain | 0 | 0 | 1 | 1 |
| Accidental Injury | 0 | 0 | 1 | 1 |
| Chest Pain | 0 | 0 | 1 | 1 |
| Overdose | 0 | 0 | 1 | 1 |
| Peritonitis | 0 | 0 | 1 | 1 |
| Sudden Unexplained Death | 0 | 0 | 1 | 1 |

| Event | Acute (N=235) | | Long Term (N=233) | |
|---|---|---|---|---|
| | Number of Events Treatment (N=119) /Sham (N=116) | Number of Subjects | Number of Events | Number of Subjects |
| Suicide | 1/0 | 1 | 0 | 0 |
| Surgical Procedure | 0 | 0 | 1 | 1 |
| Asystole | 1/0 | 1 | 0 | 0 |
| Bradycardia | 1/0 | 1 | 0 | 0 |
| Cholelithiasis | 0 | 0 | 1 | 1 |
| Constipation | 0 | 0 | 1 | 1 |
| Myasthenia | 0/1 | 1 | 0 | 0 |
| Confusion | 1/0 | 1 | 0 | 0 |
| Dizziness | 0 | 0 | 1 | 1 |
| Drug Dependence | 0 | 0 | 1 | 1 |
| Manic Depression | 0 | 0 | 1 | 1 |
| Somnolence | 0 | 0 | 1 | 1 |
| Vocal Cord Paralysis | 0/1 | 1 | 0 | 0 |
| Breast Cancer | 0 | 0 | 1 | 1 |
| Aspiration Pneumonia | 1/0 | 1 | 0 | 0 |
| Voice Alteration | 0/1 | 1 | 0 | 0 |
| Acute Renal Failure | 0/1 | 1 | 0 | 0 |
| Enlarged Uterine Fibroid | 0 | 0 | 1 | 1 |
| Urinary Retention | 1/0 | 1 | 0 | 0 |

### 6.2.2-D. Deaths

Four deaths occurred during the pivotal (D-02) study: one after the subject had given consent, but before the subject was implanted; the second, a suicide; the third, a death of unknown cause; and the fourth, a subject who developed multi-organ failure.

#### 6.2.3-D. Unanticipated Adverse Device Effects

Two events in the pivotal (D-02) study met criteria for an unanticipated adverse device effect (UADE)—see Glossary for definition. Both these events were non-specific complications of surgery related to the implant procedure and occurred before stimulation began. One UADE was an episode of acute renal failure thought to be secondary to antibiotic administration, and the other was an episode of altered mental status thought to be due to perioperative narcotic administration.

## *6.3-D. Safety Considerations Specific to Depressed Patients*

Two specific safety concerns in the use of all antidepressant therapies are the precipitation of manic or hypomanic episodes and the possible effect of antidepressant therapy on suicidal ideation and behavior.

### 6.3.1-D. Antidepressant Treatments and Manic or Hypomanic Reaction

Although patients with bipolar disorder experience manic episodes as the cardinal feature of their disorder, effective antidepressant therapies themselves can occasionally precipitate a manic or hypomanic episode. Antidepressant therapies can also occasionally precipitate a manic or hypomanic episode in patients without a prior history of mania who are being treated for a major depressive episode.

#### *6.3.1.1-D. Manic Reactions*

In the pivotal (D-02) study, six hypomanic or manic reactions were identified according to DSM IV criteria or the Young Mania Rating Scale (YMRS). Five were observed in subjects with a known history of prior

hypomanic or manic episodes. One of the events was considered serious and the subject was hospitalized.

### 6.3.2-D. Suicidal Ideation, Suicide Attempts, Suicide, and Worsened Depression

Suicidal ideation was analyzed by examining the $HRSD_{24}$ Item 3 scores. At 12 months of VNS Therapy, 90% of the subjects in the pivotal (D-02) study showed either improvement (56%) or no change (34%) in their Item 3 scores. During the acute D-02 study, 2.6% of the sham subjects and 1.7% of the stimulation subjects increased their Item 3 score by 2 or more points, indicative of an increase in suicidal ideation. During the long-term D-02 phase, 2.8% of the subjects had an increase in their Item 3 score by at least 2 points at 12 months compared to baseline. In a non-randomized control group of subjects treated with standard antidepressant therapies without VNS Therapy (the D-04 study population), 1.9% of the subjects had an increase of at least 2 points. Based on the occurrence of any increase in Item 3 score from baseline to 12 months, 10% of the D-02 subjects had an increase compared to 11% of the D-04 population. Conversely, 27% of the D-02 subjects decreased their score by at least 2 points at 12 months compared to baseline, whereas only 9% of the D-04 subjects did.

Suicide attempts and completed suicides in the D-02 and D-04 studies are shown in Table D-3. As noted above, one subject committed suicide in the acute phase and six attempted suicide during the long-term phase of the D-02 study (N = 235). One of the six subjects noted in the long-term phase attempted suicide twice. Although safety data were not prospectively collected for the D-04 study, the health care utilization form documented suicide attempts.

Three suicide attempts were reported for the D-04 study through the first year of the study (N=124).

**Table D-3. Suicide Attempt and Suicide Rates**

| | Number of Patients | Patient Years | Suicide Attempts/ Patient Years | Suicide/ Patient Years |
|---|---|---|---|---|
| D-02 | 235 | 502 | 2.4% | 0.2% |
| D-04 | 124 | 118 | 2.5% | 0.0% |

In the acute phase of the D-02 study, there were 12 reports of worsening depression, 5 in the stimulation group (4 of 119 subjects) and 7 in the sham group (7 of 116 subjects). One of the treatment-group reports occurred prior to stimulation initiation. Following acute phase exit and during the long-term phase of stimulation, 62 events were reported in 31 subjects. The number of episodes of worsening depression per subject ranged from 1 to 6. Although specific rates of worsening depression (and other safety endpoints) were not collected during the D-04 study, "hospitalizations for psychiatric illness," which might be a reasonable surrogate for worsening depression, were recorded. The rate of this event was 0.237 events per patient-year in the D-04 group compared to 0.293 events of worsening depression per patient-year in the D-02 group.

## *6.4-D. Adverse Event (AE) Relationship to VNS Therapy and Duration of Events*

The pivotal (D-02) study investigators determined whether an adverse event (AE) was possibly, probably, or definitely related to implantation of, or stimulation by, the VNS Therapy Pulse Generator and Lead.

### 6.4.1-D. Adverse Events Related to Implantation

Because all eligible study subjects in the pivotal (D-02) study were implanted with the VNS Therapy System device, no control was available to assess whether an adverse event was related to the surgery. Investigators, therefore, determined which adverse events were related to implantation. The events reported as related to implantation and occurring in at least 10% of the subjects who received VNS Therapy System implants in the pivotal (D-02) study were device site pain, device site reaction, incision pain, dysphagia, hypesthesia, pharyngitis, voice alteration, and incision site reaction. The complete list of implantation-related adverse events is shown in Table D-4 and Table D-5.

**Table D-4. Implantation-Related Adverse Events Occurring in Greater Than or Equal To 5% of Subjects During the Acute Phase of the Pivotal (D-02) Study**

| | D-02 Acute Phase Incidence of Surgery-Related AEs (n=235) |
|---|---|
| Body as a Whole | |
| Incision Pain | 36% |
| Device Site Pain | 23% |
| Device Site Reaction | 14% |
| Headache | 8% |
| Neck Pain | 7% |
| Pain | 7% |
| Digestive System | |
| Dysphagia | 11% |
| Nausea | 9% |
| Nervous System | |
| Hypesthesia | 11% |
| Paresthesia | 6% |
| Respiratory System | |
| Voice Alteration | 33% |
| Pharyngitis | 13% |
| Dyspnea | 9% |
| Cough Increased | 6% |
| Skin and Appendages | |
| Incision Site Reaction | 29% |

**Table D-5. Implantation-related Adverse Events Occurring in Less Than 5% of Subjects in Acute Phase - Pivotal (D-02) Study**

| |
|---|
| Body as a Whole |
| Abdominal Pain, Allergic Reaction, Anaphylactic Reaction, Asthenia, Back Pain, Chest Pain, Chills, Fever, Infection, Injection Site Pain, Neck Rigidity, Photosensitivity Reaction, Surgical Injury, Viral Infection, Wound Infection |
| Cardiovascular System |
| Arrhythmia, Asystole, Bradycardia, Hemorrhage, Migraine, Palpitation, Syncope, Tachycardia |
| Digestive System |
| Anorexia, Constipation, Diarrhea, Dyspepsia, Flatulence, Gastrointestinal Disorder, Vomiting |
| Endocrine System |
| Thyroid Disorder |
| Hemic and Lymphatic System |
| Ecchymosis, Lymphadenopathy |
| Metabolic and Nutritional Disorders |
| Edema, Hyperglycemia, Peripheral Edema |
| Musculoskeletal |
| Arthralgia, Joint Disorder, Myalgia, Myasthenia |
| Nervous System |
| Abnormal Dreams, Agitation, Ataxia, Dizziness, Hypertonia, Insomnia, Nervousness, Neuralgia, Neuropathy, Thinking Abnormal, Tremor, Vasodilatation, Vocal Cord Paralysis |
| Respiratory System |
| Aspiration Pneumonia, Asthma, Atelectasis, Bronchitis, Hiccup, Hypoxia, Laryngismus, Laryngitis, Lung Disorder, Respiratory Disorder, Rhinitis, Sinusitis, Sputum Increased |
| Skin and Appendages |
| Application Site Reaction, Maculopapular Rash, Pruritus, Rash, Sweating |
| Special Senses |
| Ear Disorder, Ear Pain, Tinnitus |
| Urogenital |
| Acute Kidney Failure, Dysuria, Metrorrhagia, Urinary Retention |

### 6.4.2-D. Duration of Implant-Related Adverse Events

As can be seen in Table D-6, many of the individual incidences of the most common implantation-related AEs resolved within 30 days. Hypesthesia (generally described as a localized numbness) and voice alteration, however, tended to be more persistent in some individuals. For example, in 17 of 24 reports of implantation-related hypesthesia, the event continued beyond 3 months. Hypesthesia would be an expected side effect of nerve injury during surgery. The persistence of voice alteration in some subjects is difficult to assess because it could represent surgical injury to the innervation of the larynx, but vagus nerve stimulation itself can cause voice alteration.

**Table D-6. D-02 Acute Phase Duration of Treatment-Emergent Adverse Events Related to Implantation Reported by More Than 10% of Subjects**

| Body System | Preferred Term | Duration to Resolution of Event in Days by all Implanted Subjects | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 – 7 Days | 8 – 14 Days | 15 – 30 Days | 31 – 60 Days | 61-90 Days | >90 Days |
| | | Total N = 235 through 30 days, 234 for 31 to 90, 233 for >90 days<br>Number within each box indicates number of subjects whose event resolved within the days shown (i.e. 27 subjects had the event of device site pain resolve within 7 days) | | | | | |
| Body as a Whole | Device Site Pain | 27 | 4 | 9 | 9 | 3 | 4 |
| | Device Site Reaction | 5 | 5 | 8 | 9 | 2 | 8 |
| | Incision Pain | 28 | 18 | 21 | 10 | 3 | 6 |
| Digestive System | Dysphagia | 2 | 5 | 9 | 5 | 2 | 5 |
| Nervous System | Hypesthesia | 0 | 0 | 3 | 2 | 2 | 17 |
| Respiratory System | Pharyngitis | 10 | 8 | 10 | 2 | 0 | 1 |
| | Voice Alteration | 11 | 7 | 22 | 17 | 3 | 21 |
| Skin and Appendages | Incision Site Reaction | 19 | 16 | 24 | 16 | 2 | 14 |

### 6.4.3-D. Stimulation-related Adverse Events

Among AEs judged by investigators to be stimulation-related in the D-02 study acute phase treatment group, seven events occurred at a frequency of 10% or greater: voice alteration (55%), cough increased (24%), dyspnea (19%), neck pain (16%), dysphagia (13%), laryngismus (11%), and paresthesia (10%).

Table D-7 and Table D-8 list stimulation-related adverse events that occurred during the acute phase of the pivotal (D-02) study.

**Table D-7. Stimulation-Related Adverse Events Occurring in Greater Than or Equal To 5% of Subjects in Treatment Versus Control, Acute Phase - Pivotal (D-02) study**

| | D-02 Treatment (n=119) | D-02 Sham-control * (n=116) |
|---|---|---|
| Body as a Whole | | |
| Incision Pain | 6 (5%) | 3 (3%) |
| Neck Pain | 19 (16%) | 1 (<1%) |
| Digestive System | | |
| Dysphagia | 15 (13%) | 0 (0%) |
| Nausea | 8 (7%) | 1 (<1%) |
| Nervous System | | |
| Paresthesia | 12 (10%) | 3 (3%) |
| Respiratory System | | |
| Cough Increased | 28 (24%) | 2 (2%) |
| Dyspnea | 23 (19%) | 2 (2%) |
| Laryngismus | 13 (11%) | 0 (0%) |
| Pharyngitis | 9 (8%) | 1 (<1%) |
| Voice Alteration | 65 (55%) | 3 (3%) |

*Note: These subjects were not receiving stimulation during this phase.

**Table D-8. Stimulation-related Adverse Events Occurring in Less Than 5% of Subjects in the Treatment Group, Acute Phase - Pivotal (D-02) Study**

| |
|---|
| Body as a Whole |
| Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Headache, Neck Rigidity, Pain |
| Cardiovascular System |
| Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia |
| Digestive System |
| Anorexia, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Increased Appetite, Vomiting |
| Metabolic and Nutritional Disorders |
| Weight Gain |
| Musculoskeletal |
| Myalgia, Myasthenia |
| Nervous System |
| Abnormal Dreams, Agitation, Depression, Dizziness, Emotional Lability, Hypertonia, Hypesthesia, Insomnia, Manic Reaction, Nervousness, Sleep Disorder, Somnolence, Twitching, Vasodilatation |
| Respiratory System |
| Asthma, Hiccup, Respiratory Disorder, Rhinitis |
| Skin and Appendages |
| Incision Site Reaction |
| Special Senses |
| Ear Pain, Tinnitus |
| Urogenital |
| Amenorrhea |

### 6.4.4-D. Stimulation-related Events, Long-term Phase

Table D-9 lists stimulation-related adverse events that occurred at an incidence of ≥5% during the pivotal (D-02) study. These adverse events were observed over quarters of stimulation. Note that this table also includes observations after 24 months of treatment. Subjects are counted only once within each preferred descriptive term, e.g., neck pain, nausea, pharyngitis, and time interval. Table D-10 lists stimulation-related adverse events that occurred at an incidence of <5% during the long-term phase of the D-02 study.

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**Table D-9. Stimulation-related Adverse Events Occurring in Greater Than or Equal To 5% of Subjects By Time Intervals After Initiation of Stimulation - Pivotal (D-02) Study**

| | 0-3 Mos. n=232 | >3-6 Mos. n=225 | >6-9 Mos. n=217 | >9-12 Mos. n=209 | >12-24 Mos. n=184 |
|---|---|---|---|---|---|
| Body as a Whole | | | | | |
| Neck Pain | 16% | 11% | 14% | 13% | 15% |
| Pain | 6% | 7% | 5% | 6% | 5% |
| Headache | 5% | 4% | 4% | 3% | 3% |
| Digestive System | | | | | |
| Dysphagia | 13% | 8% | 7% | 5% | 5% |
| Nausea | 6% | 2% | 2% | 1% | 1% |
| Nervous System | | | | | |
| Paresthesia | 11% | 7% | 3% | 4% | 4% |
| Respiratory System | | | | | |
| Voice Alteration | 59% | 60% | 58% | 54% | 52% |
| Cough Increased | 24% | 10% | 8% | 7% | 4% |
| Dyspnea | 14% | 16% | 15% | 16% | 14% |
| Laryngismus | 10% | 8% | 8% | 6% | 5% |
| Pharyngitis | 6% | 4% | 4% | 5% | 4% |

**Table D-10. Stimulation-related Adverse Events Occurring in Less Than 5% of Subjects, Long-term Phase - Pivotal (D-02) Study**

| |
|---|
| Body as a Whole |
| Abdominal Pain, Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Flu Syndrome, Incision Pain, Neck Rigidity, Sudden Unexptained Death, Viral Infection |
| Cardiovascular System |
| Bradycardia, Hypotension, Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia |
| Digestive System |
| Anorexia, Colitis, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Gastritis, Gastrointestinal Disorder, Increased Appetite, Vomiting |
| Metabolic and Nutritional Disorders |
| Weight Gain, Weight Loss |
| Musculoskeletal |
| Athralgia, Joint Disorder, Myalgia |
| Nervous System |
| Abnormal Dreams, Agitation, Amnesia, Anxiety, Confusion, Depression, Dizziness, Dry Mouth, Emotional Lability, Hypertension, Hypertonia, Hypesthesia, Insomnia, Manic Reaction, Manic Depressive Reaction, Nervousness, Sleep Disorder, Somnolence, Speech Disorder, Thinking Abnormal, Tremor, Twitching, Vasodilatation, Vocal Cord Paralysis |
| Respiratory System |
| Asthma, Hiccup, Respiratory Disorder, Rhinitis, Stridor |
| Skin and Appendages |
| Incision Site Reaction, Sweating |
| Special Senses |
| Amblyopia, Deafness, Ear Pain, Eye Pain, Tinnitus |
| Urogenital |
| Amenorrhea, Menstrual Disorder |

### 6.4.5-D. Late-emerging Adverse Events

After the first 3 months of stimulation, the incidence of first-reported (new event types) stimulation-related adverse events did not exceed 1.3% of total study subjects for any event (see Table D-11).

## Table D-11. Incidence of First Reported Stimulation-Related Adverse Events Experienced After 3 Months of VNS Therapy

| Body System | COSTART Term | Treatment Group (N=117) N (%) | Delayed Treatment Group (N=116) N (%) | Total (N=233) N (%) |
|---|---|---|---|---|
| Body as a Whole | Back Pain | 1 (<1%) | 0 | 1 (<1%) |
| | Flu Syndrome | 1 (<1%) | 0 | 1 (<1%) |
| | Sudden Unexplained Death | 1 (<1%) | 0 | 1 (<1%) |
| | Viral Infection | 1 (<1%) | 0 | 1 (<1%) |
| Cardiovascular System | Hypotension | 1 (<1%) | 0 | 1 (<1%) |
| | Syncope | 3 (3%) | 0 | 3 (1%) |
| Digestive System | Colitis | 2 (2%) | 0 | 2 (<1%) |
| | Gastritis | 2 (2%) | 1 (<1%) | 3 (1%) |
| Metabolic and Nutritional Disorders | Weight Gain | 1 (<1%) | 2 (2%) | 3 (1%) |
| | Weight Loss | 1 (<1%) | 0 | 1 (<1%) |
| Musculoskeletal System | Arthralgia | 0 | 1 (<1%) | 1 (<1%) |
| | Joint Disorder | 0 | 1 (<1%) | 1 (<1%) |
| | Myalgia | 0 | 1 (<1%) | 1 (<1%) |
| Nervous System | Speech Disorder | 0 | 1 (<1%) | 1 (<1%) |
| | Vocal Cord Paralysis | 0 | 1 (<1%) | 1 (<1%) |
| Respiratory System | Stridor | 1 (<1%) | 0 | 1 (<1) % |
| Special Senses | Amblyopia | 1 (<1%) | 0 | 1 (<1%) |
| | Deafness | 2 (2%) | 0 | 2 (<1%) |

Note: First reported stimulation-related AEs are defined as stimulation-related AEs that were reported after the first 3 months of VNS Therapy and for which no subject reported an AE that coded to that term during the first 3 months.

Note: AEs were coded using the COSTART 5 dictionary.

Note: Subjects were reported only once within each preferred term.

Note: Includes all AEs where relationship to stimulation was recorded as possible, probable, or definite.

### 6.4.6-D. Duration of Stimulation-related Events

Subjects who reported adverse events during the first 3 months of stimulation and continued to be observed during the next 9 months were evaluated by 3-month intervals for continuation or resolution of their events. The largest decreases were noted between the first and second quarters of stimulation. The most notable exception was voice alteration. During the first quarter, 135 of 209 subjects (65%) reported voice alteration. Of those 135 subjects, 90 continued to report it during the fourth quarter of stimulation. See Table D-12.

## Table D-12. Duration of Early Stimulation-related Events Through 1 Year (Study D-02)

VNS Therapy (N=209)

| Preferred Term | N Reporting Event During First 3 Mos.[1] | N (%) Continuing to Report Event During Succeeding Quarters[2] | | |
|---|---|---|---|---|
| | 0–3 Mos. | 3-6 Mos. | 6-9 Mos. | 9-12 Mos. |
| Voice Alteration | 135 | 115 (85%) | 101 (75%) | 90 (67%) |
| Cough Increased | 55 | 18 (33%) | 15 (27%) | 11 (20%) |
| Neck Pain | 38 | 17(45%) | 19 (50%) | 16 (42%) |
| Dyspnea | 35 | 22 (63%) | 18 (51%) | 16 (46%) |
| Dysphagia | 31 | 16 (52%) | 10 (32%) | 6 (19%) |
| Paresthesia | 26 | 12 (46%) | 6 (23%) | 4 (15%) |
| Laryngismus | 23 | 13 (57%) | 9 (39%) | 5 (22%) |
| Pharyngitis | 14 | 3 (21%) | 2 (14%) | 2 (14%) |
| Nausea | 13 | 3 (23%) | 1 (8%) | 2 (15%) |

[1]Entries are the number of subjects who experienced the AEs between implantation and 3 months.

[2]Number of subjects who continued to experience the same adverse event between months 3 and 6. months 6 and 9. and months 9 and 12.

Note: Subjects were counted only once within each preferred term and time interval.

### *6.5-D. Severity of Adverse Events*

Investigators rated adverse events as mild, moderate, or severe according to the protocol definitions: mild events were transient and easily tolerated by the subject; moderate events caused discomfort and interrupted usual activities; severe events caused considerable interference with the subject's usual activities.

Most adverse events for the feasibility (D-01) study and pivotal (D-02) study were mild or moderate. Because the pivotal (D-02) study included a sham-control group, further analysis of severity rating was performed. After 3 months of treatment, there were 280 (43%) adverse events that were categorized as mild, 293 (45%) as moderate, and 73 (11%) as severe in the sham-control group. The active VNS Therapy group had 360 (47%) adverse events categorized as mild, 349 (45%) as moderate, and 61 (8%) as severe.

### *6.6-D. VNS Therapy Continuation Rates*

Of the 295 subjects implanted during both the feasibility (D-01) and pivotal studies (D-02), 270 subjects (92%) were still receiving VNS Therapy at 12 months and 242 subjects (82%) were still receiving VNS Therapy at 24 months. This compares to 12- and 24-month continuation rates of 95% and 83%, respectively, for the subjects implanted in the epilepsy preapproval trials.

### *6.7-D. Device Performance*

The VNS Therapy System performed according to its specifications. Most device issues were communication difficulties resolved by repositioning the programming wand or replacing the programming wand batteries. One high lead impedance occurred requiring replacement; a lead break due to fatigue at the electrode bifurcation was noted. Most device complaints were resolved on the day of initial complaint.

### *6.8-D. Analysis of Medical Device Reports Submitted to the FDA from July 1, 1997 through October 8, 2004 for the VNS Therapy System Epilepsy Indication*

Once a medical device is approved for commercial distribution, the United States Food and Drug Administration (FDA) regulations require certain parties, including manufacturers of medical devices, to report to the FDA deaths and serious injuries to which a device has or may have caused or contributed. The required report is referred to as a medical device report (MDR). The FDA Office of Biometrics and Surveillance analyzed all MDRs submitted for the VNS Therapy System from July 1, 1997 through October 8, 2004. During this period, the VNS Therapy System had a single approved indication, epilepsy. The analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. By the end of the period analyzed, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. It is important to emphasize that, although the events occurred during treatment with the

VNS Therapy System, the submission of an MDR does not necessarily mean the product caused or contributed to the event being reported.

### 6.8.1-D. Deaths

A total of 524 deaths were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Of the 524 deaths, 102 (20%) were of an "unknown cause," including 24 deaths of unknown cause that occurred during sleep (5% of total deaths). Of those deaths with a reported cause, the following were the most common etiologies:

- seizure disorder (152 reports; 29% of total deaths), including sudden unexplained death in epilepsy and status epilepticus;
- respiratory events (99 reports; 19% of total deaths), including pneumonia, pulmonary edema, hypoxia;
- cardiac events (51 reports; 10% of total deaths), including cardiopulmonary arrest, infarction, and arrhythmias;
- neurovascular events (24 reports; 5% of total deaths), including stroke and cerebral hemorrhage
- malignancy (19 reports; 3% of total deaths), including brain and colon.
- Suicide (9 reports; 2% of total deaths)

### 6.8.2-D. Serious Injuries

A total of 1,644 serious injuries were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. The most frequently reported serious injury was infection (525 reports). Approximately 40% of these were known to have required device explantation. The second most common serious injury reported was increased seizure activity (324 reports). Others included:

- vagus nerve injury (181 reports) including vocal cord paralysis (109) and hoarseness (71)
- respiratory injuries (141 reports) including sleep apnea (33), dyspnea (50), and aspiration (14)
- cardiac events (123 reports) including tachycardia, bradycardia, palpitations, hypertension, hypotension, syncope, and asystole
- pain (81 reports) including chest and neck pain;
- gastrointestinal events (60 reports) including dysphagia (24) and weight loss (24)
- depression (21 reports)

Of the 1,644 reports of serious injury, 694 (42%) were associated with subsequent device explantation in that subject.

### 6.8.3-D. Device Malfunctions

A total of 708 device malfunctions were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Some of the most common malfunctions reported were high lead impedance (351), lead breakage (116), device failure (44), and device migration (20).

# 7-D. CLINICAL STUDIES — EFFECTIVENESS

## *7.1-D. Feasibility (D-01) Study*

The primary efficacy measure in the open-label feasibility (D-01) study was the percent of subjects responding (response was defined as a 50% or greater improvement in the $HSRD_{28}$ score). Of the 59 subjects with evaluable data, 18 (31%) responded at acute study exit, which was 12 weeks after implantation. Observation of subjects continued. After 1 year of adjunctive VNS Therapy, 25 of 55 subjects (45%) responded, and after 2 years, 18 of 42 (43%) responded. After 1 and 2 years of treatment, 27% and 21% of the subjects, respectively, were in remission (defined as $HRSD_{28}$ scores less than or equal to 10; . Other measures of depressive symptoms (CGI, MADRS, BDI, IDS-SR) and quality of life (MOS-36) supported the $HRSD_{28}$ scores.

## *7.2-D. Pivotal (D-02) Study*

The pivotal (D-02) study of VNS Therapy consisted of both an acute and a long-term phase to collect data regarding the safety and efficacy of VNS Therapy as an adjunctive treatment for persons with chronic or recurrent treatment-resistant depression.

### 7.2.1-D. Pivotal D-02 Study, Acute Phase

The acute phase was a 12-week (after implantation), double-blind, randomized, parallel-group sham treatment-controlled, multi-center study. Subjects were assigned randomly to either the treatment (stimulation) group or control (sham) group and results of these two groups were compared. All subjects in both groups meeting the

eligibility criteria for participation in the study were implanted with the VNS Therapy Pulse Generator and VNS Therapy Lead. The VNS Therapy System remained OFF for 2 weeks after implantation to allow for recovery from surgery. Most subjects in the pivotal (D-02) study were being treated with one or more antidepressant medications at the time of enrollment. Medications were to remain constant at the pre-implant baseline dosages throughout the acute phase for both the treatment and sham-control groups.

**Sham Control:** Sham-control group subjects were treated the same as the treatment group, except that the output current of the device remained at 0.0 mA so that it did not deliver stimulation during the acute phase.

**Treatment Group:** Two weeks after implant, stimulation was initiated for the treatment group. Over the next 2 weeks, parameters were adjusted to subject tolerance, then remained constant for the rest of the acute phase (8 weeks). Decreases in stimulation parameters were permitted to accommodate subject tolerance.

### *7.3-D. Pivotal (D-02) Study, Long-term Phase*

All pivotal (D-02) study subjects who completed the acute phase were eligible to continue into the long-term extension phase, during which all subjects received active VNS Therapy. During the first 10 weeks of the extension phase, sham-control subjects (also referred to as the delayed treatment group for the long-term phase), received stimulation parameter adjustments. Weekly or every other week clinic visits and assessments were identical to those experienced by the treatment group during the acute phase. Otherwise, the protocol specified

monthly clinic visits for both groups through 12 months of active VNS Therapy. Various assessments, including depression ratings, were performed throughout this period. During the long-term extension phase, investigational site programmers were allowed to adjust stimulation parameters as clinically indicated. Additionally, concomitant antidepressant treatments could be added, removed, or adjusted as clinically indicated.

### 7.3.1-D. Comparative Assessments

Outcomes from a non-randomized comparative study (D-04) were compared with the long-term outcomes in study D-02. D-04 was a long-term, prospective, observational study to collect data regarding usual standard-of-care for treatment-resistant chronic or recurrent depression in persons who were experiencing a major depressive episode at the time of admission. Clinical (depression assessments) and quality of life outcomes were assessed at baseline, 3, 6, 9, and 12 months.

#### *7.3.1.1-D. Concomitant Therapies*

Subjects enrolled in the comparative (D-04) study met the same enrollment criteria regarding chronicity or recurrence of depression, previous treatment failures, and severity of depression as subjects in the pivotal (D-02) study. Because the study was observational in nature, the protocol did not specify therapies for the treatment of depression; rather the physician managing the study subject's depression selected therapy according to clinical judgment. Thus antidepressant therapy in the comparative (D-04) study comprised "standard of care" treatment (also known as "treatment as usual"). The entire range of treatment options available for the comparative (D-04) study subjects was also available to the pivotal (D-02)

study subjects as concomitant treatment to their VNS Therapy. Thus subjects in both the long-term pivotal (D-02) extension and the comparative (D-04) study received standard-of-care treatment; however, only the pivotal (D-02) study subjects received VNS Therapy.

#### *7.3.1.2-D. Comparison of D-02 and D-04 Study Populations*

The comparative (D-04) study was conducted at 13 investigational sites, 12 of which were also pivotal (D-02) study sites. The similarities in the key inclusion criteria and study sites provide a basis to expect that the demographic and disease characteristics of both groups would be comparable, which was confirmed by the results of the analyses conducted to examine the comparability. The D-04 subjects provided a comparison group for the pivotal (D-02) study subjects at 12 months. See Table D-13.

**Table D-13. Description of Subjects in Pivotal (D-02) and Comparative (D-04) Studies**

| Parameter | Statistic | D-02 (N=205) | D-04 (N=124) |
|---|---|---|---|
| Age (years) | Mean | 46.3 | 45.5 |
| Male | N (%) | 74(36) | 39(31) |
| Female | N (%) | 131(64) | 85(69) |
| Caucasian | N (%) | 198(97) | 111(90)* |
| African-American | N (%) | 3(1) | 5(4) |
| Hispanic | N (%) | 3(1) | 2(2) |
| Unipolar | N (%) | 185(90) | 109(88) |
| Bipolar | N (%) | 20(10) | 15(12) |
| Recurrent | N (%) | 161(87) | 93(85) |
| Single Episode | N (%) | 24(13) | 16(15) |
| Length of Current MDE (mos) | Mean (S.D.) | 49.9(52.1) | 68.6(91.5) |
| # Failed Trials in Current MDE | Mean (S.D.) | 3.5(1.3) | 3.5(1.3) |
| Received ECT Lifetime | N(%) | 108(53%) | 32(26%)* |
| Received ECT, Current MDE | N(%) | 72(35%) | 15(12%)* |
| Duration of Illness (yrs) | Mean (S.D.) | 25.5(11.9) | 25.8(13.2) |
| Lifetime episodes of Depression* | | | |
| 0-2 | N(%) | 50(24) | 31(25) |
| 3-5 | N(%) | 69(34) | 36(29) |
| 6-10 | N(%) | 56(27) | 18(15) |
| >10 | N(%) | 19(9) | 32(26) |
| No Suicide Attempts in Lifetime | N(%) | 140(68) | 80(65) |
| Treatment induced (hypo)mania | N(%) | 16(8) | 6(5) |
| Hospitalizations for Depression | Mean (S.D) | 2.7(5.4) | 2.1(2.9) |
| ECT Treatment Within past 2yrs | N(%) | 54(26) | 19(15) |

* $p<0.05$.

This comparison analyzed evaluable populations of 205 adjunctive VNS Therapy subjects (D-02) and 124 usual standard-of-care subjects (D-04). Groups were well matched, with similar demographic, psychiatric, and mood disorder treatment histories. The only relevant significant differences between groups were previous ECT history (with higher usage of ECT found in the D-02 group) and number of lifetime episodes of depression (with a higher percentage of the D-04 group reporting >10 lifetime episodes). These differences were handled within the efficacy analysis by use of a propensity adjustment.

## *7.4-D. Data Analysis: D-02 and D-04 Studies*

### 7.4.1-D. Pivotal (D-02) study

The primary efficacy variable for both the acute and the long-term phases of the pivotal (D-02) study was the Hamilton Rating Scale for Depression-24 item ($HRSD_{24}$). For the acute-phase analysis, the $HRSD_{24}$ response rate (percentage of subjects with a ≥50% improvement from baseline to 3 months, acute phase exit) was compared between the treatment and the sham-control groups. For the long-term phase, a linear regression model was used to assess the changes in $HRSD_{24}$ raw scores. Secondary efficacy analyses included within and between-group comparisons of 1) the Inventory of Depressive Symptomatology-Self Report (IDS-SR), 2) the Clinical Global Impressions (CGI), 3) the Montgomery-Asberg Depression Rating Scale (MADRS), and 4) the Medical Outcome Survey 36-Item Short Form Health Survey (MOS SF-36).

### 7.4.2-D. Comparative (D-04) Study

The primary efficacy variable for the D-02 and D-04 comparative analysis was the IDS-SR (raw scores). Multiple assessments with the IDS-SR allowed use of a linear regression model for the analysis. The $HRSD_{24}$ was used as a secondary assessment variable to analyze differences in response rates and raw score changes between subjects in the pivotal (D-02) and comparative (D-04) studies. Subjects in the comparative (D-04) study were assessed with the $HRSD_{24}$ only at baseline and 12 months.

Secondary analyses included IDS-SR average change, IDS-SR response, IDS-SR remission, IDS-SR sustained response, and $HRSD_{24}$ remission. Other secondary analyses included the CGI response.

### 7.4.3-D. Propensity Scores

Propensity scores were calculated for the pivotal (D-02) study and comparative (D-04) study groups and used in the linear regression analysis to address the potential impact of baseline differences on differences in outcome between the two groups. Propensity scores provide a scalar summary of the covariate information (e.g., age, number of prior depressive episodes, etc). They are not limited by the constraints of traditional methods of adjustment, which can only use a limited number of covariates for adjustment.

### 7.4.4-D. Responder Rate

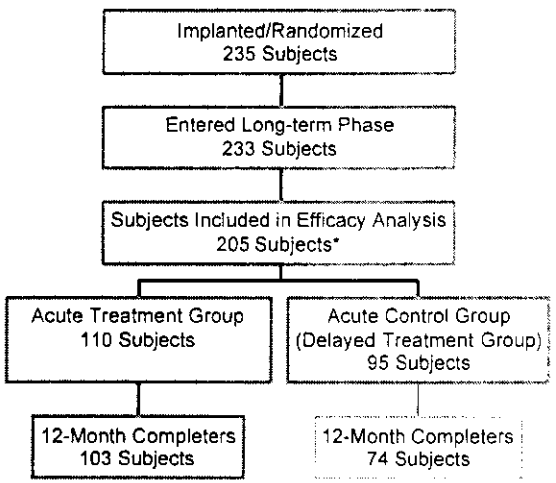
Response was prospectively defined as a ≥50% improvement from baseline for the IDS-SR, $HRSD_{24}$, and MADRS ratings and as a score of much or very much improved for the CGI improvement rating. Remission

(complete response) was prospectively defined as an $HRSD_{24}$ score of ≤9, a MADRS score of ≤10, or an IDS-SR score ≤14.

All statistical analyses were performed using the updated SAS version 8.2. All statistical tests were two-sided and performed at the 0.050 level of significance. No adjustments were made for multiple outcome measures.

**Figure D-2. Pivotal Study, Long-Term**

Flowchart: Pivotal Study, Long-term Phase




*28 subjects did not qualify for Efficacy Analysis:
21 sham-control subjects did not have required $HRSD_{24}$ score ≥ 18 at acute phase exit
4 subjects did not have long-term phase efficacy assessments
3 subjects did not meet continuation criteria for acute phase

## *7.5-D. Results: Pivotal Study (D-02)*

Figure D-2 provides a flow chart of subjects from the acute phase through the long-term phase of the pivotal (D-02) study. Information describing subjects in the pivotal (D-02) and comparative (D-04) studies is presented in Table D-13.

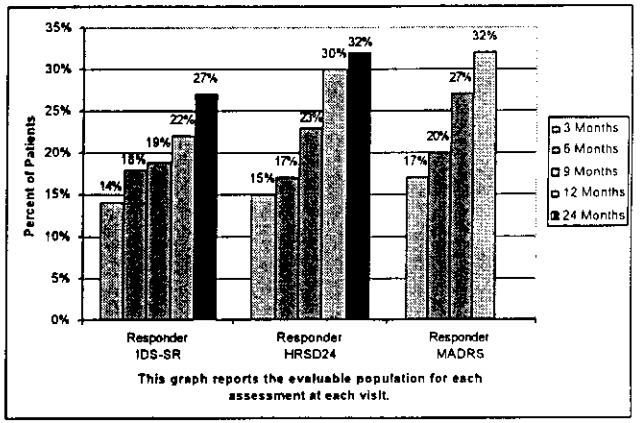
### 7.5.1-D. Results: Acute phase, pivotal (D-02) study

In the primary efficacy measure, $HRSD_{24}$ response rate, (the percentage of subjects achieving a ≥50% improvement in $HRSD_{24}$ total score from baseline to acute phase exit), 15% of the treatment group and 10% of the sham-control group were responders (p=0.238). Analyses using a secondary efficacy parameter, the IDS-SR, did show a statistically significant advantage for VNS Therapy over sham treatment: 17% response versus 7% response (p=0.032) using the last observation carried forward (LOCF) method.

### 7.5.2-D. Results: Long-Term Phase, Pivotal Study (D-02)

During long-term adjunctive VNS Therapy, the D-02 subjects exhibited statistically significant and clinically meaningful improvement. The primary analysis found statistically significant improvement from baseline in $HRSD_{24}$ scores averaged over 12 months (p<0.001). Additionally, clinical significance was shown, using the $HRSD_{24}$, IDS-SR, MADRS, and CGI (Figure D-3 and Figure D-4, evaluable population, and Table D-14, 12-month completer population).

**Figure D-3. Responder Quarterly Results for D-02 Evaluable Subjects**

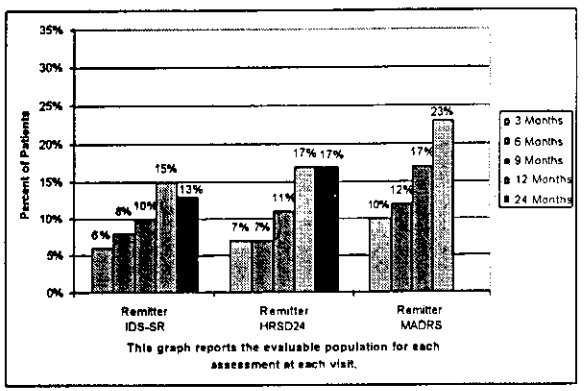



The number of evaluable subjects in each of the above analyses is as follows.

| Mos | IDSSR | HRSD | MADRS |
|---|---|---|---|
| 3 | 203 | 205 | 205 |
| 6 | 192 | 197 | 197 |
| 9 | 185 | 186 | 196 |
| 12 | 180 | 181 | 181 |
| 24 | 157 | 157 | N/A |

**Figure D-4. Remitter Quarterly Results for D-02 Evaluable Subjects**

The number of evaluable subjects in each of the above analyses is as follows.




| Mos | IDSSR | HRSD | MADRS |
|---|---|---|---|
| 3 | 203 | 205 | 205 |
| 6 | 192 | 197 | 197 |
| 9 | 185 | 186 | 196 |
| 12 | 180 | 181 | 181 |
| 24 | 157 | 157 | N/A |

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**Table D-14. Responders, Remitters, and Percent Change Pivotal (D-02) Study 12-Month Completer Population**

| | $HRSD_{24}$[a] | IDS-SR[b] | MADRS[c] |
|---|---|---|---|
| | 12-Month Visit | 12-Month Visit | 12-Month Visit |
| Responders – N (%) | | | |
| Treatment | 34/103 (33%)[2] | 25/102 (25%) | 34/103 (33%)[2] |
| Delayed treatment | 18/71 (25%) | 13/71 (18%) | 22/71 (31%)[1] |
| All 12-Month Completers | 52/174[a] (30%)[3] | 38/173 (22%)[1] | 56/174 (32%)[3] |
| Remitters – N (%) | | | |
| Treatment | 19/103 (18%)[2] | 16/102 (16%)[1] | 25/103 (24%)[2] |
| Delayed treatment | 10/71 (14%) | 10/71 (14%) | 16/71(23%)[1] |
| All 12-Month Completers | 29/174 (17%)[2] | 26/173 (15%)[2] | 41/174 (24%)[3] |
| Mean Percent Change from Baseline | | | |
| Treatment | 31.9%[3] | 27.8%[3] | 32.9%[3] |
| Delayed treatment | 26.5%[3] | 17.3%[3] | 26.3%[3] |
| All 12-Month Completers | 29.7%[3] | 23.5%[3] | 30.2%[3] |

[1] $p<0.05$; [2] $p<0.01$; [3] $p<0.001$; Response and Remitter used the Exact McNemar's test compared with 3 months; Percent Change used the paired t-test (change from pre-stimulation baseline.

[a] Three subjects did not have 12-month $HRSD_{24}$ assessments. (These 3 subjects did have 11-month assessments).

[b] One subject did not have a baseline IDS-SR assessment and several others did not have 12-month assessments, which accounts for the varying Ns in the comparison of $HRSD_{24}$ with IDS-SR data.

[c] Two delayed-treatment subjects did not have 12-month MADRS assessments.

### 7.5.3-D. Quality of Life Assessment

The observed improvement in depression among subjects in the pivotal (D-02) study long-term phase was supported by improved quality of life as measured by the MOS SF-36. Significant improvement was observed in several of the MOS SF-36 subscales: Vitality, Social Functioning, Role Functioning – Emotional, Mental Health ($p<0.01$), and the Physical and General Health Perceptions ($p<0.05$).

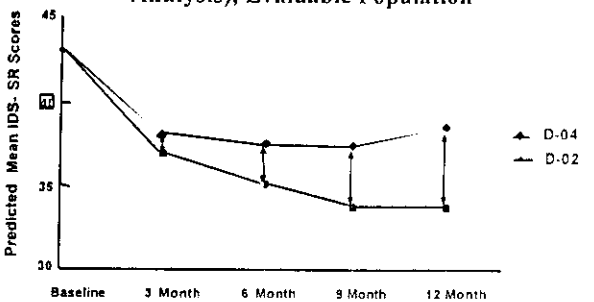
## *7.6-D. Results: Comparison of D-02 and D-04 Studies*

The D-04 study provided a control group of similarly ill subjects who received usual standard-of-care therapies for 12 months but were not implanted with the VNS Therapy device. See Table D-13.

### 7.6.1-D. Primary Effectiveness Outcome

The primary and secondary analyses comparing subjects treated with VNS Therapy plus usual standard–of-care (pivotal, D-02) with subjects treated with usual standard-of-care alone (comparative, D-04) showed that adjunctive VNS Therapy produced statistically significantly greater improvement in depressive symptoms over 1 year of treatment. The primary efficacy analysis, a repeated measures linear regression analysis of the IDS-SR over 1 year, showed a statistically significant ($p<0.001$ evaluable; $p<0.001$ intent to treat) difference favoring adjunctive VNS Therapy. (See Figure D-5.)

**Figure D-5. Comparison of IDS-SR Scores of Pivotal (D-02) Versus Comparative (D-04) Study Subjects by Quarter (Repeated Measures Linear Regression Analysis), Evaluable Population**




| | B/L | 3 mos | 6 mos | 9 mos | 12 mos |
|---|---|---|---|---|---|
| Mean D-04 Scores | 43.0 (N=124) | 38.1 (N=120) | 37.5 (N=119) | 37.3 (N=116) | 38.5 (N=112) |
| Mean D-02 Scores | 43.0 (N=201) | 36.9 (N=200) | 35.1 (N=195) | 33.7 (N=183) | 33.7 (N=177) |
| Predicted Mean Difference | 0 | -1.2 | -2.4 | -3.6 | -4.8 |
| Actual Mean Difference | -0.9 | -4.6 | -4.1 | -5.0 | -6.6 |

### 7.6.2-D. Secondary Analyses

Additionally, the following secondary analyses were statistically significant and showed adjunctive VNS Therapy improved depressive symptoms more than usual standard-of-care alone after 12 months of therapy. See Figure D-6 and Figure D-7.

**Figure D-6. Secondary Analyses: Categorical Outcomes at 12 Months (Evaluable Observed Analysis)**

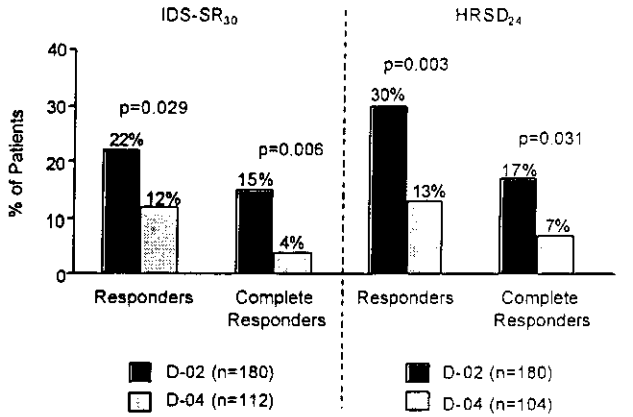
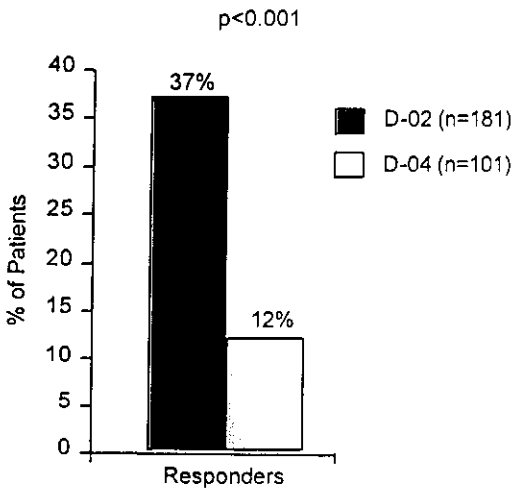


**Figure D-7. Secondary Analyses: CGI-I Categorical Outcome at 12 Months (Evaluable Observed Analysis)**

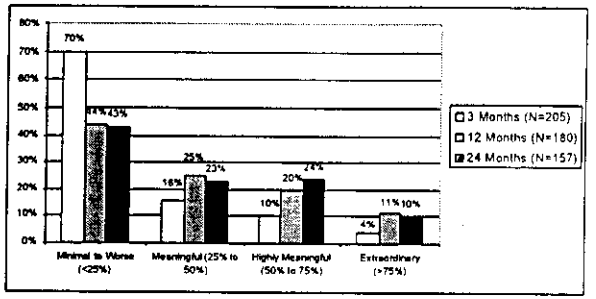



## *7.7-D. Clinical Benefit Over Time*

To explore whether these subjects were receiving benefit that was not fully reflected in the response rates, they were assigned to categories according to "clinical benefit." Clinical benefit was prospectively defined as extraordinary (≥75% improvement in $HRSD_{24}$), highly meaningful (50% to <75%), meaningful (25% to <50%), minimal (0% to <25%), and worsened (less than 0%). This scale is consistent with studies in many chronic illnesses that define less than a 50% improvement as a clinically meaningful response (e.g., schizophrenia, obsessive compulsive disorder).

As shown in Figure D-8, clinical benefit increased over time. The percent of subjects realizing at least a meaningful clinical benefit at 12 months was significant when compared to those experiencing a similar benefit after 3 months (Stuart-Maxwell test, $p<0.001$).

**Figure D-8. Clinical Benefit after 3, 12 and 24 months; D-02 Evaluable Population; $HRSD_{24}$**




The subjects realizing at least a meaningful clinical benefit after 12 months of adjunctive VNS Therapy included subjects who sustained their 3-month meaningful or greater benefit and those who had minimal to no 3-month benefit and accrued at least a meaningful benefit after 12 months. Of the 56 subjects who had at least a meaningful benefit at 3 months, 41 (73%) continued to have at least a meaningful benefit at 12 months and 34 (61%) of these same 56 subjects had at least the *same* level of clinical benefit after 12 months of adjunctive VNS Therapy as they did after 3 months. Of the 118 subjects who realized minimal-to-worse clinical benefit after 3 months of adjunctive VNS Therapy, 56 (47%) had

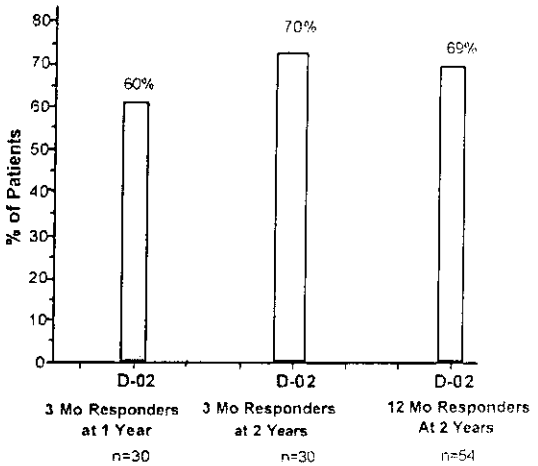
at least a meaningful benefit after 12 months of adjunctive VNS Therapy.

A majority (56%) of evaluable subjects treated with adjunctive VNS Therapy realized at least a meaningful clinical benefit after 12 months of treatment. After 24 months of VNS Therapy, 57% of evaluable subjects realized at least a meaningful clinical benefit.

### *7.8-D. Maintaining Response (2 Year Data)*

An analysis of subjects having an initial ≥50% reduction in HRSD score at the designated "early" visit (3 months or 12 months) and then maintaining at least a ≥40% reduction at the later visit (1 or 2 years), was performed for the D-02 Study. Data are presented below in a bar graph (Figure D-9), with each bar showing the percent of subjects that maintained their early response at the later observation.

**Figure D-9. Maintenance of Adjunctive VNS Therapy Response (% of HRSD Responders who Maintained Response at 1 and 2 Years)**




When IDS data were used instead of HRSD data, similar results were observed (61% of 3-month responders were also responders at 12 months, 57% of 3-month responders were also responders at 24 months, and 85% of 12-month responders were also responders at 24 months). By contrast, no D-04 3-month responder maintained that response at the 12-month observation.



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## 7.9-D. *Standard-of-Care Antidepressant Treatments During the Long-term Phase of Study D-02 and During Study D-04*

### 7.9.1-D. Electroconvulsive Therapy

Electroconvulsive therapy (ECT) use was similar among the pivotal (D-02) and comparative (D-04) study subjects (7% and 6%, respectively) during the first year of observation.

### 7.9.2-D. Antidepressant Drugs and Response

Antidepressant drug use was significantly greater among pivotal (D-02) study subjects who were non-responders and comparative (D-04) study subjects overall than among the pivotal (D-02) study subjects who achieved a response (p<001). During the 12 months, 77% of the pivotal (D-02) study non-responders and 81% of all comparative (D-04) study subjects either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more. By contrast, only 56% of the pivotal (D-02) study subjects who were responders to VNS Therapy either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more.

For the evaluable group at 12-months, 61 subjects were responders while 144 subjects were non-responders (N=205). On a percentage basis twice as many pivotal (D-02) study responders had no ARR changes or removed or decreased medications by at least one ARR level or were

not taking medications as compared to the non-responders (44% versus 23%, respectively).

### 7.9.3-D. Medication Censoring Analyses

Additional medication censoring analyses were performed using the D-02 and the D-02 versus D-04 repeated measures linear regression methods to evaluate further the potential effect of medication changes. This censoring approach used a missing data paradigm to calculate the D-02 results that would have been observed under conditions where no intercurrent changes in medications would have occurred in the D-02 group. The approach censors the D-02 IDS-SR scores after the point at which a subject had a significant medication increase (ARR increase) or ECT treatment, and the last pre-censored score is carried forward and used for subsequent assessment periods. The censoring had the effect of truncating the VNS treatment benefit from 12 months to an average of 7 months. In the D-02 censored analysis, the average $HRSD_{24}$ change from baseline was –0.25 points per month in the repeated measures linear regression ($p<0.001$).

The D-02 censored versus D-04 IDS-SR repeated measures linear regression comparison was an asymmetric comparison of the VNS group treated for 7 months with VNS plus no changes from baseline treatments versus the D-04 group treated for a full 12 months with unlimited standard-of-care treatments (no censoring was performed on the D-04 data). The results of the censoring analysis approached but did not reach statistical significance in the comparison of the D-02 group with the D-04 group ($p = 0.052$; 95% CI -0.37, 0.00) for the evaluable population.

### *7.10-D. Bibliography*

A bibliography of animal, clinical, and mechanism of action studies is available from Cyberonics on request.

## 8-D. INDIVIDUALIZATION OF TREATMENT

Patients should be started on stimulation at a low current output setting (0.25 mA), and the current should be increased gradually to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until a comfortable tolerance level is reached. Physicians should appreciate that some patients will accommodate to stimulation levels over time and should therefore allow further increases (in 0.25 mA steps) in output current, if needed. (See the Model 250 VNS Therapy Software Physician's Manual.)

Table D-15 lists the stimulation parameters reported at 12 months of VNS Therapy in the pivotal (D-02) study.

**Table D-15. Stimulation Parameters at 12 months of VNS Therapy in the Pivotal (D-02) Study**

| Stimulation Parameters | Median Value at 12 months | Range |
|---|---|---|
| Output current | 1.0 | 0 to 2.25 |
| Frequency | 20 Hz | 2 to 30 Hz |
| Pulse width | 500 μsec | 130 to 750 μsec |
| ON time | 30 sec | 7 to 60 sec |
| OFF time | 5 min | 0.3 to 180 min |

The magnet output current should be set to 0 mA.

## 9-D. PATIENT COUNSELING INFORMATION

In the event of uncomfortable adverse events, continuous stimulation, or other malfunction, the patient must be advised to hold or tape the magnet directly over the implanted Pulse Generator to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify the patient's physician.

## 10-D. CONFORMANCE TO STANDARDS

The VNS Therapy System conforms to the following standards:

- American National Standards Institute (ANSI) and Association for the Advancement of Medical Instrumentation (AAMI) NS15 — Implantable, peripheral nerve stimulators
- EN 45502-1 — Active Implantable Medical Devices: Requirements for the safety, marking, and information to be provided by the manufacturer