

4. SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Attached is a detailed Summary of Safety and Effectiveness for the VNS Therapy System. The document was prepared in accordance with the Pre-Market Approval (PMA) Manual (1998). A CD ROM containing a soft copy of this document (formatted in Microsoft Word) was submitted with this PMA Supplement and is labeled VNS Therapy System for depression - Summary of Safety and Effectiveness.

Summary of Safety and Effectiveness

I. GENERAL INFORMATION

Device Generic Name:

Stimulator, Vagus Nerve

Device Trade Names:

VNS Therapy™ System

VNS Therapy™ Pulse Model 102 Generator

VNS Therapy™ Pulse Duo Model 102R Generator

VNS Therapy™ Programming Wand Model 201

VNS Therapy™ Magnet Model 220

VNS Therapy™ Software Model 250

VNS Therapy™ Lead Model 302

VNS Therapy™ Tuner Model 402

VNS Therapy™ Accessory Pack Model 502

Applicant's Name and Address:

Cyberonics, Inc.

100 Cyberonics Boulevard

Cyberonics Building

Houston, Texas 77058 USA

PMA Number:

P970003

Date of Panel Recommendation:

_____, 2004

Date of Notice of Approval to the Applicant:

_____, 2004

II. INDICATIONS FOR USE

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode that has not had an adequate response to two or more adequate antidepressant treatments.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. 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 (loss of seizure control) would then be applicable.

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

B. Warnings

?? The safety and efficacy of the VNS Therapy System has not been established for uses not covered in the “Intended Use/Indications” section of this manual.

?? 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.

?? 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. Cyberonics recommends against stimulation at these combinations of ranges.

?? 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.

?? Aspiration may result from the increased swallowing difficulties reported by some patients during stimulation. Patients with pre-existing swallowing difficulties are at greater risk for aspiration.

?? 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.

?? Susceptible patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been studied as part of controlled clinical trials to establish the safety of

VNS Therapy System treatment in these patients. 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. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

- ?? Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Cyberonics recommends care when treating patients with pre-existing OSA. Lowering stimulus frequency or prolonging OFF time may prevent exacerbation of OSA.
- ?? Physicians should warn patients that VNS Therapy has not been proven to be a cure for depression.

C. Precautions

- ?? Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.
- ?? Dyspnea may result from stimulation. Patients with chronic obstructive pulmonary disease may have an increased risk of dyspnea.
- ?? It is important to follow recommended implantation procedures and intraoperative product testing described in the Physician's 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 Advance 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.

- ?? Reversal of lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important to make sure that the lead connector pins are correctly inserted (white marker band/serial number to + connection) into the lead receptacle(s).
- ?? 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.
- ?? 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.
- ?? 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.
- ?? 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. Cyberonics recommends that the patient be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the operation.

Cyberonics recommends frequent irrigation of both incision sites with generous amounts of bacitracin or equivalent solution 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.

- ?? 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.

?? Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath; physicians should be familiar with vagal anatomy, particularly the cardiac branches; and they should be trained in the surgical technique relating to implantation of the VNS Therapy System. See the section “Physician Training/Information” in the Physician’s Manual.

?? A neck brace can be used by the patient for the first week to help ensure proper lead stabilization.

?? 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.)

IV. DEVICE DESCRIPTION

On July 16, 1997, Cyberonics, Inc. (Cyberonics or Sponsor) received PMA approval for the VNS Therapy™ System (P970003) for the treatment of epilepsy. The VNS Therapy System used for vagus nerve stimulation (VNS), consists of the implantable VNS Therapy Pulse Generator, the VNS Therapy Lead and the external programming system used to change stimulation settings. The pulse generator is an implantable, multiprogrammable, pulse generator that delivers electrical signals to the vagus nerve. The pulse generator is housed in a hermetically sealed titanium case and is powered by a single battery. Electrical signals are transmitted from the pulse generator to the vagus nerve by the lead. The lead and the pulse generator make up the implantable portion of the VNS Therapy System. The external programming system includes a programming wand, the Model 250 Programming Software, and a compatible computer. The software allows a physician, with the programming wand placed over the implanted pulse generator, to identify, read and change device settings.

The commercially available VNS Therapy Systems were used to conduct the depression pilot and pivotal clinical studies.

VNS Therapy System used for the D-01 Study:

The commercially available pulse generator used for the D-01 study was an improved pulse generator from the original Model 100 approved by PMA P970003. The improved Model 100C (P970003/S04) permitted increased longevity (from 4.9 to 6.36 years) and incorporated an Elective Replacement Indicator (ERI) flag for the user during external programming. All of the programmable, diagnostic and therapeutic functions remained unchanged.

VNS Therapy System used for the D-02 Study:

The commercially available pulse generator used for the D-02 study was the Model 101 (P970003/S22); an improved pulse generator from the original Model 100C Pulse Generator used in the D-01 study. The improved Model 101 provided patients with a smaller, more comfortable pulse generator. The Model 100C measured 2 in x .5 in (55 mm x 13.2 mm) and weighed 2 oz (55 g) while the Model 101 measured 2.1 in x 2.1 in x .41 in (54 mm x 54 mm x 10.3 mm) and weighed 1.34 oz (38 g). All of the programmable, diagnostic and therapeutic functions remained unchanged.

Shortly after all D-02 pivotal study subjects were implanted with the Model 101, further size, weight and human factor improvements unrelated to the study were made to the commercially available VNS Therapy System pulse generator and lead. These improvements resulted in the single connector, Model 102 Pulse Generator measuring 2.1 in x 0.27 in (52.2 mm x 6.9 mm) and weighing 0.88 oz (25 g), which accommodates a new single connector pin, Model 302 Lead (P970003/S40). The Model 102R was designed as a replacement for Model 100, Model 100C and Model 101 Generators with dual connector Model 300 leads nearing end of service. Cyberonics modified the Model 102 Pulse Generator to incorporate the Model 101 header assembly with the dual connectors. This design change resulted in the Model 102R (P970003/S47). The Model 102R measures 2.0 in. x 2.3 in. x 0.27 in. (52 mm x 58.4 mm x 6.9 mm) and weighs 0.95 oz. (27 g). The Model 102R is slimmer, lighter and easier to implant than its dual connector predecessor, the Model 101 Generator. All of the programmable, diagnostic and therapeutic functions remained unchanged. The FDA approved these design changes based

on the technical data presented in the aforementioned PMA-Supplements, thereby agreeing with Cyberonics that these design improvements do not require additional clinical data to support the change.

Thus the clinical data collected to support the safety and effectiveness for the VNS Therapy depression indication using the model 101 and 300 series leads are directly applicable to the currently commercially distributed VNS Therapy™ System which includes the following products:

VNS Therapy™ Pulse Model 102 Generator

VNS Therapy™ Pulse Duo Model 102R Generator

VNS Therapy™ Programming Wand Model 201

VNS Therapy™ Magnet Model 220

VNS Therapy™ Software Model 250

VNS Therapy™ Lead Model 302

VNS Therapy™ Tunneler Model 402

VNS Therapy™ Accessory Pack Model 502

The pulse generator, a device similar to a cardiac pacemaker, is surgically placed in the left chest. The lead is then connected to the pulse generator and attached to the left vagus nerve. The VNS Model 402 Tunneler is used during implantation to create a subcutaneous path for the lead and is used in its placement as well.

The VNS Therapy System operates when electrical signals are transmitted from the pulse generator to the vagus nerve via the lead. Peripheral components are used to non-invasively activate, program, and retrieve information from the pulse generator.

Patients are provided with magnets that, by placing the magnet over the implanted pulse generator can deactivate (turn OFF) programmed stimulation. Programmed stimulation resumes when the magnet is removed.

A. VNS Therapy™ Pulse Model 102 and Pulse Duo Model 102R Generators

The VNS Therapy™ Pulse Model 102 and Pulse Duo Model 102R Generators are implantable, multiprogrammable pulse generators that deliver electrical signals to the vagus nerve. Constant current, capacitively coupled, charge-balanced signals are transmitted from the Generator to the vagus nerve by the lead. The pulse generator is housed in a hermetically sealed titanium case. Feedthrough capacitors are used to filter electromagnetic interference from the pulse generator circuitry. The major components and functions of the pulse generator are as follows: a microprocessor, a voltage regulator, a 76.8 kHz crystal oscillator, one antenna to transmit information and another antenna to receive information, communication circuitry, DC-DC voltage generation and control circuitry, constant current control circuitry, a dual pole magnetic reed switch for manual activation of the pulse generator and for inhibition of the output pulses, and a lithium thionyl chloride cell to provide power for stimulation and circuit operation. The lithium thionyl chloride battery chemistry has the low impedance and high energy density characteristics required for the rapid pulsing needed in peripheral nerve stimulation, and similar batteries have been previously used in cardiac pacemakers, implantable spinal cord stimulators, and implantable drug pumps. VNS Therapy™ Pulse Model 102 generator is used for initial implants and is compatible with the VNS Therapy™ Lead Model 302. The VNS Therapy™ Pulse Duo Model 102R Generator is used for replacing pulse generators nearing end of service that are only compatible with dual connector leads.

1. Therapy

The pulse generator has a number of programmable settings, which allow the physician to optimize the treatment for a patient. Those settings include pulse width, magnet-activated output current, output current, magnet-activated ON time, signal frequency, magnet-activated pulse width, signal ON time and signal OFF time. Information on the settings used in the clinical trials is contained in the Physician's Manual.

2. Diagnostic and Safety Characteristics

The pulse generator has telemetry capability that supplies information about its operating characteristics, such as parameter settings, lead impedance and history of magnet use. The pulse generator has a number of characteristics to enhance operational reliability and safety, such as electromagnetic interference (EMI) filter capacitors, a series battery resistor to limit temperature

rise in the event of short circuit, defibrillation protection diodes, direct current-blocking capacitors on both leads that prevent direct current (DC) from being applied to the patient, a software watchdog timer to prevent continuous stimulation, and protection against voltage dips on the battery that could disrupt microprocessor memory.

B. VNS Therapy™ Lead Model 302

The lead delivers electrical signals from the pulse generator to the vagus nerve. The lead has two helical electrodes with a helical anchor tether on one end and on the other end a 3.2-millimeter (mm) connector. The helix of the lead is available in two sizes of inner diameter (2.0-mm and 3.0-mm) to allow for appropriate fit on different sized nerves. The helical design is soft, pliable, and expands or contracts with changes in nerve diameter, which may occur immediately post implant. These design features allow the 2-mm inside diameter helical electrode to fit most vagus nerves. The lead is insulated with silicone rubber and is non-bifurcated. The lead wire is quadrifilar MP-35N, and the electrode is a platinum ribbon.

C. VNS Therapy™ Tunneler Model 402

The tunneler is designed for use during implantation of the lead. The tunneler consists of 4 basic components: a stainless steel shaft, 2 fluorocarbon polymer sleeves and a stainless steel bullet tip. It is recommended for subcutaneous tunneling of the lead connector from the neck to the chest. The Tunneler is supplied sterile and is for single use only.

D. VNS Therapy™ Programming Wand Model 201

The programming wand is used with the VNS Therapy™ Software Model 250 installed on either a compatible handheld or laptop computer to activate, program, reprogram and interrogate the pulse generator. Capabilities of the programming wand include revision of the programmable parameters of the pulse generator, retrieval of telemetry data, and resetting of the pulse generator's microprocessor.

E. VNS Therapy™ Software Model 250

The programming software is a computer program that permits communication with the implanted pulse generator. The programming software is menu-driven and uses on-screen messages and prompts to assist the operator in using the system. Whenever the programming

software is initialized, a self-test is automatically run to verify checksum, file lengths, and file names. The programmed parameters and operational status can be interrogated. One or more parameters can be programmed at one time, and the programmed values are verified and displayed. The programming system uses a strict communications protocol designed to minimize the possibility of "phantom" programming (i.e., inadvertent programming via environmental sources of electromagnetic interference or partial programming of a parameter).

F. VNS Therapy™ Accessory Pack Model 502

The accessory pack contains replacement components for the VNS Therapy System. These components are back-ups for items that may become unusable during routine surgery and include a hex screwdriver, test resistors and lead tie downs. The hex screwdriver can also be used during a pulse generator explantation. These are supplied sterile.

G. VNS Therapy™ Magnet Model 220

Cyberonics provides patients two magnets—a watch-style magnet and a pager-style magnet. The pulse generator recognizes a magnetic field so that when a magnet is passed or held over the pulse generator, the magnetic field causes a reed switch within the pulse generator to close. This switch works like a gate: when the magnet closes it, the normal signal (stimulation) cannot pass (the pulse generator is temporarily turned OFF). When the magnet is removed, the switch (gate) opens immediately, and the pulse generator is turned back ON and can stimulate again. The magnet is placed over the pulse generator to stop stimulation.

V. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently three major treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode: pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy, and electroconvulsive therapy (ECT). ADDs are the usual first line treatment for depression. Clinical trials have demonstrated efficacy for a number of pharmacologic classes of ADDs. Commonly the initial drug selected is a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine (Prozac), or another of the newer ADDs such as venlafaxine (Effexor). Several forms of psychotherapy are used to treat depression. Among these, there is good evidence for the efficacy of cognitive behavior therapy and interpersonal therapy, but these treatments are used less often than are ADDs. Phototherapy is an additional treatment option that may be appropriate monotherapy for mild cases of

depression that exhibit a marked seasonal pattern. Physicians usually reserve ECT for treatment-resistant cases or when they determine a rapid response to treatment is desirable.

Many patients do not respond to initial antidepressant treatment. Currently there are no treatments with an FDA-approved indication specifically for the treatment of such non-responders. Broadly speaking, physicians generally use one or more of the following strategies to treat patients who do not respond adequately to initial antidepressant treatment: (1) switching to an alternative first-line ADD, (2) switching to a second-line ADD (for example, a tricyclic ADD such as desipramine), (3) adding psychotherapy, a second ADD, or an augmentation agent. Augmentation agents are drugs that are not generally considered to have significant antidepressant activity when administered alone, but they can enhance the effectiveness of an ADD when they are administered in combination with the ADD. Augmentation agents include drugs such as lithium, triiodothyronine, or atypical antipsychotic drugs such as olanzapine. Additional options for treatment-resistant patients, especially for patients who fail on the above alternatives, include monoamine oxidase inhibitors and ECT. For treatment-resistant cases that exhibit a marked seasonal pattern, adding phototherapy to pharmacotherapy may also be an option.

Despite the widespread availability of these treatment modalities, it is estimated that 10% to 20% of patients do not respond to treatment. Even among patients who do respond, many do not respond completely, ie, they do not achieve symptom remission. Such partial responders remain at substantial risk for suicide, future recurrences of full syndromic depression, and significant functional impairment. Moreover, there is little published evidence that any of the treatment strategies described above produces effective long-term control of depression in patients who fail to respond to initial antidepressant treatment. Furthermore, many treatments used for patients who do not respond at all or only respond partially to the first or second attempt at antidepressant therapy are poorly tolerated and/or are associated with significant toxicity. For example, tricyclic antidepressant drugs often cause anticholinergic effects and weight gain leading to premature discontinuation of therapy, and they can be lethal in overdose (a significant problem in depressed patients). Lithium is the augmentation strategy with the best published evidence of efficacy (although there are few published studies documenting long-term effectiveness), but lithium has a narrow therapeutic index that makes it difficult to administer; among the risks associated with lithium are renal and thyroid toxicity. Monoamine oxidase inhibitors are prone to produce an interaction with certain common foods that results in hypertensive crises. Even selective

serotonin reuptake inhibitors can rarely produce fatal reactions in the form of a serotonin syndrome. ECT too is associated with significant risks: long-lasting cognitive impairment following ECT significantly limits the acceptability of ECT as a long-term treatment for depression.

VI. MARKETING HISTORY

Cyberonics, Inc. was founded in 1987 to design, develop and market medical devices to improve the lives of people touched by epilepsy, depression and other chronic disorders that may prove to be treatable with our patented Vagus Nerve Stimulation Therapy (VNS Therapy™).

To date, more than 22,000 patients in 44 countries have accumulated over 56,000 patient-years of experience using VNS Therapy for the treatment of epilepsy. The first human implant of the VNS Therapy System occurred in 1988 in a patient with epilepsy. The FDA approved Cyberonics' patented VNS Therapy on July 16, 1997 (P970003) for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory partial onset seizures. The commercial use of the VNS Therapy System continues to expand as VNS Therapy System has been approved by governmental regulatory bodies around the world as safe and effective for the treatment of epilepsy.

The VNS Therapy System has not been withdrawn from marketing in the U.S. or any other country for any reason related to the safety or effectiveness.

A. Foreign Marketing History

Since June 1994, the VNS Therapy System has been approved for sale as a treatment for epilepsy in all the member countries of the European Union. Currently, the VNS Therapy System is commercially distributed in Canada, Argentina, Brazil, Chile, Australia, Austria, Belgium, China, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, S. Korea, Liechtenstein, Luxembourg, Malaysia, New Zealand, The Netherlands, Norway, Poland, Portugal, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey and the United Kingdom.

In March 2001 Cyberonics received CE Mark Approval to begin commercial distribution of the VNS Therapy System for the treatment of depression in all the member European Community (EC) countries. Subsequently, in April 2001 Cyberonics received the license to begin commercial distribution of the VNS Therapy System for the treatment of depression in Canada. Approximately 100 patients have received the VNS Therapy System for the treatment of depression outside the United States.

As of October 10, 2003 92 patients have received the VNS Therapy System for the treatment of depression in the European Union. Nearly half of these patients have been enrolled in the ongoing European open-label, non-randomized, single-arm, longitudinal depression Post-Marketing Study, D-03. Preliminary effectiveness results showed that at 3 months 14 of 34 (41%) subjects were responders (a 50% or greater decrease in HRSD₂₄ from baseline) and 10 of 34 (29%) subjects were remitters (a HRSD₂₄ score of less than or equal 10). Furthermore, after one year of stimulation, the results showed 7 of 17 (41%) subjects were responders and 5 of 17 (29%) subjects were remitters. These results are comparable or better than those seen in the pivotal trial D-02 discussed later in this document. The preliminary adverse event profile in the D-03 study is very similar to the one seen in previous epilepsy studies as well as in the current depression studies presented later in this document: D-01 (Feasibility) and D-02 (Pivotal).

The Sponsor has received six (adverse event) complaints from the approximately 50 depression patients that were implanted commercially in Europe but not enrolled in the D-03 Study.

These events are similar to adverse events reported in the use of the VNS Therapy System for epilepsy and the D-01 and D-02 Clinical Studies for depression.

B. U.S. Marketing History

Since July 1997 the VNS Therapy System has been approved for sale as a treatment for epilepsy in United States. Two off-label depression implants in the U.S. reported adverse events. These adverse events are similar to those reported in the use of the VNS Therapy System for epilepsy and the D-01 and D-02 Clinical Studies for depression.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The possible complications of VNS System treatment for chronic or recurrent depression include those related to implantation, those related to performance of the implanted pulse generator, and those related to long-term patient tolerance of the implant.

Except for lead positioning, implantation of the pulse generator is similar to implantation of a cardiac pacemaker. In addition to the normal risks associated with a surgical procedure, complications associated with implantation include, but may not be limited to, skin irritation; pain at the incision site; infection; extrusion or migration of the pulse generator and/or lead; dislodgment, disconnection (lead from pulse generator), breakage (lead), or corrosion of the stimulating lead; hematoma; fluid accumulation; cyst formation; inflammation; and histotoxic reactions. These phenomena may occur either acutely or chronically and may require device replacement to correct the complication.

Complications can include damage to the vagus nerve, either due to surgical trauma, compression by the electrode, or excessive stimulation. Hoarseness not associated with the stimulation suggests possible nerve irritation which can be investigated immediately. Persistent hoarseness may be caused by nerve constriction, nerve fatigue, or a pulse generator malfunction.

The implant-related events in study D-02 that occurred in 10% or more of subjects were device site pain, device site reaction, incision pain, dysphagia, hypesthesia, pharyngitis, voice alteration and incision site reaction. Adverse events that the investigators judged were at least possibly stimulation-related and which occurred at a frequency of 10% or greater in the VNS Therapy group in the acute phase (first 3 months) of the D-02 study were neck pain (16%), dysphagia (13%), paresthesia (10%), cough increased (24%), dyspnea (19%), laryngismus (11%), and voice alteration (55%).

Intolerable stimulation-related adverse events can generally be reduced or eliminated by a reduction in the output current, frequency, or pulse width. Most of the reported events were mild to moderate and well tolerated; very few clinical study patients discontinued therapy due to side effects.

VIII. SUMMARY OF STUDIES

A. Summary of Non-Clinical Laboratory Studies

1. Pre-Clinical Laboratory Studies

Pre-clinical laboratory studies previously submitted to FDA in the Original PMA application and its Supplements (P970003) were referenced in this PMA supplement and support the safety of the commercially available VNS Therapy System for the new indication of depression. Therefore, no additional pre-clinical laboratory studies were required to evaluate the safety of VNS Therapy for the treatment of patients with depression. A summary of these studies can be found in the Summary of Safety and Effectiveness Document for P970003.

2. Pre-Clinical Animal Studies

Pre-clinical animal studies previously submitted to FDA in the Original PMA application and its Supplements (P970003) were referenced in this PMA supplement and support the safety of the commercially available VNS Therapy System for the new indication of depression. Therefore, no additional pre-clinical animal studies were required to evaluate the safety of VNS Therapy for the treatment of patients with depression. A summary of these studies can be found in the Summary of Safety and Effectiveness Document for P970003.

Although no additional animal studies were required to evaluate the safety of VNS Therapy for the treatment of patients with depression, a study studying the effectiveness of VNS in a rat model of depression was performed by Krahl, et al.¹ Using a validated animal (Wistar Kyoto rat) model for major depression, the authors found that VNS significantly reduced the percentage of time that the rats were immobile in the swim test as compared to the non-stimulated control group ($p < 0.05$) and further stated that “antidepressant efficacy in [this model] is positively correlated with clinical efficacy.” Additionally the authors stated, “the antidepressant efficacy of VNS was not statistically different from that obtained with desipramine and electroconvulsive shock (ECS), two standard clinical treatments that are known to be effective” in this animal model.

¹ Krahl S.E., Senanayake S.S., Pekary A.E., Sattin A. Vagus nerve stimulation (VNS) is effective in a rat model of depression. *Journal of Psychiatric Research*. Submitted.

3. Risk Analysis

As a part of the Sponsor's Design and Development Program, the commercially available VNS Therapy System's Risk Analysis was re-evaluated for treatment-resistant depression (TRD). Since epilepsy and depression subjects undergo the same implantation procedure using the same commercially available VNS Therapy System, no new surgical risks were identified. The results of this evaluation provide supporting evidence of the safety of the VNS System for the treatment of chronic or recurrent depression. Since depression is a mood disorder, the Sponsor evaluated the potential risks associated with patients who are implanted with a VNS Therapy System and are having a TRD episode. The risks associated with this TRD population which are included in the VNS Therapy Risk Analysis include suicide attempt/suicide, manic depressive reaction, anxiety, confusion, overdose, and worsening depression. These potential risks were determined to be unrelated to the VNS Therapy System and associated to the underlying nature of this severe mood disorder. No design related mitigation solutions could be developed.

B. Summary of Clinical Investigations

Cyberonics has conducted three depression studies to establish the scientific evidence to support that the VNS Therapy System is safe and effective for its intended use in the treatment of chronic or recurrent treatment-resistant depression. The first clinical trial conducted was a feasibility trial (D-01); the second clinical study was a randomized, controlled clinical trial with a long-term open-label extension (D-02); and the third trial was an observational study of subjects receiving standard-of-care treatments but not receiving VNS Therapy (D-04). Baseline demographic and disease characteristics of the D-04 subjects were well matched to the D-02 subjects for comparison.

The objective of the feasibility study (D-01) was to assess the safety and efficacy of VNS using the VNS Therapy System in treating subjects with unipolar or bipolar depression. The objective of the pivotal trial (D-02) was to establish that adjunctive VNS Therapy is a safe and effective long-term therapy for patients with chronic or recurrent treatment-resistant depression.

Additional mechanism of action studies of VNS have been performed and are summarized in this section.

1. Feasibility Study D-01

This was an open-label, nonrandomized, single-treatment arm, longitudinal, multicenter, feasibility study of VNS for the treatment of subjects in a treatment-resistant major depressive episode (MDE). The first subject enrolled in the study on June 25, 1998. The acute phase was a 12-week (after implantation) phase that was followed by the long-term phase, which continues to be conducted.

Seventy-one subjects enrolled in the study, 11 of whom discontinued prior to implantation; therefore, 60 subjects were implanted. One implanted subject failed to meet continuation criteria until the long-term phase, at which point stimulation was initiated. Fifty-nine of the 60 subjects completed the acute phase. All 60 subjects continued into the long-term phase. Fifty-nine of the 60 subjects (98%) continued after 12 months of VNS Therapy treatment and as of 10/29/02, 52 of the 60 (87%) continued in the study.

Table 1 describes the demographic characteristics and psychiatric history of the enrolled subjects.

Table 1
Baseline Demographic Characteristics and Psychiatric History
(N=60)

Parameter	Statistic	Result
Age (years)	Mean	46.8
Gender		
Male	N (%)	21 (35)
Female	N (%)	39 (65)
Ethnic Origin		
Caucasian	N (%)	59 (98)
Other	N (%)	1 (2)
Current Diagnosis		
Unipolar	N (%)	44 (73)
Bipolar	N (%)	16 (27)
Length of Current Diagnosis (Years)	Mean	9.9

Primary efficacy analysis of the 28-item Hamilton Rating Scale for Depression (HRSD₂₈) showed 18 (31%) of the 59 observed evaluable subjects responded at acute phase exit (Visit 12), 25 of 55 (45%) responded after one year of VNS Therapy, and 18 of 42 (43%) responded after two years of VNS Therapy, where response was defined as a greater than or equal to 50% reduction of HRSD₂₈ score. Furthermore, after one year of stimulation, 13 of the 18 acute responders (72%) maintained their response and 12 of the acute non-responders (29%) responded. Secondary measures of efficacy confirmed the primary efficacy measure. Of the 30 subjects who had extraordinary, highly meaningful, or meaningful clinical benefit at acute exit, 20 (67%) continued to have the same or better benefit at 12 months and 23 (77%) maintained at least a meaningful clinical benefit at 12 months. Thirteen of the 25 (52%) subjects who did not have a meaningful or better clinical benefit at acute phase exit had a meaningful or better clinical benefit at 12 months. Of the subjects included in the evaluable population, 15%, 27% and 21% reached remission (HRSD₂₈ score less than or equal to 10) at acute exit and after 1 and 2 years, respectively, of treatment. CGI, MADRS, GAF, BDI-II, and IDS-SR scales showed similar improvements at both acute and long-term time points.

No subjects died during the acute phase. One subject died during long-term follow up; this death was not attributed to VNS Therapy (sepsis following colorectal surgery). A second subject died after she was diagnosed with lung cancer and had her device explanted, following withdrawal from the study. The most commonly reported adverse events (those reported by more than 10% of subjects) considered at least possibly related to stimulation were voice alteration, neck pain, pain, dyspnea, headache, dysphagia, and increased cough. The most commonly reported adverse events (reported by more than 10% of subjects) considered at least possibly related to implantation were device site reaction, device site pain, incision pain, neck pain, pain, and voice alteration. In general, adverse events (AEs) were mild to moderate and well-tolerated and were comparable to the D-02 and epilepsy studies.

A total of 16 device observations were reported during the D-01 study; there were no complications noted. The observations included 6 instances of difficulty communicating, 1 of difficulty completing device diagnosis, 3 of user error, 2 of no stimulation, 3 of painful stimulation and 1 instance where the generator would not deliver the programmed output current of 3.5 mA, but would deliver 2.5 mA.

2. Pivotal D-02 Acute and Long-Term Study and D-02/D-04 Comparison Study

D-02 consisted of an acute and a long-term phase designed to collect data regarding outcomes of VNS Therapy in subjects with chronic or recurrent treatment-resistant depression. The first subject enrolled in the study on July 27, 2000. Clinical (depression assessments), quality of life, and safety data were collected monthly or quarterly during the long-term phase of the study.

The acute phase of D-02 was a 12-week (after implantation), double-blind, randomized, parallel-group, sham treatment-controlled, multi-center, pivotal study of adjunctive vagus nerve stimulation (VNS) using the VNS Therapy System in subjects with treatment-resistant depression. In the acute portion, 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. After implantation, subjects were randomized to either the treatment (stimulation) group or control (sham) group and results of these two groups were compared. The VNS Therapy System remained OFF for 2 weeks after implantation to allow for recovery from surgery and to provide an opportunity to assess possible placebo response. Two weeks after surgery (Visit 2), treatment group subjects had the device turned ON and the output current was adjusted to a comfortable and tolerable level during a 2-week period. Sham-control group subjects were treated identically; however, the output current of the device (for both normal and magnet current) was set at 0.00 milliamperes (delivering no stimulation - OFF) throughout the acute phase. Two weeks after device activation, the treatment group subjects' stimulation parameters were to remain constant and were, therefore, not changed for the remainder of the study (8 weeks). Stimulation parameters were permitted to be decreased, however, to accommodate for events possibly related to tolerance. During the acute phase of the study, antidepressant medications were to remain unchanged from baseline.

After completion of the acute phase, subjects could continue in an open-label long-term phase, during which time subjects in the treatment group continued VNS Therapy and stimulation was initiated for subjects in the sham-control group. Sham-control group subjects followed the same treatment schedule that the treatment group received during the acute phase with 2 weeks of stimulation adjustment followed by 8 weeks of fixed stimulation parameters. Subjects were seen approximately monthly for the first year of VNS Therapy treatment and then seen quarterly thereafter.

D-04 was a long-term, observational, prospective study to collect data regarding depression and health care utilization outcomes during usual standard-of-care treatment for treatment-resistant chronic and/or recurrent depression in people who were in a major depressive episode at the time of admission. The usual standard-of-care was defined as the treatment strategy the physician and subject chose to follow (standard-of-care). Clinical (depression assessments), quality of life and economic outcomes were assessed at baseline, 3, 6, 9 and 12 months. The first subject enrolled in the study on January 17, 2001. D-04 provides a comparison group to D-02 for the long-term analysis through 12-months. No safety data were collected in D-04; however, data from efficacy assessments (eg, HRSD) addressed suicidal ideation and worsening depression. Although serious adverse events were not collected during Study D-04, the health services information form (HSUPC; data reported in the electronic dataset) did capture hospitalizations associated with psychiatric illness (therefore not recorded specifically as worsened depression). If these data are used as a surrogate, 28 hospitalizations were reported in the D-04 subjects during 118 patient-years of experience for a total rate of 0.237. VNS Therapy hospitalizations for “worsened depression” compare favorably with this rate.

The following table (Table 2) summarizes enrollment at each site and the figure that follows (Figure 1) describes the study scheme for the D-02 and D-04 studies.

Table 2
Dispositions of Subjects for D-02 Acute/Long-Term and D-04

Study Site # / Investigator Institution	Implanted	Entered D-02 LT ^a	D-02 Evaluable ^c	D-02 12-Month Completer ^d	D-04 ^e Enrolled	D-04 Evaluable	D-04 12-Month Completer
040 / Rittberg University of Minnesota	16	16	15	15	15 ^e	6	5
041 / Goodnick (Dominguez) ^d U. of Miami School of Medicine	10	10 ^b	9	7	3	3	1
042 / Conway St. Louis U. School of Medicine	10	10	9	7	-	-	-
043 / Carpenter Brown University/Butler Hospital	13	13	12	10	11 ^e	8	7
044 / Marangell Baylor College of Medicine	17	17	13	10	12	12	12
045 / George Medical U. of South Carolina	18	18	18	15	13	13	10
046 / Ninan Emory U. School of Medicine	13	13	11	10	3 ^e	2	2
047 / Burke, W. ^d U. of Nebraska Medical Center	9	9	7	7	-	-	-
048 / Barry Stanford U. School of Medicine	7	7	7	7	-	-	-
049 / Schwartz SUNY Upstate Medical U.	12	12	10	9	11	11	11
050 / Burke, M. Psychiatric Research Institute (Via Christi)	11	10	9	8	8	8	6
051 / Rapaport (Soliman) U. of California San Diego MC	9	9	7	3	-	-	-
052 / Zajecka Rush Presbyterian-St. Luke's MC	9	9	8	7	-	-	-
053 / Ginsberg New York University MC	4	4	3	2	-	-	-
054 / Moreno University of Arizona HC	13	13	12	12	15	15	14
055 / Husain U. of Texas Southwestern MC	8	8	5	4	-	-	-
056 / Nierenberg Massachusetts General Hospital	9	9	9	9	-	-	-
057 / Dunner University of Washington	6	6	5	5	17	16	14
058 / Howland University of Pittsburgh	19	19	17	14	14	14	14
059 / Kling University of Maryland	19	18	16	13	12	12	12
060 / Cooke University of Toronto	3	3	3	3	-	-	-
071 / Krystal Duke University Medical Center	N/A	-	-	-	4	4	4
Totals	235	233	205	177	138^e	124	112

^aTwo subjects withdrew during the acute phase. Four subjects continued into the long-term phase but did not complete a visit.

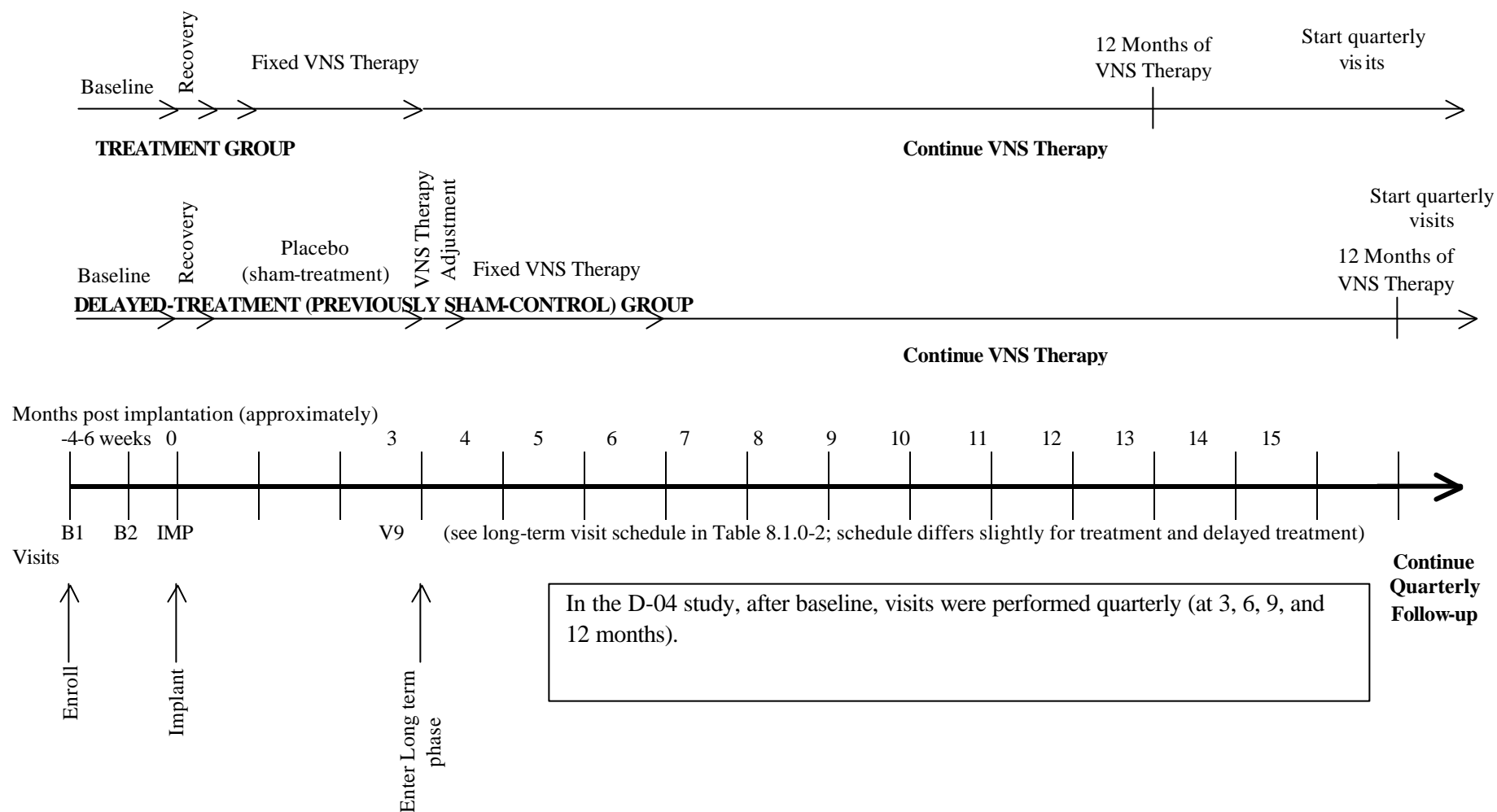
^bSubject 041-184 elected not to continue into the long-term phase; however, mistakenly completed a visit. The subject was included for long-term phase analysis.

^cWithdrawn subjects were included in the intent-to-treat, evaluable and 12-month completer populations if they met the respective definitions.

^dSite 47 was originally involved in the D-04 study, however the site was closed since no subjects were enrolled. The IRB for site 41 closed the D-04 study when the investigator left the site.

^e11 subjects only signed informed consents and never provided any clinical data.

Figure 1 - D-02 Long-Term Phase Scheme



a) Subject Selection

To be considered for enrollment in the D-02 and D-04 studies, subjects were required to meet the inclusion/exclusion criteria which were designed to 1) permit enrollment of subjects with either unipolar or bipolar depressive disorder in a current MDE; 2) maximize the quantity, quality, reliability, and comparability of the data collected; and 3) ensure subject safety. Study entry criteria were similar for both studies. Most of the differences in the criteria were due to the need for D-02 subjects to undergo implantation, ie, the D-02 protocol had more exclusion criteria than D-04 to ensure that only subjects suitable for the implant surgery would be enrolled. These added criteria would not be expected to differentially influence the level of treatment resistance in the two subject groups. Additionally, D-02 subjects were required to have failed psychotherapy to ensure exposure to this treatment modality prior to undergoing VNS Therapy surgery.

b) Inclusion/Exclusion Criteria

D-02: To be eligible for the study, patients were required to be in a chronic (duration ≥ 2 years) current major depressive episode (MDE) and/or have had a history of recurrent MDEs (at least four lifetime depressive episodes, including the current episode) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Additionally, subjects were required to have a HRSD₂₄ score of at least 20 at the acute phase baseline. Continuation criteria required an HRSD₂₄ score ≥ 18 . Subjects had to have failed at least two but not more than six mood disorder treatments from different treatment categories during the current MDE. Treatment failure was determined by an Antidepressant Resistance Rating (ARR) score ≥ 3 using the modified version of the Antidepressant Treatment History Form.

D-04: The principal inclusion criteria for the D-04 study were the same as those for the D-02 study (see above); differences included: 1) D-04 subjects were not required to have a history of treatment with psychotherapy or to be stable on antidepressants, atypical anti-psychotics or anticonvulsant medications at least 4 weeks prior to the baseline visit, (2) D-04 subjects were not limited to receiving five or fewer antidepressants for treating their current episode, and (3) D-04 subjects were also not excluded for: pregnancy; history of myocardial infarction or cardiac arrest; history of cervical fracture that would make implantation of the VNS Therapy System difficult; receiving general anesthesia within 30 days of enrollment; having a demand cardiac pacemaker, implantable defibrillator, or other implantable stimulator; potential future need for a whole body MRI, short-wave diathermy, microwave diathermy or ultrasound diathermy; or relocating to an area distant from the study site (which was exclusionary for D-02).

Exclusions for both studies included atypical depression or psychotic symptoms; schizophrenia, schizoaffective disorder, or delusional disorders; rapid cycling; delirium, dementia, amnestic, or other cognitive disorders; not having an acceptable clinical response due to failure with ≥ 7 antidepressant treatments during the current MDE; recent suicide attempts (or suicide risk); recent alcohol or substance dependence or abuse (other than nicotine); subject had other progressive neurological disease, significant central nervous system (CNS) disease or injury; current enrollment in another investigational study or currently using an investigational device; a history of, or evidence of, significant brain malformation or significant head injury, clinically apparent cerebral vascular events, or prior brain surgery such as cingulotomy; or previous implantation with the VNS Therapy System.

Concomitant Mood Disorder Treatments

D-04 subjects were allowed to have mood disorder treatments changed according to the investigator and subject's determination of the best treatment regimen throughout the course of the study.

For the D-02 study, since the objective was to investigate VNS Therapy, continuation of stable baseline mood disorder treatments was allowed, but *changes* to these treatments were not allowed during the acute phase. Due to the severe treatment-resistant nature of the study population, changes to the mood disorder treatments were allowed during the long-term phase, although such changes were discouraged. Subjects taking antidepressant, atypical antipsychotic, and anticonvulsant medications were required to receive stable doses for at least 4 weeks prior to the first baseline visit. If these medications were changed during this period, Visit B1 and Visit B2 were to be repeated after the antidepressant medications were stable for a total duration of at least 4 weeks.

Subjects were required to maintain a stable regimen of all antidepressant, atypical antipsychotic, and anticonvulsant medications throughout the D-02 acute phase. Additionally, electroconvulsive therapy (ECT) was not allowed during the acute phase, but was permitted in the long-term phase.

c) Study Population

The following figure (Figure 2) and tables (Tables 3 and 4) describe the population of the D-02 and D-04 studies.

Figure 2
Protocol D-02 Long-Term Phase Subject Flowchart

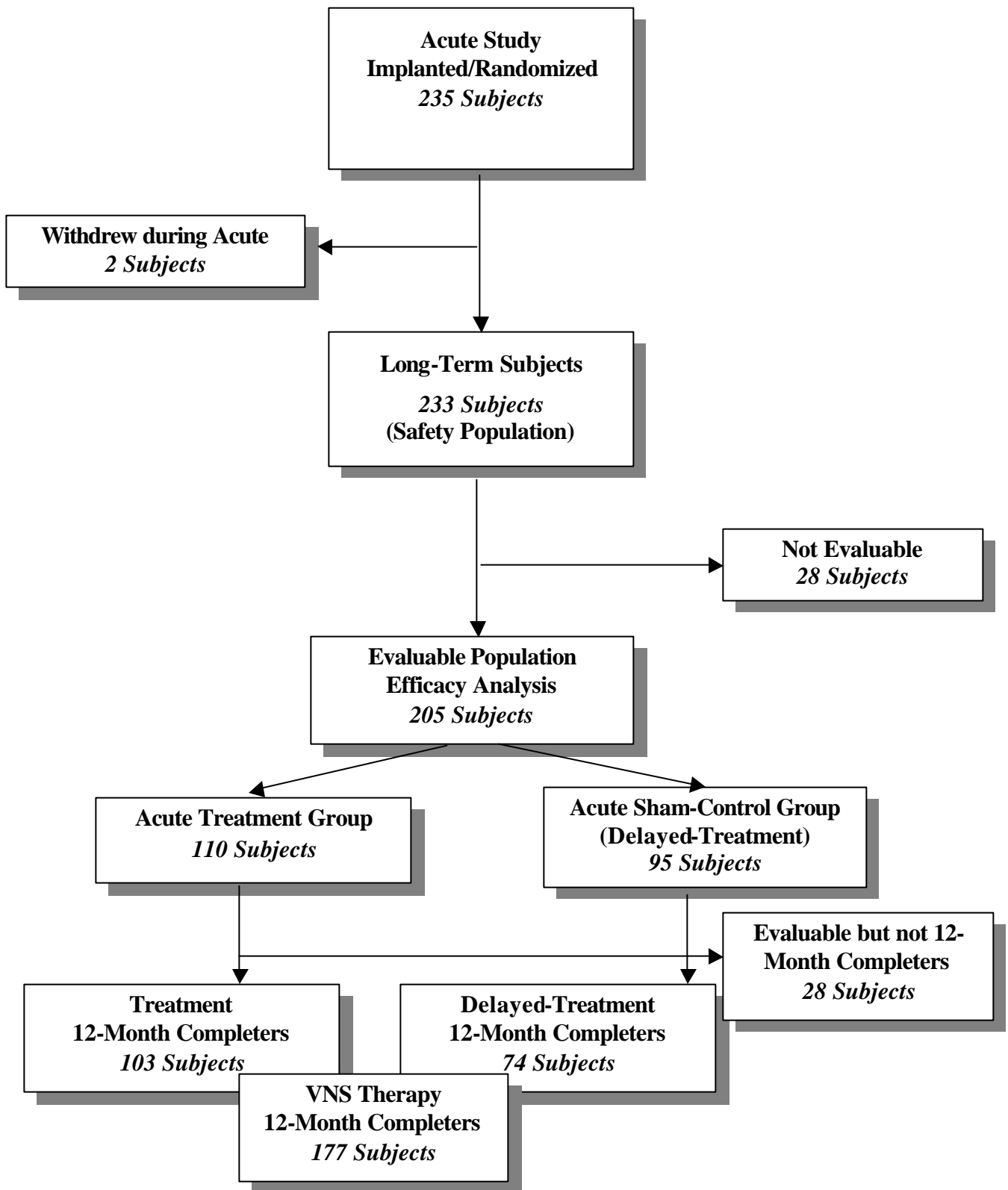


Table 3
D-02 Populations Defined for Long-Term Phase Analysis

Population	Patients Included	Variables Analyzed
Safety	All subjects implanted with the VNS Therapy System	Patient Accounting, Safety (N = 235)
Intent-to-treat (ITT)	Subjects were included in the ITT population if they were ?? Implanted, randomized, and met the acute phase continuation criteria	Efficacy (N = 231) 4 of 235 implanted subjects did not meet acute phase continuation criteria
Evaluable	Subjects were included in the evaluable population if they ?? Met protocol D-02 inclusion criteria 1, 2, 3 and 5 and ITT criteria ?? Completed two baseline HRSD ₂₄ assessments ?? Received VNS Therapy during the acute phase (if in the treatment group) ?? Had no stimulation after day 35 through acute phase exit (if in the sham-control group [delayed treatment]) ?? Completed an HRSD ₂₄ assessment at V8 or V9 ?? Had an acute exit HRSD ₂₄ score of 18 or greater (if in the delayed treatment group) ?? Received VNS Therapy during the long-term phase ?? And met at least one of the following criteria <ul style="list-style-type: none"> ○ Completed at least one HRSD₂₄ assessment post-acute phase exit ○ Were considered a treatment failure any time during the study <p>The evaluable population is the primary population for the comparison of efficacy across 12-months for the D-02 vs D-04 analysis.</p>	Efficacy (N=205) Of the 235: 2 subjects did not enter the long-term phase 3 subjects did not meet acute continuation criteria 4 subjects had no HRSD ₂₄ assessments post-acute phase exit 21 delayed-treatment subjects (one also did not meet acute continuation criteria) did not have an acute exit HRSD ₂₄ ≥ 18
12-month completer	Subjects were included in the 12-month completer population if they ?? Met criteria for the evaluable population ?? Received VNS Therapy for at least 12 months and the device was turned ON for at least 80% of the time within the 12 months from initiating VNS Therapy ?? Completed an HRSD ₂₄ assessment at 11 or 12 months of VNS Therapy The 12-month completer population is the primary population for the evaluation of long-term efficacy in the D-02 Long Term analysis.	Efficacy (N=177) Of the N=205 evaluable group: 17 discontinued prior to one-year 6 did not have >80% stimulation 5 did not have 11 or 12 month assessments

Table 4
D-04 Analysis Populations

Population	Subjects Included	Variables Analyzed
Enrolled	Subjects admitted to the study by the sites via a signed informed consent document.	Accountability N = 127 provided any data
Evaluable	Subjects were considered evaluable if they: met Protocol D-04 inclusion criteria #1, 2, 3 and 5; completed baseline IDS-SR assessment; had baseline HRSD ₂₄ score ≥ 20 ; and completed at least one IDS-SR assessment post-baseline	Efficacy (N = 124) 3 of 127 only provided baseline
12-Month Completer	Subjects were included in the 12-month completer population if they: met the criteria for the evaluable population; completed a IDS-SR assessment at 12 months post-baseline The evaluable population is the primary population for the comparison of efficacy across 12-months for the D-02 vs D-04 analysis	Efficacy (N=112) 12 of 124 did not complete an IDS-SR at 12-months

The following tables (Tables 5, 6 and 7) describe the subjects enrolled in the D-02 and D-04 studies.

Table 5
Baseline Demographic Characteristics Evaluable Populations

Parameter	Statistic	D-02 Study (N=205)	D-04 Study (N=124)
Age (years)	Mean	46.3	45.5
Gender			
Male	N (%)	74 (36)	39 (31)
Female	N (%)	131 (64)	85 (69)
Ethnic Origin			
Caucasian	N (%)	198 (97)	111 (90)
Other	N (%)	7 (3)	13 (10)

Table 6
Psychiatric History – Current Episode Diagnosis
Evaluable Populations

Parameter	Statistic	D-02 Study (N=205)	D-04 Study (N=124)
Diagnosis	N	205	124
Unipolar	N (%)	185 (90)	109 (88)
Bipolar	N (%)	20 (10)	15 (12)

Table 7
Summary of Baseline Psychiatric Characteristics
Evaluable Populations

Parameter	Statistic	D-02 Study (N=205)	D-04 Study (N=124)
	N	205	124
Length of Current MDE (months)	Mean (S.D.)	49.9 (52.1)	68.6 (91.5)
Number of Failed Adequate Trials in Current MDE	Mean (SD)	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)
Number of Lifetime Episode of Depression	N	205	124
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)
Unknown	N (%)	11 (5)	7 (6)
Number of Prior Hospital Admissions For Mood Disorders in Lifetime	Mean (S.D.)	2.7 (5.4)	2.1 (2.9)

d) Safety Data**Vital Signs and Physical Examination Observations**

The physical and neurological examinations performed at the end of the acute and long-term phases of D-02 were essentially unchanged from the baseline examination, revealing no clinically relevant changes. Vital signs, including blood pressure, heart rate, and respiratory rate were also assessed at these time points; there were minimal changes in the vital signs over time. Moreover, the distribution of the changes was essentially symmetrical (as many increases as decreases). These results are reassuring and even more remarkable given the fact that many of these subjects were on multiple medications with known effects on weight and other vital signs. Additionally, baseline weight showed that many of these subjects were in the obese category ($\text{BMI} \geq 30 \text{ kg/m}^2$), which is typically associated with more medical complications and vital sign fluctuations.

Adverse Reactions, Serious Adverse Events, Discontinuations, and Device Failures/Replacements**Adverse Events**

In the D-02 acute phase all treatment-emergent adverse events were collected, irrespective of the relationship between the AE and the VNS device (implantation or stimulation). The majority of these AEs were mild to moderate.

The majority of implantation related AEs were events that one would expect with this kind of surgical procedure or manipulation of the neck area or of the vagus nerve and were no different from what is described in the FDA-approved VNS Therapy epilepsy labeling. Stimulation-related AEs were also examined and are reported in the following tables (Tables 8 and 9).

Table 8
D-02 Acute Phase Incidence of Treatment-Emergent Adverse Events $\geq 5\%$
At Least Possibly Related to Stimulation

Preferred Term	Treatment (N=119) N (%)	Sham- control (N=116) N (%)
Incision Pain	6 (5)	3 (3)
Neck Pain	19 (16)	1 (<1)
Dysphagia	15 (13)	0
Nausea	8 (7)	1 (<1)
Paresthesia	12 (10)	3 (3)
Cough Increased	28 (24)	2 (2)
Dyspnea	23 (19)	2 (2)
Laryngismus	13 (11)	0
Pharyngitis	9 (8)	1 (<1)
Voice Alteration	65 (55)	3 (3)

The seven events identified below as stimulation-related and occurring at a frequency = 10% in the VNS Therapy group were analyzed further to determine how long they persisted.

Table 9
D-02 Acute Phase Duration of Treatment-Emergent Adverse Events
Related to Stimulation, Treatment Group

		Duration in Days for an Event to Resolve¹					
		1 - 7 Days	8 - 14 Days	15 - 30 Days	31 - 60 Days	60 - 90 Days	>90 Days
N		119	119	119	118	118	117
Body as a Whole	Neck Pain	4	3	5	4	1	3
Digestive System	Dysphagia	0	3	0	2	2	3
Nervous System	Paresthesia	1	1	2	1	2	3
Respiratory System	Cough Increase	1	7	5	4	1	9
	Dyspnea	5	4	1	5	1	9
	Laryngismus	1	0	2	3	0	7
	Voice Alteration	1	3	5	2	4	53

Note: All numbers refer to the number of adverse events.

¹Number within each box indicates number of subjects whose event resolved within the days shown (ie 4 subjects had the event of neck pain resolved within 7 days)

Note: Adverse events that had start/stop dates during the acute phase and those adverse events that were ongoing at Visit 9 (with known stop dates) are listed in this table; adverse events that had a start date at Visit 9 are not listed in this table.

Note: AEs included in this table are stimulation-related AEs with a frequency of $\geq 10\%$ in the treatment group.

Table 10 shows a cohort of subjects who reported adverse events during the first three months of VNS Therapy and who also had follow-up visits during months 9 through 12 (N=209). This table identifies those events reported by the subjects during the first three months and follows them over time. Reported events decrease over time. 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.

Table 10
Prevalence of Most Commonly Reported Stimulation-Related Adverse Events
in Subjects Who Experience the Event Within the First 3 Months
of Stimulation in Study D-02, VNS Therapy (N=209)

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

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

²Number 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: Adverse events were coded using the COSTART 5 dictionary.

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

Note: For the intervals between months 3 and 6, months 6 and 9, and months 9 and 12, the denominator is the number of subjects who experienced that particular adverse event between implantation and 10 weeks. Note: 3 months, 6 months, 9 months, and 12 months denote post-stimulation.

Note: Most commonly reported adverse events are those occurring with a frequency greater than 2% during the first quarter of VNS stimulation in either the treatment group or the delayed treatment group.

Serious Adverse Events

A serious adverse event (SAE) was defined as an event that resulted in death, was life-threatening, resulted in or prolonged hospitalization, resulted in a persistent disability, or involved a congenital anomaly. Pregnancy and cancer were also treated as SAEs. SAEs were identified without regard to their relationship to treatment. In the acute phase of study D-02, there were 30 SAEs following implantation. Of these, 11 were considered to be related to the implant procedure (wound infection, asystole, bradycardia, abnormal thinking, vocal cord paralysis, aspiration pneumonia, voice alteration, device site reaction [2 reports], acute renal failure and urinary retention). Investigators did not report any SAE to be related to stimulation. In the long-term phase of study D-02 through October 10, 2002, there were 96 SAEs. Of these, only 6 were considered to be at least possibly related to stimulation (sudden death of unknown cause, syncope [2 reports], dizziness, a manic depressive reaction in a subject with bipolar disorder, and an incident of worsening depression for which the investigator considered VNS therapy a possible but unlikely contributor). SAEs reported in the ongoing D-02 long-term phase through May 30, 2003 are described in the Comprehensive VNS Safety Summary, Depression Experience which is located in [Section VIII B 3 a)] of this report.

In this treatment-resistant subject population, one would expect episodes of depression requiring hospitalization to occur throughout the study, of note, there were three SAEs of worsening depression and two SAE of suicide attempt *prior to* implantation of the VNS device. The most common SAE in the acute and long-term phases of D-02 was worsening depression (*regardless of relationship to VNS Therapy; all except one depression event were reported as not even possibly related to VNS Therapy*). During the acute phase of the D-02 study, there were 12 serious adverse event reports of worsened depression, 5 in the treatment (stimulation) group [in four of 119 subjects] and 7 in the Control (no stimulation) group [in 7 of 116 subjects]. However, one of the treatment-group reports occurred prior to stimulation initiation (reported during the recovery period after implantation but before stimulation initiation). These results indicate that worsened depression rates are similar or somewhat lower in subjects who receive vagus nerve stimulation as compared to subjects who receive no stimulation.

The 7 reports for the Control group over a 10-week period (all events occurred between Visit 2 and end of acute study) can be used to calculate an incidence rate of “worsened depression” in a group of treatment-resistant subjects who do not have VNS Therapy (the control group did not receive stimulation). The rate of 7 reports in 116 subjects over the 10-week period (22.3 patient-

years) translates into a rate of 0.314 events per patient-year. This is the amount of worsened depression events that may be expected to occur in this patient population without VNS Therapy. Another way to look at the data would be that if 116 subjects had 7 events over a 10-week period, then they would be expected to report about 36 events over a 52-week period ($7 * 5.2$). So, the total population of implanted subjects (235) would be expected to report approximately 73 events ($36 * 235 / 116$). These 73 events of worsened depression would be the *expected* amount in this population over a one-year period *without* VNS Therapy.

An analysis of the 235 D-02 subjects who received VNS Therapy, analyzing only the period of time that stimulation was received (months 0-12 after implantation for the treatment group and months 3-15 after implantation for the delayed-treatment group) indicates that 63 events were reported. The 63 events from subjects receiving stimulation are less than the projected number of events from the population originally not receiving stimulation.

If patient-years are used for the calculation, the difference is similar. The 63 events of worsened depression in the first year of VNS Therapy in Study D-02 were reported in approximately 215 patient-years of stimulation (0.293). The rate reported by the sham-treatment group while receiving no stimulation was 0.314 events per patient-year. Subjects reported similar or somewhat lower rates of worsened-depression while receiving VNS Therapy than did subjects not receiving therapy.

Several subjects attempted suicide; they had received VNS stimulation on the average of 6.4 months with the range from 3 to 11 months of stimulation. Since suicide is to be expected in this subject population, suicidal ideation was investigated by examining item 3 of the Hamilton Rating Depression Scale. In both the acute and the long-term phases, subjects generally improved their ratings of this item. Comparison of suicide rates and attempts occurring during all of the depression studies to the rates in published literature is addressed in Table 20 of the SAE discussion.

Although two unanticipated adverse device effects (UADEs) were reported, they were actually associated with medications given during the surgical implantation procedure and not the device itself.

Discontinuations

Table 11 identifies subjects who discontinued during the D-02 acute and long-term phases. The continuation rate for VNS Therapy after 12 months of treatment was 90% (211/235) in this study.

(Acute Phase)

Two discontinuations occurred during the acute phase. Subject 059-109 successfully committed suicide approximately 6 weeks after the surgical procedure for VNS Therapy implantation and subject 050-045, the second discontinuation, had three SAEs after implantation. She was implanted on 11/22/00, began stimulation on 12/7/00, and developed a wound infection within several weeks of implantation at the incision site in her neck (then later at the incision site in her chest). The subject had surgery on 12/20/00 for irrigation, debridement and closure of both wounds. She was hospitalized on 01/18/01 for device site reaction, which occurred when the lead wire was visible through her neck incision. Surgery was performed on the same day (01/18/01) to reposition and secure the lead wire. Even though the subject was on antibiotics most of the time after implantation, the incision wound continued to be infected and the device was explanted on 02/23/01. This subject also was hospitalized for worsening depression with suicidal ideation on 01/22/01. During the hospitalization, medications were adjusted and she was discharged on 02/2/01 with major depression but suicidal ideation no longer present. The subject was discontinued from the study on 02/23/01.

(Long-Term Phase)

There were 28 discontinuations during the long-term phase. Six of the 28 subjects discontinued the long-term phase for adverse events, two of these adverse events were serious adverse events. The six subjects who had adverse events included subject 041-184 who had the adverse event of hoarseness, subject 051-155 who had the adverse event of lightheadedness, subject 055-105 who had the adverse event of post-op pain, subject 050-150 who had the adverse event of shooting pain down the left chest and arm area, subject 047-163 who had the SAE of sudden unexplained death that occurred shortly after Visit 9, and subject 043-091 who had the SAE of worsening depression.

Combining the discontinuations across all phases, 8 (3%) D-02 subjects discontinued due to adverse events.

Table 11
Number of Subjects Withdrawn (With Subject ID Numbers)
as of October 10, 2002

Withdrawal	Acute (≤ 90 Days)	Before 1 Year of Therapy (> 90 – 365 Days)	After 1 Year of Therapy (> 365 Days)
Lack of efficacy	0	11 (042-006, 043-092, 044-008, 044-055, 044-141, 051-106, 051-264, 058-062, 058-144, 058-181, 059-241)	4 (051-080, 040-038, 043-073, 051-028)
AE (acute infection, hoarseness, lightheadedness, post-op pain, arm/chest pain, worsened depression)	1 (050-045)	4 (041-184, 043-091, 051-155, 055-105)	1 (050-150)
Death (suicide, undetermined)	1 (suicide; 059- 109)	1 (unknown; 047-163)	0
Other (MRI, subject decision likely lack of efficacy, but not officially documented as such)	0	6 (044-049, 045-236, 049-042, 049-067, 053-123, 059-247)	1 (MRI; 043-014)
Total Acute and Long-Term	2	22	6

Device Failures and Replacements

For the purposes of this study, the reported events related to device performance were identified as observations or complications. An observation was defined as an event that was resolved by reprogramming, wand battery replacement, wand replacement or programming computer replacement. This category also included those events where no action was taken for resolution of the event. A complication was defined as a symptomatic or asymptomatic event with potential adverse affects that could not be treated or resolved by reprogramming or replacements of the wand, wand battery or computer.

In this study most of the reported events were observations; the most common observation was “difficulty communicating.” This observation was easily remedied during the visit at which the investigator was made aware of the difficulty or shortly thereafter. In the observations that were thought to be “erratic stimulation,” the site had programmed the parameters incorrectly and in the observation of “no stimulation,” the site had inadvertently set the device to deliver no output

current. There were two instances of complications and both were high lead impedance, one due to a broken lead and the other did not have high impedance upon investigation.

Of the 30 withdrawn subjects, 28 had the generator portion of the VNS Therapy System explanted (subject 047-163's device was removed after death) and 26 had the lead portion explanted (two leads were left implanted in subjects whose generator was explanted). One subject refused explant and the family of a deceased subject (suicide; 059-109) decided not to have the device explanted.

Two VNS Therapy systems (generator and lead), although removed, were discarded and never returned to the Sponsor. All 26 returned VNS Therapy Generators were analyzed by the Sponsor's product analysis department; 24 leads were returned and analyzed. No anomalies were found other than those thought to be likely associated with the explant procedure (body fluids on device, scratches on device consistent with manipulation during removal, etc.). One additional non-implanted generator was returned for analysis; the lead would not fit into the generator at implantation.

In summary, the VNS Therapy device system performed according to its labeling and provided reliable therapy access to subjects.

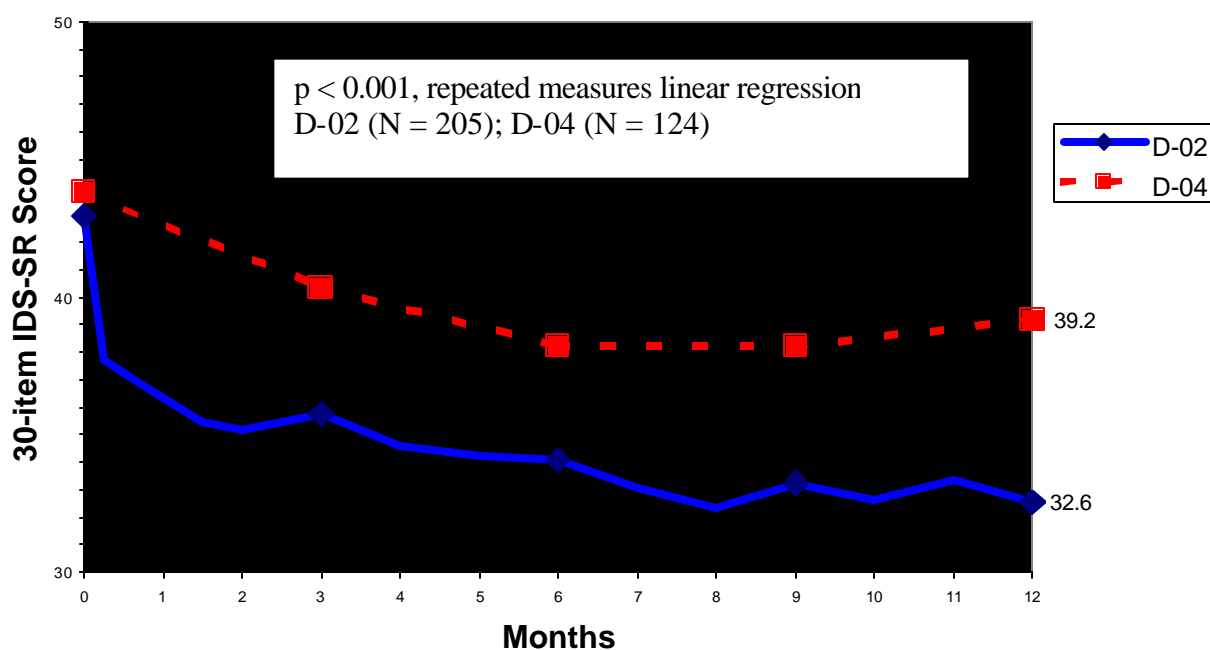
e) Effectiveness Data

The primary objective of the D-02 and D-04 comparison was to compare the changes in depressive symptomatology during 12 months of VNS Therapy plus usual standard-of-care (D-02 sample) with 12 months of usual standard-of-care alone (D-04 sample). The primary efficacy analysis constituted a comparison of the change over time (slope) of the IDS-SR raw scores for the D-02 versus the D-04 subjects across 12-months with a repeated measures linear regression model. Because the IDS-SR was rated at more visits than the HRSD in the D-04 study, it was chosen as the primary analysis variable for the repeated measures linear regression comparing D-02 and D-04. A statistically significant difference ($p < 0.001$) was demonstrated in the estimated IDS-SR raw scores per month between the D-02 and D-04 evaluable populations, ie, the average amount of improvement in the IDS-SR score per month that subjects in D-02 experienced was statistically significantly greater than the improvement experienced by the subjects in D-04 (-0.397 estimated average difference per month).

Moreover, the divergence between D-02 and D-04 continued to widen over time. The difference in D-02 and D-04 IDS-SR total scores increased in each of the four quarters. The cumulative estimated predicted differences at the end of each quarter were -1.190, -2.379, -3.569, and -4.785 points. These findings are based on the raw IDS-SR scores from equivalent visits that were matched based on duration of stimulation for D-02 subjects and the time post-baseline for D-04 subjects. The primary outcome result is presented graphically in the following figure (Figure 3).

Baseline demographic and illness characteristic differences were controlled in the primary repeated measures linear regression analysis by incorporating the 5-level grouped propensity score identified in the two stage propensity adjustment strategy described in the D-02 vs D-04 statistical plan. This 5-level grouped propensity score did not contribute to the statistical significance of the primary outcome ($p = 0.831$). Thus, neither the observed baseline demographic and illness characteristics, or by implication the unobserved differences between the two groups, contributed to the difference in primary outcome between the D-02 and D-04 populations.

Figure 3
D-02 Comparison to D-04
1 Year IDS-SR Scores by Month (Evaluable Population)



When the analysis was repeated on the populations representing all implanted D-02 subjects compared to all D-04 subjects having any data (D-02 N = 235; D-04 N = 127), the results remained statistically significant ($p < 0.001$).

Secondary Analyses (D-02 vs D-04 Comparison)

IDS-SR 12-Month Results

For the long-term evaluable population at 12 months, the D-02 subjects showed a highly statistically significantly greater decrease from baseline in the average IDS-SR raw scores than did the D-04 subjects ($p < 0.001$; ANCOVA). The percentage of D-02 subjects meeting the “response” criteria (50% or greater decrease in the IDS-SR raw score between baseline and month 12) was significantly greater than the percentage of D-04 subjects. Significantly more D-02 subjects met the criteria for a “complete” response, which corresponds with the concept of remission (IDS-SR raw score of 14 or less at month 12). The results are presented below in Table 12. Where “LOCF” is discussed, the reference is made to the last observation carried forward. This analysis technique uses the last available data point for subsequent time points where data is missing.

Table 12
IDS-SR Scores – D-02/D-04 Comparisons
Evaluable Observed Populations

	D-02	D-04	P-Value +
N	180	112	
Baseline Average Raw Score (RS)	42.4	43.8	
12 Month Data			
Average RS	32.6	39.2	
Median RS	32	40	
Average Change	-9.8	-4.6	<0.001**
LOCF Average Change	-9.3 (N=204)	-5.0 (N=124)	<0.001**
Median Change	-8.5	-3.5	
Avg. % Change	23.4	8.1	
Median % Change	20.6	7.9	
Response (% of Subjects)	22	12	0.029*
LOCF Response (% of Subjects)	20 (N=204)	12 (N=124)	0.108
Complete Response (% of Subjects)	15	4	0.006**
LOCF Complete Response (% of Subjects)	13 (N=204)	3 (N=124)	0.007**

+Absence of a p-value indicates no statistical test was applied.

* Significant at < 0.050 level. ** Significant at < 0.010 level. (exact logistic regression)

Sustained Response

Since the first D-04 study HRSD assessment after baseline was not performed until one year, the HRSD was not appropriate for a sustained response comparison between the D-02 and D-04 studies. Therefore the IDS-SR, which was collected quarterly in D-04, was used in an exploratory analysis between the two populations. Using the convention of Rush, et. al., IDS-SR sustained response was defined as a 50% improvement or better at the last two measured quarters (for this analysis 9- and 12-months was chosen).

Based on the above definition, statistically significantly more D-02 subjects (13%) had sustained response than D-04 subjects (4%) [$p = 0.005$, evaluable population, exact logistic regression].

HRSD₂₄ 12-Month Results

For the long-term evaluable population at 12 months (see Table 13), the D-02 subjects showed a highly statistically significantly greater decrease from baseline in the HRSD₂₄ scores than did the D-04 subjects ($p=0.006$; ANCOVA). The percentage of D-02 subjects meeting the “response” criteria (50% or greater decrease in the HRSD₂₄ score between baseline and month 12) was significantly greater than the percentage for the D-04 subjects. More than twice as many of the D-02 subjects met the criteria for a “complete” response (HRSD₂₄ of 9 or less at month 12) than D-04 subjects (17% vs 7%; $p = 0.031$).

Table 13
HRSD₂₄ Scores – D-02/D-04 Comparisons
Evaluable Observed Populations

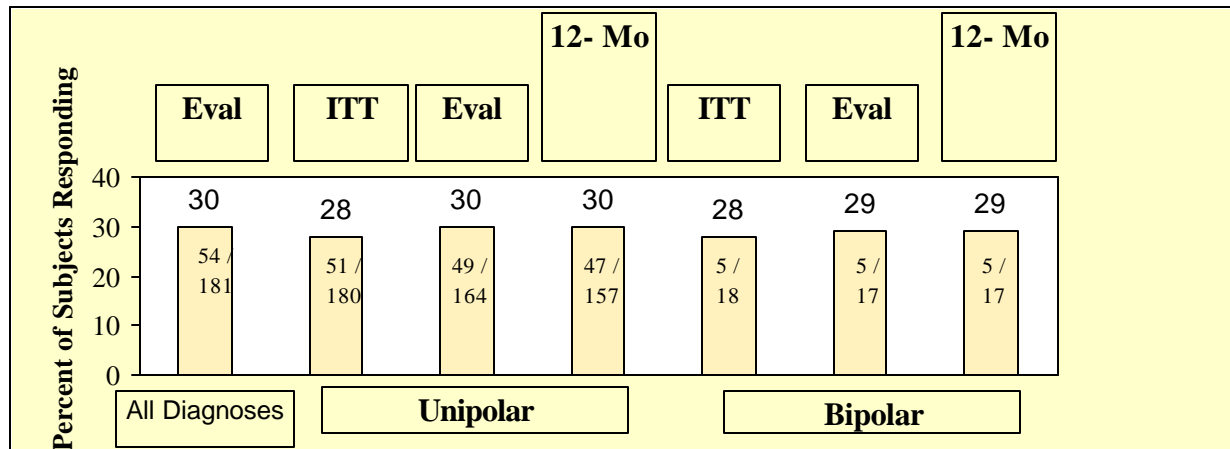
	D-02	D-04	P-Value
N	180	104 ¹	
Baseline Average	27.9	27.8	
12 Month Data			
Average	19.6	22.8	
Median	19.5	23.5	
Average Change	-8.2	-4.9	0.006**
LOCF Average Change	-7.4 (N=205)	-4.9 (N=104)	0.040*
Median Change	-7.5	-5.0	
Avg. % Change	29.6	16.6	
Median % Change	28.4	15.6	
Response (% of Subjects)	30	13	0.003**
LOCF Response (% of Subjects)	27 (N=205)	13 (N=104)	0.011*
Complete Response (% of Subjects)	17	7	0.031*
LOCF Complete Response (% of Subjects)	17 (N=205)	7 (N=104)	0.059

1 – 20 D-04 subjects did not have HRSD's performed at their 12-month visit; the 12-month HRSD was added after study initiation and several sites did not have IRB approval prior to subjects reaching one-year in the study.

+Absence of a p-value indicates no statistical test was applied. *Significant at the 0.050 level. ** Significant at the 0.010 level. (exact logistic)

Separate analyses for both unipolar and bipolar groups were performed and found to show identical results for the evaluable, ITT, or 12 month completer populations. As shown in Figure 4, the unipolar and bipolar results closely parallel the results seen in the original (combined) evaluable, ITT and 12 month completer analyses. Because of the decreased sample size of the subgroups, some statistical power is lost, though most of the unipolar analyses retain statistical significance due to the marked difference in one-year outcomes in the comparison between D-02 and D-04. The bipolar group sample size was too small for most of the outcomes to reach statistical significance, and indeed for many analyses was too small to perform a valid analysis (e.g. categorical outcomes).

Figure 4
HRSD₂₄ Response by Diagnosis

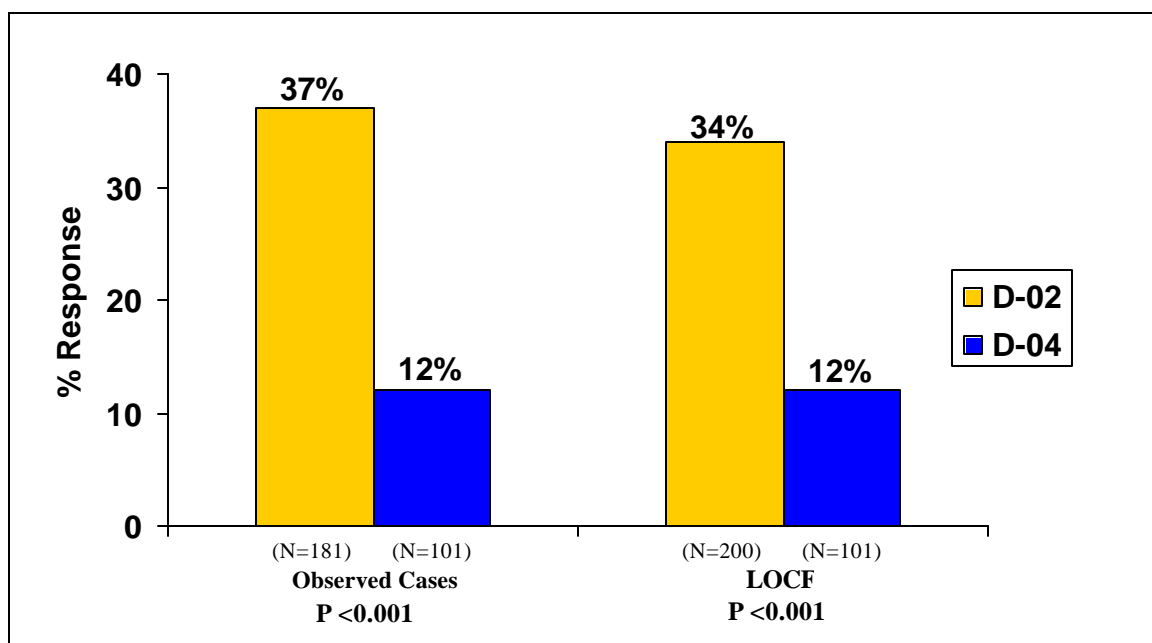


It should be noted that due to the very small number of bipolar patients, the full logistic regression model (with 17 covariates) used to generate the propensity score could not be calculated for the Bipolar patients.

CGI-I (Clinical Global Impression – Improvement)

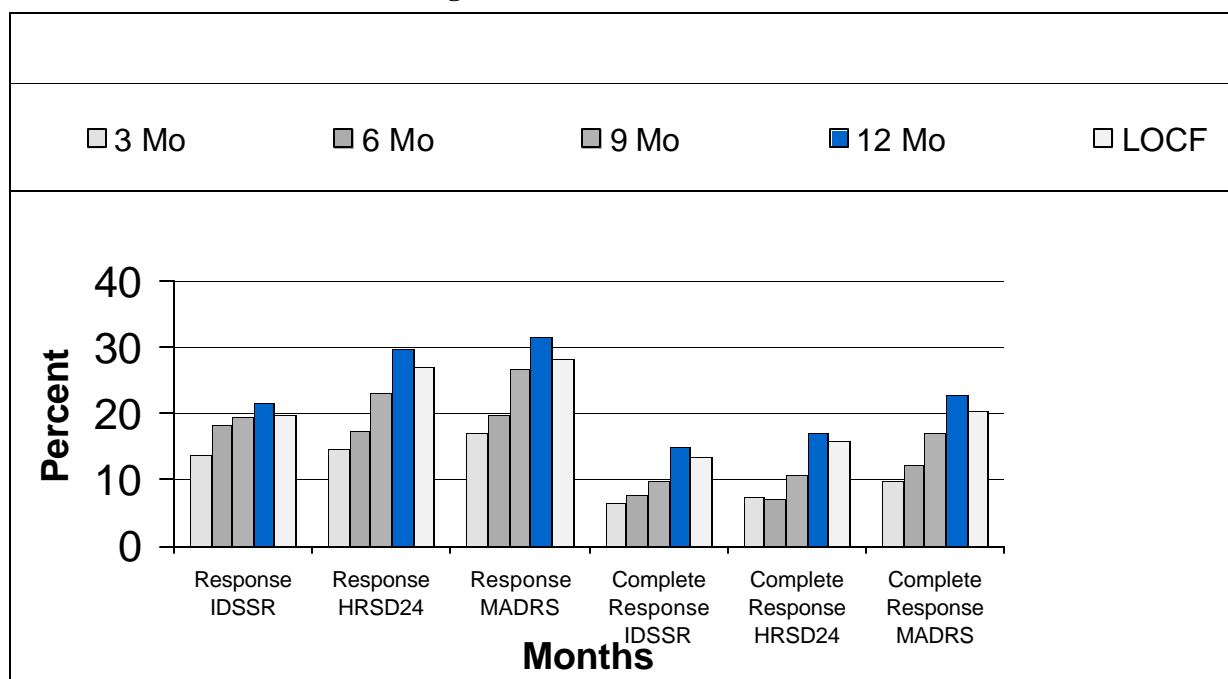
Further support for the effect of VNS Therapy is demonstrated by the results from the CGI-I; three times as many D-02 subjects (37%) were rated as much improved or very much improved at 12 months than the D-04 subjects (12%; $p < 0.001$; LOCF 34% vs. 12%, $p < 0.001$; evaluable population; exact logistic regression). The magnitude of these differences indicates robust clinical significance in addition to the statistical significance. The results are shown in the following figure (Figure 5).

Figure 5
Clinical Global Impression – Improvement (CGI-I) at
12 Months, D-02 and D-04 (Evaluable Population)



Sustained Response - 12-Month Completer Population

Figure 6
D-02 IDS-SR, HRSD₂₄ & MADRS Response and Complete Response
(Long-Term D-02 Evaluable)



Note: N's vary depending on observed data for each assessment at each visit (see Appendix tables); LOCF N's range from 200 to 202, depending on the assessment.

The figure above (Figure 6) demonstrates continuing improvement over time for the treatment population. To show that individual responders maintained their response the Sponsor performed a sustained response analysis. This analysis was developed and analyzed to show whether subjects were sustaining a response over a period of time rather than just responding at one point in time. Sustained response is characteristic of true treatment response whereas transient response is characteristic of placebo response. Additionally, because of the chronic and recurrent nature of the illness, sustained response is a more clinically relevant outcome.

Subjects were assessed over the last four visits of the first year of VNS Therapy (months 9, 10, 11, and 12) to ascertain which subjects were sustained responders (defined in the statistical plan as the key clinical endpoint). Subjects who had at least one visit with a 50% or greater response

and at least an additional two visits with at least a 40% or greater response were classified as sustained responders.

Of 177 subjects in the 12-month completer population (both groups combined), 47 (27%) were sustained responders. This is a significant portion of subjects considering the treatment resistant nature of the population. The importance of this endpoint is magnified by the fact that this treatment resistant depression population by definition had shown little response prior to the trial.

Long Term Clinical Benefit Analyses

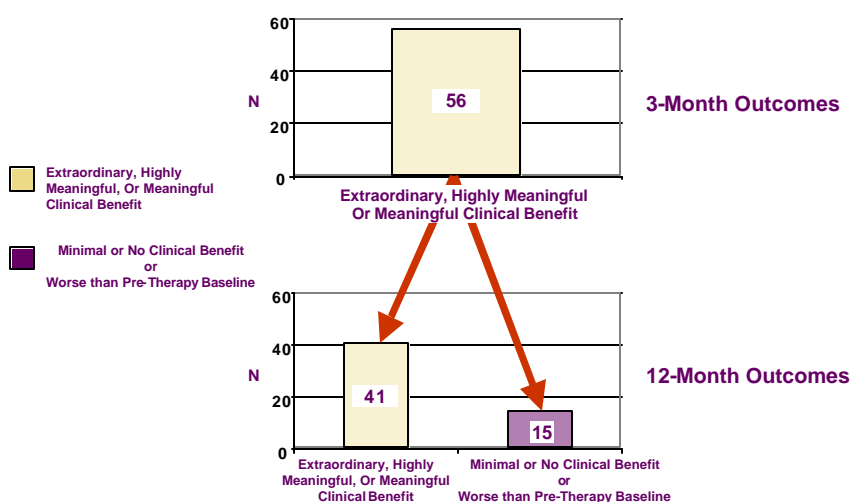
As defined by the statistical plan, subjects were also evaluated categorically by assigning them into groups according to “clinical benefit.” Clinical benefit was categorized as extraordinary ($\geq 75\%$ improvement in HRSD₂₄), highly meaningful (50% to $<75\%$), meaningful (25% to $<50\%$), minimal (0% to $<25\%$) and worsened (less than 0%). This was done to explore if these treatment-resistant depression (TRD) subjects were receiving benefit that was not fully reflected in the response rates. This is consistent with studies in many chronic illnesses that define lower percentages ($<50\%$ improvement) as a clinically meaningful response (eg schizophrenia, obsessive compulsive disorder).

This analysis is based on 12-month HRSD₂₄ scores; although 177 subjects are in the 12-month completer population, 3 subjects had 11-month scores but not 12-month scores, therefore only 174 subjects are displayed. Based on this categorization, 30% of subjects in the 12-month completer group experienced either an extraordinary or a highly meaningful clinical benefit while an additional 25% had a meaningful benefit at 12 months of VNS Therapy (56% had at least a meaningful benefit). This benefit was greater at 12 months compared with 3 months (Stuart-Maxwell test, $p < 0.001$)

The clinical benefit categorization can also be analyzed to further characterize benefit over time. Both those who had early benefit and those who did not were assessed later (12-months). Of the 56 12-month completer subjects who had extraordinary, highly meaningful, or meaningful clinical benefit at 3-months, 41 (73%) *continued to have extraordinary, highly meaningful, or meaningful clinical benefit at 12-months* (see Figure 7). Conversely, *of the 118 subjects who were without meaningful benefit at 3-months, 56 (47%) had at least meaningful clinical benefit by 12-months of VNS Therapy* (see Figure 8). This indicates that a large portion of those who do not

benefit early will eventually receive meaningful clinical benefit. More importantly for a TRD population, most subjects who have early meaningful clinical benefit continue to maintain this meaningful benefit at 12-months. As a point of reference, it is widely recognized that the powerful acute effect of ECT diminishes over time. A recent ECT study shows that within six months of achieving remission ($\text{HRSD} \leq 10$), the relapse rate was 64%.²

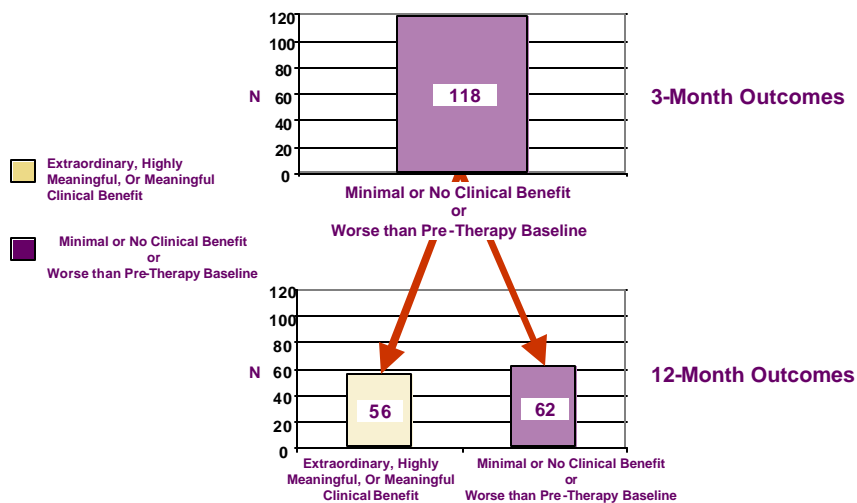
Figure 7
12-Month Outcomes of D-02 Subjects with Extraordinary, Highly Meaningful or Meaningful Clinical Benefit At 3-Months (N=56)



? **73% (41/56) of subjects maintained at least a meaningful benefit.**

² Prudic J, Olfson M, Marcus SC, Fuller RB, and Sackeim HA. The effectiveness of electroconvulsive therapy in community settings. *JAMA*. 2003; in press.

Figure 8
12-Month Outcomes of D-02 Subjects with Minimal or Less Clinical Benefit
At 3-Months (N=118)



? 47% (56/118) of subjects with minimal or less benefit after 3 months of VNS Therapy obtained meaningful to extraordinary benefit after 12 months of VNS Therapy.

Responders, Complete Responders, Percent Change, Raw Score, and Percent Change from 3 Months to 12 Months

The following table (Table 14) presents the proportion of subjects for the HRSD₂₄, IDS-SR, and MADRS achieving response (proportion of subjects with a 50% or greater improvement in assessment score compared with the pre-therapy baseline and not a treatment failure), complete response (subjects with an assessment score below a preset value), average percent change from baseline, raw score change, and median percent change from 3 months of therapy. For each of these outcomes at the 12-month visit, the result for the 12-month completer population was statistically significant, as were the corresponding last observation carried forward (LOCF) analyses. As previously discussed, this analysis technique uses the last available data point for subsequent time points where data is missing. Note that the LOCF analysis makes little to no difference in this study, because retention at one year is 90%. Results across assessments and populations (evaluable and 12-month completer) were similar, statistically significant, and supportive of a robust treatment effect.

Table 14
Responders, Complete Responders & Percent Change (HRSD₂₄, IDS-SR, MADRS)
12-Month Completer Population in D-02

	HRSD ₂₄		IDS-SR ^b		MADRS	
	12-Month Visit	LOCF	12-Month Visit	LOCF	12-Month Visit	LOCF
Responders – N (%)						
Treatment	34/103 (33%) ²	34/103 (33%) ²	25/102 (25%)	26/103 (25%)	34/103 (33%) ²	34/103 (33%) ²
Delayed treatment	18/71 (25%)	18/74 (24%)	13/71 (18%)	13/73 (18%)	22/71 (31%) ¹	22/74 (30%)
All 12-Month Completers	52/174 ^a (30%) ³	52/177 (29%) ³	38/173 (22%) ¹	39/176 (22%) ¹	56/174 (32%) ³	56/177 (32%) ³
Complete-Responders – N (%)						
Treatment	19/103 (18%) ²	19/103 (18%) ²	16/102 (16%) ¹	16/103 (16%) ¹	25/103 (24%) ²	25/103 (24%) ²
Delayed treatment	10/71 (14%)	10/74 (14%)	10/71 (14%)	10/73 (14%)	16/71 (23%) ^{1 c}	16/74 (22%)
All 12-Month Completers	29/174 (17%) ²	29/177 (16%) ²	26/173 (15%) ²	26/176 (15%) ²	41/174 (24%) ³	41/177 (23%) ³
Percent Change - % (S.D.)						
Treatment	31.9% (33.1) ³	31.9% (33.1) ³	27.8% (30.6) ³	28.1% (30.6) ³	32.9% (36.4) ³	32.9% (36.4) ³
Delayed treatment	26.5% (32.8) ³	24.8% (34.4) ³	17.3% (32.8) ³	16.7% (32.5) ³	26.3% (38.0) ³	24.3% (39.7) ³
All 12-Month Completers	29.7% (33.0) ³	28.9% (33.7) ³	23.5% (31.9) ³	23.4% (31.8) ³	30.2% (37.1) ³	29.3% (38.0) ³
Raw Score – \bar{x} (S.D.)*						
Treatment	19.3 (9.5)	19.3 (9.5)	32.0 (15.6)	31.9 (15.5)	20.7 (11.4)	20.7 (11.4)
Delayed treatment	19.9 (9.9)	20.2 (9.9)	33.4 (15.1)	33.6 (15.0)	21.8 (11.9)	22.1 (11.8)
All 12-Month Completers	19.6 (9.7)	19.7 (9.7)	32.6 (15.4)	32.6 (15.3)	21.2 (11.5)	21.3 (11.5)
Median % Change 3 Months						
Treatment	22.2% ²	22.2% ²	10.6%	10.6%	20% ³	20.0% ³
Delayed treatment	15.4% ²	13.1% ²	8.6% ¹	8.8% ¹	12%	12.0%
All 12-Month Completers	19.7% ³	19.4% ³	10.2% ²	10.3% ²	17.2% ³	16.7% ³

¹ p<0.05; ² p<0.01; ³ p<0.001; Response and Complete Response used the Exact McNemar's test compared with 3 months; Percent Change used the paired t-test (change from pre-stimulation baseline); Median percent change used the Wilcoxon Signed Rank test to determine whether the median was different from zero.

^a – Three subjects did not have 12-month HRSD₂₄ assessments (these 3 did have 11-month assessments).

^b – One subject did not have a baseline IDS-SR assessment while several others did not have 12-month assessments. This explains the varying N's when comparing

^c – two delayed treatment subjects did not have 12-month MADRS assessments.

* - No statistical testing was performed on the raw values.

Concomitant Treatments Received

ECT

No subjects received ECT during the acute phase of D-02. A total of 14 subjects (delayed-treatment subjects 042-0238, 043-0015, 043-0245, 044-0033, 044-0055, 050-0032, 051-0106, 059-0241; treatment subjects 041-0192, 050-0125, 053-0035, 055-0119, 056-0218, 059-0095) received ECT during the D-02 long-term phase through 12 months of VNS Therapy. All 14 subjects were evaluable (7% of the evaluable population), while 8 of the 14 were 12-month completers (5% of the 12-month completer population). ECT was used more frequently in non-responders and was unlikely to substantially affect the results. Four subjects were responders, two of which were complete responders; none of the subjects were sustained responders (HRSD₂₄). Only one of the four responders received ECT in proximity to the 12-month visit.

A similar percentage of D-04 subjects (7 of 112 subjects - 040-007, 050-003, 057-014, 058-002, 071-001, 071-002, 071-003; 6%) received ECT through 12-months. Two of the 7 were responders at 12-months.

Therefore, ECT usage was similar, with similar results, in both study D-02 and D-04.

Mood Medication Changes (Long-Term Phase & D-02 vs D-04 Comparison)

Mood medication changes were permitted during the long-term phase; they are important to analyze in relationship to response. To ascertain mood medication changes over the course of the long-term phase, an antidepressant resistance rating (ARR) score was determined for each medication for each subject. Changes were then assessed by responder or non-responder classification to ascertain whether responders ($\geq 50\%$ improvement in HRSD₂₄ at 12-months) had more changes in mood medications than non-responders ($< 50\%$ improvement in HRSD₂₄ at 12-months). An additional analysis was performed for remitters (HRSD₂₄ score less than 10) and non-remitters.

More *non-responders* (77%) than responders (56%) added or increased mood medications during 12-months of VNS Therapy. Additionally, almost twice as many responders (44%) had no ARR changes or removed or decreased medications by at least one ARR or were not taking medications as compared to non-responders (23%). Changes were similar when comparing complete responders (remitters) with non-complete responders. This information suggests that medication changes were unlikely to have had a significant impact on outcomes

When compared to D-02, D-04 ARR changes were similar to the non-responders from D-02. Over 81% of all D-04 subjects added or increased mood medications by at least one ARR. Only 7% of subjects reduced or discontinued medications by at least one ARR without any increase in a corresponding mood medication by at least one ARR. Data also indicated that the “strength” of changes were similar between D-02 and D-04 subjects.

This information is important for two reasons. First, it internally validates that the D-04 group was receiving significant medication changes (which is important for verifying that D-04 is a relevant reference group for D-02). Secondly, it provides a validation that the D-02 responders had less medication changes than might typically be expected. The lower frequency of medication changes among D-02 responders compared to D-04 subjects and D-02 non-responders is strong evidence that improvement in the D-02 subjects is due to VNS Therapy and not medication.

Robustness of the Efficacy Results

The statistical plan specified that the efficacy analyses would be performed on an evaluable population using observed data. To further evaluate the robustness of the results described in the preceding sections, several additional analyses were performed. These included statistical testing of an intent-to-treat (ITT) analysis of the primary efficacy model and last observation carried forward (LOCF) analyses on the D-02 vs. D-04 secondary analyses. Additionally, the subset of D-02 sites also involved in the D-04 study was analyzed descriptively. Finally, the primary efficacy analysis was performed with censoring of the D-02 data for concomitant antidepressant treatment use. The purpose of these additional analyses was to demonstrate that the superior D-02 outcomes (1) were not altered if all D-02 implanted subjects were included in the primary analysis, (2) were not altered when missing observations were accounted for, (3) were not explained solely by depression improvement in subjects from the D-02 sites that did not participate in the D-04 study, and (4) were not due to concomitant antidepressant treatment.

An ITT analysis typically includes all randomized subjects regardless of whether they receive adequate treatment or continue for an adequate duration. Therefore this is a conservative approach to analyzing treatment outcomes that eliminates any potential bias that may arise by excluding certain subjects from the efficacy analysis. For this analysis, the four acute continuation criteria failure subjects were not included as a further conservative approach

(response prior to stimulation initiation). Therefore the ITT analysis included 231 D-02 subjects and 124 D-04 subjects. The ITT analysis results of the primary efficacy model were statistically significant ($p < 0.001$).

An LOCF analysis is a technique often used by statisticians to address the impact of missing data. It uses the last available observation for subsequent time points where data are missing. For treatments associated with an increasing effect over time, LOCF understates the true treatment effect. LOCF analyses were performed on all D-02/D-04 secondary comparisons, and statistical significance was maintained for all comparisons except for the IDS-SR evaluable response rates and HRSD₂₄ evaluable complete response rates; in these latter two analyses, the results approached statistical significance.

Where sites are not identical between two studies, the differential outcomes among these sites can contribute to biasing the outcome. Since the D-02 and D-04 studies had some different sites, this was a potential concern. Therefore results were examined from sites that were only involved in both the D-02 and D-04 studies. This examination (a response rate analysis using the HRSD₂₄) yielded results similar to the analysis that included all the sites (27% HRSD₂₄ responder rate at 12-months for the D-02 sites that also participated in the D-04 study vs. 30% for all D-02 sites). A formal statistical analysis was not performed because the decreased sample size would not ensure adequate power.

An additional conservative statistical analysis was performed to confirm the results of the descriptive medication analyses presented above. In this alternative analysis, D-02 subjects' scores were censored when the addition of an antidepressant treatment or an increase in an existing treatment by an ARR level of one or more occurred. The analysis incorporated additions or changes in either antidepressant drugs or ECT. In other words, if a D-02 subject added or increased a concomitant antidepressant treatment, his or her subsequent IDS-SR scores were not used in this confirmatory repeated measures linear regression analysis. Instead the subject's last IDS-SR score before the concomitant antidepressant treatment change was used for subsequent assessment points (ie, a last-observation-carried-forward approach). Consequently this analysis removes from the VNS Therapy group outcome any potential benefit from an addition or increase in concomitant antidepressant treatment. The approach is asymmetric as no censoring is

performed on the D-04 data. It is an overly conservative approach because it penalizes VNS Therapy by removing all incremental benefit that is attributable to VNS Therapy after the censoring time point. Therefore, it understates the treatment effect of VNS Therapy.

Despite using this very conservative approach, the repeated measures linear regression analysis of IDS-SR scores was still marginally statistically significant ($p = 0.052$). This constitutes very strong evidence that the superior outcome in the VNS Therapy group is not due to concomitant antidepressant treatment. The 95% confidence interval (-0.37 to 0.00 for the D-02/D-04 difference in IDS-SR score per month where negative values indicate D-02 superiority) shows that the addition of VNS Therapy alone (ie, without any additions or increases in concomitant antidepressant treatments) for less than one year of treatment was virtually always more effective than were *multiple* medication/ECT additions or increases over a full year of treatment using any currently available therapeutic option (standard-of-care).

When primary analysis of IDS-SR data are performed looking at only shared D-02/D-04 study sites ($p=.002$) or at only unipolar subjects ($p<.001$), the results continue to be statistically significant.

In summary, several alternative analyses as described above were applied to the comparisons of the D-02 and D-04 efficacy outcomes. The objective of these alternative analyses was to determine if applying conservative statistical approaches to address the potential biases that might be inherent in the primary and secondary analysis strategies would alter the statistical significance or the conclusions of the D-02/D-04 comparisons. When the D-02 and D-04 results were compared with the conservative alternative analyses, the D-02 outcomes almost always remained statistically significantly superior to the D-04 outcomes. Thus the robust statistical significance demonstrated in the primary and secondary analyses was confirmed by more conservative supplemental analyses.

3. Comprehensive VNS Safety Summary

a) Depression Experience

This section provides an integrated summary of safety data from studies D-01, D-02, and D-03. SAE data are current through a data cutoff date of 05/30/03.

As previously stated, D-04 was a long-term, observational study and no safety data was collected.

Disposition of Subjects

The following table (Table 15) provides an overview of the implantation and follow-up for each study.

Table 15
Summary of Subject Disposition

Study	Implanted	Completed 10 Weeks of Stimulation	Completed 12-Months of Stimulation	Total Withdrawn as of Report
Study D-01	60	60	59	8
Study D-02	235	233	211	30
Study D-03	47	43	23	9
Totals	342	336	293	47

During the three studies, the VNS Therapy System performed according to its labeling. Most device issues were associated with communication difficulties and were easily resolved by repositioning the programming wand or replacing the programming wand batteries. One high lead impedance occurred requiring replacement of the lead. Analysis of this lead revealed a lead break due to fatigue at the electrode bifurcation. It is important to note that overall lead survivability is excellent at greater than 98.8% at 71 months.

The following table (Table 16) shows acute phase implantation-related treatment emergent adverse events. The determination whether an event was related to implantation was made by the investigator. Events reported at a $\geq 5\%$ incidence considered to be possibly, probably, or definitely related to implantation were incision pain, voice alteration, incision site reaction (typically redness or swelling at the incision site), device site pain, device site reaction (typically soreness, swelling or tenderness near the generator site), pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia, and increased cough.

These events are all expected during the type of surgical procedure associated with VNS Therapy implantation, and except for headache are addressed in the current labeling for VNS Therapy.

Table 16
D-01 and D-02 Acute Phase Incidence of Treatment-Emergent Adverse Events (AEs)
Related to Implantation $\geq 5\%$

Body System	Preferred Term	D-01 (N=60) N (%)	D-02 (N=235) N (%)
Number of Subjects with at Least One Adverse Event		48 (80)	208 (89)
Body as a Whole	Device Site Pain	10 (17%)	54 (23%)
	Device Site Reaction	4 (7%)	33 (14%)
	Headache	5 (8%)	18 (8%)
	Incision Pain	10 (17%)	84 (36%)
	Neck Pain	2 (3%)	16 (7%)
	Pain	7 (12%)	17 (7%)
Cardiovascular System	None $\geq 5\%$	-	-
Digestive System	Dyspepsia	3 (5%)	
	Dysphagia	2 (3%)	26 (11%)
	Nausea	2 (3%)	20 (9%)
Endocrine System	None $\geq 5\%$	-	-
Hemic and Lymphatic System	None $\geq 5\%$	-	-
Metabolic and Nutritional Disorders	Healing Abnormal	4 (7%)	0%
Musculoskeletal System	None $\geq 5\%$	-	-
Nervous System	Hypesthesia	3 (5%)	25 (11%)
	Paresthesia	0%	13 (6%)
Respiratory System	Cough Increased	1 (2%)	15 (6%)
	Dyspnea	2 (3%)	20 (9%)
	Pharyngitis	1 (2%)	31 (13%)
	Voice Alteration	11 (18%)	78 (33%)
Skin and Appendages	Incision Site Reaction	6 (10%)	67 (29%)
Special Senses	None $\geq 5\%$	-	-
Urogenital	None $\geq 5\%$	-	-

Note: Percentages are relative to the number of subjects in the safety population. Note: Subjects are counted only once within each body system and preferred term. Note: Includes all AEs where relationship to implantation was recorded as possible, probable, or definite.

The following table (Table 17) shows all events $\geq 5\%$ in the D-01 and D-02 studies reported by investigators during acute phase treatment as possibly, probably, or definitely related to stimulation.

Table 17
D-01 and D-02 Acute Phase Incidence of Treatment-Emergent Adverse Events (AEs) Related to Stimulation $\geq 5\%$

Body System	Preferred Term	D-01 Treatment (N=60) N (%)	D-02 Treatment (N=119) N (%)	D-02 Sham-control (N=116) N (%)
Number of Subjects with at Least One Stimulation-Related Adverse Event		56 (93%)	100 (84%)	34 (29%)
Body as a Whole	Headache	11(18%)	5 (4%)	1 (<1%)
	Incision Pain	0%	6 (5%)	3 (3%)
	Neck Pain	13 (22%)	19 (16%)	1 (<1%)
	Pain	9 (15%)	4 (3%)	2 (2%)
	Reaction Unevaluable	3 (5%)	5 (4%)	0%
Cardiovascular System	Palpitation	3 (5%)	3 (3%)	1 (<1%)
Digestive System	Dyspepsia	4 (7%)	4 (3%)	0%
	Dysphagia	5 (8%)	15 (13%)	0%
	Nausea	4 (7%)	8 (7%)	1 (<1%)
Metabolic and Nutritional Disorders		None $\geq 5\%$	None $\geq 5\%$	None $\geq 5\%$
Musculoskeletal System		None $\geq 5\%$	None $\geq 5\%$	None $\geq 5\%$
Nervous System	Dizziness	4 (7%)	3 (3%)	0%
	Hypertonia	3 (5%)	2 (2%)	1 (<1%)
	Insomnia	3 (5%)	4 (3%)	0%
	Manic Reaction	3 (5%)	1 (<1%)	0%
	Paresthesia	3 (5%)	12 (10%)	3 (3%)
Respiratory System	Cough Increased	10 (17%)	28 (24%)	2 (2%)
	Dyspnea	8 (13%)	23 (19%)	2 (2%)
	Laryngismus	2 (3%)	13 (11%)	0
	Pharyngitis	3 (5%)	9 (8%)	1 (<1%)
	Voice Alteration	33 (55%)	65 (55%)	3 (3%)
Skin and Appendages		None $\geq 5\%$	None $\geq 5\%$	None $\geq 5\%$
Special Senses	Ear Pain	3 (5%)	1 (< 1%)	0%
Urogenital		None $\geq 5\%$	None $\geq 5\%$	None $\geq 5\%$

Note: Subjects are counted only once within each body system and preferred term. Note: Includes all AEs where relationship to stimulation was recorded as possible, probable, or definite. Note: Percentages are relative to the number of subjects in the safety population.

Duration of event was analyzed in Study D-02. As expected, surgical events dissipated significantly over the first several weeks after device implantation. However, hypesthesia and vocal cord paralysis (events which may involve some nerve damage to either surrounding sensory nerves in the neck or directly to the vagus nerve) may take much longer to resolve or be permanent. These events are already adequately described in labeling (known events from the epilepsy studies).

Stimulation related events also typically dissipate over time. Either by a quarter analysis of all subjects or by analyzing the cohort of subjects reporting events during the first 3-months and seeing if events continue to be reported in those subjects, stimulation related events dissipate by 25% to 89% over one year. The decrease depends on the specific AE, and the most common AE of hoarseness (voice alteration) does show the least amount of decrease over one-year.

Physical and Neurological Examinations, Vital Signs Assessments, & Holter Monitor Recordings

Investigators performed physical and neurological examinations in D-01 and D-02 study subjects at baseline, end of acute phase, and one-year of VNS Therapy. The post-baseline examinations were essentially unremarkable except for the presence of healed surgical scars and the occasional presence of voice alteration. For the D-02 Study, changes from baseline were plotted graphically for blood pressure, heart rate, respiratory rate and weight. The changes conformed to a symmetric distribution suggesting an absence of effect associated with VNS Therapy.

Holter monitor recordings were obtained as part of the D-01 study. The recordings did not show any evidence of significant changes after VNS Therapy was initiated. This agreed with previous findings from the epilepsy studies. Therefore, in agreement with FDA, no Holter monitoring was required for the D-02 study.

Serious Adverse Events (SAE)

A serious adverse event (SAE) was defined as an event that resulted in death, life-threatening event, a hospitalization or prolongation of existing hospitalization, a persistent disability, a congenital anomaly, and pregnancy or cancer. Important medical events that did not result in death, were not life threatening, or did not require hospitalization may have been considered an SAE when, based upon appropriate medical judgment if they may have jeopardized the subject

and may have required medical or surgical intervention to prevent one of the outcomes listed above.

It is important to note that SAE's were determined without regard to possible relationship to VNS Therapy. Particularly during the long-term phase the subjects underlying psychiatric and medical conditions and their concomitant treatments (including antidepressant medications) were important potential contributors to the SAEs. Most of the SAE's described during the studies were not considered by the investigator or Sponsor to be related to VNS Therapy; only SAE's considered related to VNS Therapy implantation or treatment are included in this summary.

Summary Table of SAEs

The following table (Table 18) lists the overall incidence of serious adverse events at least possibly related to VNS Therapy by event for each subject during the acute and long-term phases of studies D-01, D-02, and D-03 (including events reported during ongoing treatment past the 12-month long-term phases).

Table 18
Summary of Serious Adverse Events at Least Possibly Related
to VNS Therapy (Safety Population for Each Study)¹

Body System	COSTART Term	D-01	D-02	D-03
Study N		60	235	47
Body as a Whole	Overdose or Suicide Attempt	2	0	0
	Pain (calf of leg)	1 (I)	0	0
	Sudden Unexplained Death	0	1	0
	Wound Infection	1 (I)	1 (I)	0
Cardiovascular	Asystole	0	1 (I)	0
	Bradycardia	0	1 (I)	0
	Deep Thrombophlebitis	1 (I)	0	0
	Myocardial Infarction	1	0	0
	Syncope	0	1 (I) + 2 ²	1
Digestive	Diarrhea	1	0	0
	Esophagitis	1	0	0
	Hemorrhage GI	0	1	0
	Vomiting	1	0	0
Nervous System	Agitation	1	0	0
	Depression	3	1	1
	Dizziness	0	1	0
	Dysphoria	1	0	0
	Manic-Depressive Rx	1	1	0
	Paresthesia	0	1	0
	Thinking Abnormal	0	1 (I)	0
	Vocal Cord Paralysis	0	2 (I) + 1 ²	0
Respiratory System	Pulmonary Embolism	0	0	1 (I)
	Aspiration Pneumonia	0	1 (I)	0
	Voice Alteration	0	1 (I)	0
Skin & Appendages	Device Site Reaction	0	2 (I)	0
Urogenital	Acute Renal Failure	0	1 (I)	0
	Urinary Retention	0	1 (I)	0
TOTALS		15	22	3

¹Cut-off date is 05/30/03. ² Event for one subject (047-171) also noted as possibly related to implantation. I = implant

Of the D-01 SAE's reported as at least possibly related to VNS Therapy, *only one was judged definitely related*; this was the event of wound infection associated with implantation. All other D-01 events were rated as "possibly" related. These were events that the investigator could not rule out as having a possible relationship to stimulation, but were not necessarily related to stimulation.

Of the D-02 SAE's reported as at least possibly related to VNS Therapy, *6 events were judged definitely related to implantation* (voice alteration, vocal cord paralysis, asystole, 2 device site reactions [reposition of generator, extrusion of leads], and wound infection). The other

implantation related events included three probably related to implantation (acute renal failure, abnormal thinking and urinary retention) and four possibly related (aspiration pneumonia, bradycardia, syncope, and vocal cord paralysis). These events are known complications of surgery in general (infection, urinary retention), or were caused by medications administered peri-operatively (acute renal failure, abnormal thinking) or are specific to VNS Therapy surgery (vocal cord paralysis, asystole/bradycardia).

No D-02 SAE's were reported as definitely related to stimulation. One SAE was reported as probably related (paralysis of the vocal cord) to stimulation. Eight SAE's were reported as possibly related to stimulation, since the investigator could not rule out having a possible relationship to stimulation, although these events were not necessarily related to stimulation. These events included depression, manic-depressive reaction, gastrointestinal bleed, paresthesia, dizziness, sudden unexplained death, and syncope. The syncope and vocal cord paralysis were also noted as possibly related to implantation, although the events occurred at least 10 months after implantation.

Of the D-03 SAE's reported at least possibly related to VNS Therapy, *one event was judged definitely related to implantation* and two were possibly related to stimulation. An event of pulmonary embolism was thought definitely related to implantation while the events of depression and syncope were considered possibly related to stimulation. An additional D-03 subject experienced vocal cord paralysis associated with surgery that was not reported as an SAE.

The most common SAE during acute treatment was depression (all studies, regardless of relationship to VNS Therapy). Although more properly considered a lack of efficacy than an AE, these events were categorized as SAEs because the subjects required hospitalization, thus triggering the designation of SAE. Although only a small number (5) of these worsened depression events were reported as even possibly associated with VNS Therapy, the SAEs of depression are discussed here for completeness. Hospitalization for depression was reported in similar numbers in each D-02 acute phase group (five [5] in the treatment group and seven [7] in the sham-control group [no stimulation]). Additionally in D-02, three SAEs of the nine SAEs occurring *prior* to implantation were for worsened depression/suicidal ideation; another two of these pre-implantation SAEs were for hospitalization associated with suicide attempts (subjects 049-042 and 058-129). This information underscores the severity of this population and that

worsened depression and suicide attempts are expected in this group. There does not appear to be any relationship to VNS Therapy.

After reviewing the published literature and comparing it to the combined D-01, D-02, and D-03 studies, it is clear that completed and attempted suicide rates for subjects receiving adjunctive VNS Therapy are not greater than for standard-of-care treatment alone. The following table (19) provides completed and attempted suicide rates for implanted patients in D-02 and for all patients combined in D-01, D-02, and D-03, and compares them to rates published by Khan, 2000 in his article which reviewed an FDA clinical database consisting of 45 studies for all antidepressants approved in the US during the years January 1987 to December 1997. This comparison to Khan is justified due to their large patient database of about 20,000 patients, coming from the FDA clinical trials database. Note that the antidepressants included in this review were from studies of depressed patients (not treatment-resistant).

Table 19
Suicide Rates and Attempts reported in Khan¹ review of the FDA Database
and in the D-01, D-02 and D-03 Combined Database

	N	Incidence of Suicide Attempts N (%)	Incidence of Suicide N (%)	Patient years	Incidence of Suicide Attempt/ patient year	Incidence of Suicide / patient year
D-01, D-02, D-03 combined	342	24 (7%)	3 (0.9%)	689	3.5%	0.4%
D-02 total	235	11 (5%)	1 (0.4%)	437	2.5%	0.2%
Investigational drug-Khan ²	12,879	90 (0.7%)	27 (0.2%)	3,206	2.8%	0.8%
Active comparator-Khan ³	3,681	25 (0.7%)	5 (0.1%)	729	3.4%	0.7%
Placebo-Khan	3,079	15 (0.5%)	2 (0.06%)	556	2.7%	0.4%

¹Khan, A, Warner HA, Brown, WA, Symptom Reduction and Suicide Risk in Patients Treated with Placebo in Antidepressant Clinical Trials, Arch Gen Psychiatry, 57, 2000, 311-317

²Investigational drugs included sertraline, paroxetine, nefazodone, mirtazapine, bupropion

³Comparator drugs included imipramine, amitriptyline and trazodone

This data reflects the serious adverse event data reported to the Sponsor as of 05/30/03. The terminology of “suicide attempt” includes those reported as suicide attempt and overdose. The aggregate VNS data comes from the 342 D-01, D-02 and D-03 subjects with treatment-resistant depression followed for up to 48 months for a total follow-up of 689 patient years.

Summary of Deaths

A total of seven deaths were reported during the D-01, D-02 and D-03 studies after implantation. Six of the seven were reported as not related to VNS Therapy by the investigators; one death, although unlikely to be related, was reported as possibly related since the investigator could not determine the exact cause of death.

Unanticipated Adverse Device Effects (UADEs)

There were no unanticipated adverse device effects (UADEs) reported for the D-01 or D-03 studies. Two D-02 UADEs were reported. The D-02 UADEs were related to concomitant medications administered during surgery (device implantation), not due to the device directly.

Summary and Conclusions

In general, adverse events were mild to moderate, similar to those reported in epilepsy, and were typically well-tolerated by subjects as evidenced by the high continuation rates. Most of the serious adverse events reported during the D-01, D-02, and D-03 studies were related to the patients' underlying illness, comorbid illnesses, medications, or other intercurrent events and not to VNS Therapy.

Over this year (and longer, as information was available past one-year), the VNS Therapy System performed according to its labeling. Most device issues were communication difficulties easily 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. It is important to note that overall lead survivability is excellent at greater than 98.8% at 71 months.

Adverse events were similar between studies. The most common implant related AE's were incision pain, voice alteration, incision site reaction (typically redness or swelling at the incision site), device site pain, device site reaction (typically soreness, swelling or tenderness near the generator site), pharyngitis, dysphagia, and hypesthesia. The most common stimulation related AEs were voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, and paresthesia. These events are already adequately described in labeling (known events from the previous epilepsy studies).

Duration of event was analyzed in Study D-02. As expected, surgical events dissipated significantly over the first several weeks after device implantation. However, hypesthesia and vocal cord paralysis (events which may involve some nerve damage to either surrounding sensory nerves in the neck or directly to the vagus nerve) may take much longer to resolve or be permanent. These events are already adequately described in labeling (known events from the epilepsy studies).

Stimulation related events also typically dissipate over time. Either by a quarter analysis of all subjects or by analyzing the cohort of subjects reporting events during the first 3-months and seeing if events continue to be reported in those subjects, stimulation related events dissipate by 25% to 89% over one year. The decrease depends on the specific AE, and the most common AE of hoarseness (voice alteration) does show the least amount of decrease over one-year.

Physical and neurological examinations in D-01 and D-02 study subjects at baseline, end of acute phase, and one-year of VNS Therapy suggested an absence of effect associated with VNS Therapy. Holter monitor recordings were obtained as part of the D-01 study. The recordings did not show any evidence of significant changes after VNS Therapy was initiated. This agreed with previous findings from the epilepsy studies.

Only a small number of serious adverse events (SAE's) were reported as even possibly related to VNS Therapy in Studies D-01, D-02 and D-03. An even smaller number (8) were felt to be definitely related to VNS Therapy; all eight were implant surgery related (expected events, such as infection, vocal cord paralysis, asystole, etc.). The SAEs that were reported as possibly related to VNS Therapy were typically events that the investigator could not rule out as having a possible relationship to stimulation, although these events were also not necessarily related to stimulation. The only two unanticipated adverse device effects reported were actually associated with medications administered during implant surgery.

In summary, the events seen in the depression studies, both typical adverse events and serious adverse events, were similar to those seen in epilepsy studies. VNS Therapy is a safe and tolerable therapy (90% continuation rate at one-year) for patients with treatment resistant depression.

b) Epilepsy Experience (E-01 through E-05 and Post Marketing Data)

The epilepsy experience of the VNS Therapy System is relevant to its use in depression since the surgical implantation is identical and the therapeutic use (device and its settings) is essentially the same. This summary provides a discussion of the clinical safety profile of the VNS Therapy System from the E-01 through E-05 Epilepsy Clinical Studies with an analysis of the 5 year commercial post-marketing experience including relevant safety information that was added to the VNS Therapy's labeling as a result of the post-marketing experience, the commercial marketing history and other important safety information as it relates to VNS Therapy System.

A clinical development program involving more than 450 patients in five clinical protocols examined the efficacy and safety of VNS Therapy for the treatment of epilepsy. These studies, starting in 1988, led to commercial approval in July 1997. Today, more than 22,000 people (>56,000 patient-years) worldwide have been implanted with Cyberonics' VNS Therapy System for difficult to control epilepsy.

VNS Therapy Surgery

The most common surgical side effects reported during the epilepsy clinical studies were infection and nerve injury.

Infection is an event that is possible with any surgical procedure. The percentage of subjects associated with device explant during the epilepsy clinical studies was 1.1% or 5/454 subjects (These data were derived from Summary of Safety and Effectiveness for the NCP Vagus Nerve Stimulation System, Table 13, P970003, Jan. 16, 1998). Following commercial approval, the percentage of patients experiencing an infection was 1.47% or 363/24,640 subjects of which 1.01% or 249/24,640 subjects went on to have their device explanted. Compared to other implantable pulse generators such as cardiac pacemakers, the rates are very favorable. Adhering to proper operating room technique and using prophylactic antibiotics can minimize the risk of infection.

Infection is an event that is possible with any surgical procedure. The rate associated with device explant during the epilepsy clinical studies (5/454; 1.1% derived from the Summary of Safety and Effectiveness for the NCP Vagus Nerve Stimulation System, Table 13, P970003, Jan. 16, 1998 – Attachment A) and during commercial use (total of 363/24,640 = 1.47%; associated with explant is 249/24,640 = 1.01%) is less than that reported for similar implantable devices. The risk of

infection can be minimized by adhering to proper operating room technique, and using prophylactic antibiotics.

Nerve injury is typically associated with either excessive manipulation of the nerve or blood supply during wound retraction. Nerve injury is typically manifested by left vocal cord paralysis or left facial paralysis. The rate of all nerve injuries reported during the epilepsy clinical studies was approximately 1% while the reported rate during commercial use is lower (less than 0.5%). These rates are both lower than nerve injuries reported from carotid endarterectomy (CEA), an operation in a similar area of the neck as VNS Therapy implantation.

Two other uncommon events associated with surgery that were never reported during the clinical studies, but were reported during commercial use included Horner's syndrome and bradycardia/asystole. Horner's syndrome has been reported after VNS Therapy surgery (12/24,640; 0.049%; noted as Horner's or ptosis or miosis). Horner's Syndrome is caused by damage or interruption of the sympathetic nerve to the eye, and is usually noted as a drooping of the eyelid on the same side of the damage. It is not necessary to treat Horner's syndrome since it is not painful and does not interfere with vision; depending on the nerve damage, full recovery may occur. This outcome is reported in the literature as associated with other neck surgeries, and Cyberonics' physician's manuals were updated to include this event (P970003/S004/A004 - submitted 3/9/98).

The other uncommon event associated with surgery is significant bradycardia or asystole during the first lead testing performed intraoperatively. No events of this nature were reported during the epilepsy clinical studies. However, 47 events (0.191% of implants) have been reported during commercial use. This event appears to be a vagal response associated with the initial stimulation during surgery. Patients experiencing bradycardia intraoperatively typically continue with the implant procedure, although some surgeons have decided not to implant the device after the event.

Cyberonics' Physician's Manual was updated in PMA Supplement P970003/S48 to recommend that:

1. During the intraoperative Lead Test, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).
2. Stimulation should not be programmed on until approximately 2 weeks following surgery to allow the wound to heal and allow the nerve time to accommodate to the electrode placement.
3. If a patient experiences asystole or severe bradycardia (heart rate < 40 BPM) or clinically significant changes in heart rate during a lead test during the initial implantation, the patient should be placed on a cardiac monitor during initial stimulation.

Therapeutic Side Effects and Tolerability

The two randomized, double-blind, controlled studies (E-03 and E-05) are the most appropriate to use when discussing adverse events. The following adverse events were found to occur more frequently acutely, in either High or Low stimulation, than in baseline in at least one of the two studies (E-03 High Group Rate, E-05 High Group Rate):

Table 20

Event	E-03 High Group¹	E-05 High Group¹
Cough	12.3%	52.6%
Dyspepsia	Not reported	21.1%
Dyspnea	10.5%	27.4%
Infection	3.5%	14.7%
Pain	Not reported	33.7%
Paresthesia	15.8%	24.2%
Throat Pain*	7.0%	42.1%
Voice Alteration / Hoarseness	38.6%	72.6%
Vomiting	1.8%	17.9%

* Throat pain includes pain in throat, laryngismus, and pharyngitis combined. (derived from Table 10, SS&E)

¹ High Group defined as receiving therapeutic stimulation

More than 95% of patients in the epilepsy clinical studies have continued to receive VNS Therapy for at least one year. This continuation rate for VNS Therapy is extremely high and indicates that VNS Therapy is well tolerated. [This rate is similar to the one-year continuation rate seen during the depression studies (92% for the D-01 study and 90% for the D-02 study).]

Cardiac Holter Safety Data and Mortality Rates

Holter monitor studies suggest there is no evidence of adverse cardiac effects associated with left cervical VNS using the VNS Therapy System, NCP System, and there appears to be no evidence of adverse cardiac effects associated with left cervical VNS using the NCP VNS Therapy System in patients 50 years and older.

Summary

More than 450 epilepsy study patients and more than 22,000 commercially implanted have proven that VNS Therapy is safe for its intended use when used in accordance with its labeling.

There are non-negligible surgical sequelae that are possible with VNS Therapy surgery, they are typical of those seen with other implantable devices (infections) or other similar surgeries (nerve damage), and are adequately described in the labeling and can be minimized through proper surgical technique and training. Additionally, the rates of these events seen with VNS Therapy surgery are similar to lower than those reported in the literature for similar devices and surgeries.

The most common events associated with VNS Therapy, are hoarseness and coughing, which occur during the actual stimulation (usually 30 seconds of stimulation every five minutes). Modifying stimulation settings can reduce these events. High continuation rates at one year support the overall tolerability of VNS Therapy. Holter monitor studies have demonstrated no evidence of adverse cardiac effects associated with left cervical VNS using the VNS Therapy System.

4. Other Information from Clinical Investigations

a) Comparison: D-02 vs. ECT Study

Many psychiatrists consider ECT to be the most effective acute therapy available for the treatment of depression. Owing to poor patient acceptance and safety concerns (particularly adverse cognitive effects), however, physicians generally reserve the use of ECT for patients who do not respond to or cannot tolerate pharmacotherapy, situations in which a rapid response is deemed desirable, and certain other limited situations (eg, psychotic depression). These same

concerns severely limit the use of ECT as a maintenance therapy. Consequently while some responders to an acute course of ECT receive longer-term maintenance ECT, most receive maintenance pharmacotherapy.

Prudic et al.³ recently completed an observational study of the effectiveness of ECT at seven community hospitals in the New York City metropolitan region. One of the investigators (Harold Sackeim, Ph.D.) of that study defined a subset of the study subjects in an attempt to provide a cohort that was well-matched to the D-02 study subjects. This provided a unique opportunity to compare the long-term effectiveness of VNS Therapy plus standard-of-care treatment (ie, the outcomes from study D-02) with the effectiveness of standard-of-care post-ECT maintenance treatment (the outcomes in the matched ECT cohort from the Prudic study).

Dr. Sackeim created the matched ECT cohort by excluding from the full data set subjects with the following characteristics that would have excluded the subjects from enrollment in the D-02 study:

1. Age less than 18 or greater than 72;
2. Baseline HRSD₂₄ score = 19;
3. Presence of psychotic symptoms;
4. Diagnosis of schizoaffective disorder.

The resulting matched ECT cohort comprised 172 of the 347 subjects in the original study population. The matched ECT cohort was similar to the D-02 long-term phase evaluable population (N=205) in sex distribution (65% female vs. 64% female, respectively), baseline mean HRSD₂₄ score (31 vs. 28), and mean age (48 years vs. 46 years). The matched ECT cohort had a greater proportion of subjects with a diagnosis of bipolar disorder than did the D-02 group (20% vs. 10%, respectively) and an older mean age of onset of mood disorder (29 years old vs. 22 years old, respectively). Overall, however, the D-02 group appears to comprise a more treatment-resistant population than does the matched ECT cohort because the D-02 group presented with a longer mean current episode duration than did the matched ECT cohort (50 vs. 11 months, respectively), a greater proportion of subjects with a history of prior ECT (53% vs. 32%), more

³ Prudic J., Olfson M., Marcus S.C., et al. The effectiveness of electroconvulsive therapy in community settings. *JAMA* 2003;290(8):1091-1093.

prior hospitalizations for depression (mean of 2.7 vs. 1.5), a longer mean duration of illness (26 years vs. 19 years), and more failed adequate treatments in the current episode (a mean of 3.5 vs. 1.7).

Dr. Sackeim determined response and remission rates for the matched ECT cohort. He defined response as a 50% or greater improvement from baseline in HRSD₂₄ score. He defined remission as a 60% or greater improvement from baseline to a score of 10 or less on the HRSD₂₄ rating. (The definition of complete response [remission] used in analyzing the D-02 long-term results was slightly different in that it used a cutoff score of 9 or less but no percentage change criterion.) In the matched ECT cohort, 58% of the subjects achieved response and 44% of the subjects achieved remission following acute treatment with ECT. Maintenance of remission, however, was poor among these subjects. Six months following the completion of the acute course of ECT, 41% of the matched ECT cohort met the criterion for response; only 20% met the criteria for remission. Thus, response and remission were not maintained after a successful acute course of treatment with ECT despite the availability and use of standard antidepressant treatments.

By contrast, response and remission rates, as determined from the HRSD₂₄ ratings, increased from the end of month 3 to the end of month 12 during continuous treatment with VNS Therapy plus standard-of-care treatment. In the D-02 evaluable population, 14% (29/205) met the response criterion and 7% (14/205) met the remission criterion after 3 months of treatment. After 12 months of VNS Therapy plus standard-of-care treatment, 27% (55/205) met the response criterion and 15% (30/205) met the remission criterion. (Note that the D-02 response and remission rates described above differ from those described earlier, because the rates described here are derived from a more conservative analysis that more closely corresponds to the analysis done by Dr. Sackeim. In the earlier response and remission calculations, the rates were calculated based only on subjects with actual observations. Here rates are calculated by dividing the number of subjects meeting the response or remission criterion by the entire sample of 205.)

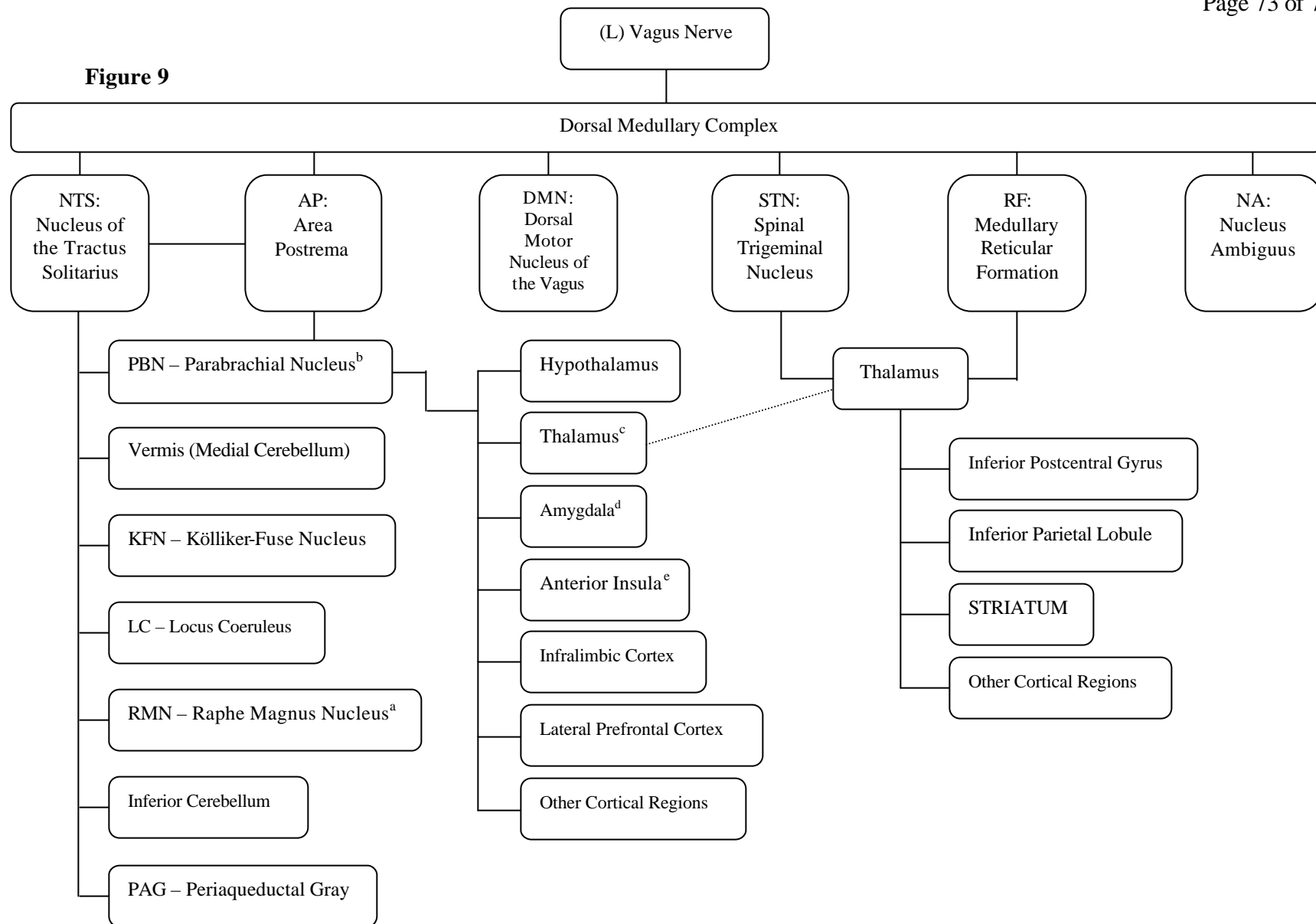
Substantial differences in the study designs, analysis methods, and subject populations of these two studies preclude any definitive conclusions. Nonetheless, the striking contrast between the *declining* response and remission rates during post-ECT standard-of-care maintenance treatment and the *improving* response and remission rates during maintenance VNS Therapy plus standard-

of-care treatment provides additional supportive evidence of the long-term effectiveness of VNS Therapy plus standard-of-care treatment.

b) Mechanism of Action (MOA) Studies

(1) Summary of Previous MOA Studies

Understanding the primary and secondary projections of the vagus within the central nervous system (CNS) can help elucidate the neural mechanisms underlying the therapeutic effects of VNS as well as some of its potential side effects. Though no single finding explains the mechanism of action of VNS, the combination of presently known studies strongly support the involvement of a widespread array of autonomic, reticular and limbic structures found in the brainstem and throughout both hemispheres of the brain (see figure 9 below discussion). The beneficial effects of VNS most likely occur through its effects on these systems. The overlap between these systems and the systems associated with antidepressant effects strongly implies a potential mechanism for possible VNS induced antidepressant efficacy. By overlapping with brain areas associated with antidepressant effects or with mood regulation, and by affecting the neurotransmitters norepinephrine and serotonin (both strongly associated with antidepressant effects) the potential paths for possible VNS induced antidepressant effects are clear.

Figure 9

^a And other multiple raphe nuclei

^b PBN – Major autonomic relay for gustatory, pulmonic, and other autonomic information

^c Thalamus – Especially the intralaminar nuclei and the parvicellular portion of the ventral posteromedial nucleus

^d Amygdala – Particularly the central and basolateral nuclei

^e Anterior Insula – Likely the primary gustatory cortex which densely projects to inferior and inferolateral frontal cortex

(2) Summary of Depression Imaging Studies

Neuroimaging studies show that VNS Therapy modulates activity in regions of the brain believed to be involved in mood regulation. Aspects of these studies that emphasize the more immediate VNS-induced cerebral effects report the involvement of areas that are consistent with the known projections of the vagal nerve such as the prefrontal cortex, cerebellum, inferior parietal lobe, hypothalamus, and insula. The studies exploring the effects of VNS treatment over time report the involvement of brain regions that have been previously reported in neuroimaging studies of mood regulation and mood disorders. Similar to previous depression imaging studies, these VNS imaging studies of TRD patients report the involvement of cortical regions (orbitofrontal, superior frontal, and parietal cortex), involvement of subcortical regions (such as the basal ganglia, hypothalamus, and cerebellum), and involvement of limbic and paralimbic regions (the insula, cingulate, hippocampus, and possibly the amygdala) that are implicated in a emerging limbic-cortical model of depression. That vagal projection areas overlap brain regions implicated in the neural correlates of emotional regulation further strengthens the likelihood that VNS directly affects brain regions that are important to mood regulation and the treatment of mood disorders.

IX. CONCLUSIONS DRAWN FROM STUDIES

Valid scientific evidence is necessary to establish that there is reasonable assurance the VNS Therapy System is safe and effective for its use for the adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode that has not had an adequate response to two or more adequate antidepressant treatment. The clinical investigations under IDE G980099, combined with the non-significant risk parallel control study (D-04), provide reasonable assurance that the VNS Therapy System is safe and effective when used as indicated. Therefore, the clinical trial results meet the requirement of 21 CFR § 860.7(c) for statistically valid investigations.

The safety of the VNS System has been demonstrated in the treatment of epilepsy as well as in clinical trials for the treatment of depression. The side effects reported during the clinical trials for depression are almost identical to those reported for the treatment of epilepsy.

The clinical studies conducted for the treatment of depression included clearly and concisely stated study objectives, endpoints and hypotheses. Patient eligibility for study enrollment was

based upon defined inclusion and exclusion criteria, providing assurance that the patient population was well defined and that the patients selected were suitable for study.

The results from the comparison of depression ratings between D-02 study subjects (receiving VNS therapy plus standard-of-care treatment) and D-04 study subjects (receiving only standard-of-care treatment; no VNS therapy) over 12 months of observation provide valid scientific evidence of the effectiveness of VNS therapy for the treatment of chronic or recurrent major depressive episodes resistant to at least two adequate antidepressant treatments.

The primary efficacy analysis (a repeated measures linear regression analysis of IDS-SR scores) showed a highly statistically significant difference ($p < 0.001$) in favor of the VNS therapy group.

The secondary efficacy analyses also demonstrated statistically significant results in favor of the VNS therapy group vs. the standard-of-care only treatment group. These included the change from baseline to 12 months in the HRSD-24 score (difference of 3.3 points; $p = 0.006$), IDS-SR response rates (22% vs. 12%; $p = 0.029$), IDS-SR complete response rates (15% vs. 4%; $p = 0.006$), IRS-SR sustained response rate (13% vs. 4%; $p = 0.005$), HRSD-24 response rates (30% vs. 13%; $p = 0.003$), and CGI improvement response rates (37% vs. 12%; $p < 0.001$).

Alternate statistical analysis techniques using intent-to-treat-analysis and last-observation-carried forward approaches demonstrated the robustness of the results described above. Additionally, a subset analysis limiting the D-02 data to only those investigational sites also participating in the D-04 study provided further evidence of the robustness of the primary analysis result.

Extensive analyses of baseline patient and disease characteristics and concomitant antidepressant treatment use during the 12-month studies demonstrate that (1) differences between the D-02 and D-04 subjects in baseline patient and disease characteristics were few and do not account for the difference in efficacy outcomes between the subject groups and (2) differences in the use of concomitant antidepressant treatments do not account for the difference in efficacy outcomes between the D-02 and the D-04 subject groups.

X. PANEL RECOMMENDATION (To be completed by FDA)

On _____, (year), the Neurological Devices Panel recommended that the Pre-Market Approval Application for the VNS Therapy System for the treatment of depression be approved subject to the Sponsor's acceptance of the conditions outlined in the approval letter of _____, (date).

XI. CDRH DECISION (TO BE COMPLETED BY FDA)

FDA concurred with the recommendations of the Neurological Devices Panel of _____, (date), and issued an approvable letter on _____, (date). On _____, (date) Cyberonics submitted amendments to the application as requested by FDA.

XII. APPROVAL SPECIFICATIONS (To be completed by FDA)

Continued approval of the device is contingent upon the submission of post approval reports to the Food and Drug Administration as described in the approval order (Attachment ____). A copy of the draft final labeling is attached (Attachment ____).