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Barbi Sofia
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent 5,299,569
 Issued: April 5, 1994
 To: Joachim F. Wernicke, Reese S. Terry, and Jacob Zabara
 Assignee: Cyberonics, Inc.
 For: TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION

Assistant Commissioner for Patents
 Box Patent Extension
 Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT
 TERM UNDER 35 U.S.C. § 156

Sir or Madam:

Applicant, Cyberonics, Inc., a company organized and existing under the laws of Texas, represents that it is the assignee of the entire interest in and to Letters Patent of the United States 5,299,569 granted to Joachim F. Wernicke, Reese S. Terry, and Jacob Zabara on April 5, 1994, for TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION by virtue of an assignment in favor of Cyberonics, Inc. (Attachment A). By the Power of Attorney enclosed herein (Attachment B), Applicant appoints the law firm of Howrey, LLP, as attorneys of Cyberonics, Inc. with regard to this application for extension of the term of U.S. Patent 5,299,569 and to transact all business in the United States Patent and Trademark Office in connection therewith.

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Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156 of the patent statute by providing the following information required by the rules promulgated by the United States Patent and Trademark Office at 37 C.F.R. § 1.740 of the Code of Federal Regulations. For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format that will follow the requirements of 37 C.F.R. § 1.740. Attachments C – J attached hereto are submitted in support of this application and are incorporated by reference.

37 C.F.R. § 1.740(a)(1) – Identification of the Approved Product

The approved product is a vagus nerve stimulation (“VNS”) Therapy System manufactured and sold by Cyberonics, Inc. of Houston, Texas as a long-term adjunctive therapy for treatment resistant depression (“TRD”). The VNS Therapy System is comprised of an implanted pacemaker-like pulse generator and nerve stimulation electrodes, which apply intermittent electrical stimulation to a patient’s vagus nerve for delivery to areas of the patient’s brain that regulate mood. Following implantation pursuant to a prescription by a psychiatrist, the pulse generator generates electrical pulses of a programmed frequency, pulse duration, and current, and applies those pulses to the vagus nerve according to a programmed interval of on and off time periods. The VNS Therapy System is indicated for the 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 adequate antidepressant treatments.

For at least two reasons, the VNS Therapy System as a long-term adjunctive therapy for TRD is different from a previously approved VNS Therapy System for treatment of epilepsy. First, the electrical pulses delivered to the vagus nerve by the pulse generator are typically programmed to provide a different level of stimulation for patients with TRD than for patients with epilepsy. These differences are summarized in Attachment C. Second, the use and operation of the VNS Therapy System in the treatment of epilepsy incorporates a magnetic actuator that a patient can use to manually initiate or interrupt the cycle of electrical stimulation delivered to the vagus nerve to treat an epileptic seizure. The VNS Therapy System for TRD does not generally permit similar use of the magnetic actuator because patients with treatment-

resistant depression, in contrast to epilepsy patients, do not experience acute episodes that are amenable to immediate treatment such as epileptic seizures.

37 C.F.R. § 1.740(a)(2) – Identification of the Statute under which the Regulatory Review Occurred

The regulatory review of the VNS Therapy System for treatment of depression occurred under Section 515 of the Federal Food, Drug and Cosmetic Act (“FFDCA”).

37 C.F.R. § 1.740(a)(3) – Identification of the Date on which the Product Received Permission for Commercial Marketing or Use

The Food and Drug Administration (“FDA”) approved the VNS Therapy System for treatment of depression for commercial marketing and use on July 15, 2005. A copy of the Pre-Marketing Approval Letter from the FDA is attached as Attachment D.

37 C.F.R. § 1.740(a)(4) – Identification of Active Ingredient for Drug Products

This section is not applicable to medical devices such as the VNS Therapy System for the treatment of depression.

37 C.F.R. § 1.740(a)(5) – Statement of Timely Filing of Patent Term Extension

This application is timely submitted within the 60-day period pursuant to 37 C.F.R. § 1.720(f). The FDA approved the VNS Therapy System for treatment of depression for commercial marketing and use on July 15, 2005. Accordingly, the last day that this application for extension of the patent term for United States Patent No. 5,299,569 is September 13, 2005.

37 C.F.R. § 1.740(a)(6) – Identification of the Patent

The patent for which a patent term extension is sought is United States Patent No. 5,299,569, which issued to Joachim F. Wernicke, Reese S. Terry, and Jacob

Zabara on April 5, 1994. United States Patent No. 5,299,569 is currently set to expire on May 3, 2011.

37 C.F.R. § 1.740(a)(7) – Copy of the Patent

A copy of United States Patent No. 5,299,569 is attached as Attachment E.

37 C.F.R. § 1.740(a)(8) – Copies of Disclaimers, Certificates of Correction, Receipts of Maintenance Fee Payments, and Reexamination Certificates

Copies of the maintenance fee payment receipts for United States Patent No. 5,299,569 are attached as Attachment F. No disclaimers, certificates of correction, or reexamination certificates have been filed for United States Patent No. 5,299,569.

37 C.F.R. § 1.740(a)(9) -- Statement and Showing Regarding the Approved Product and the Patent Claims

Many claims of United States Patent No. 5,299,569 cover the VNS Therapy System for treatment of depression. The showing below lists each pertinent patent claim. The Physician's Manual for the VNS Therapy System for the Treatment of Depression (Attachment G) and the Patient's Manual for the VNS Therapy System for the Treatment of Depression (Attachment H) also provide guidance in demonstrating how these particular claims cover the VNS Therapy System for the Treatment of Depression.

Claim	Claim Language	VNS Therapy System for Treatment of Depression
1	A method of treating patients with neuropsychiatric [sic] disorders, which includes selecting a patient suffering from [sic] a neuropsychiatric disorder, determining the type of neuropsychiatric disorder exhibited by the patient, and selectively applying a predetermined electrical stimulus to the patient's vagus nerve for modulating the electrical activity thereof in a manner to alleviate the symptoms of the neuropsychiatric disorder exhibited by the patient being treated.	The VNS Therapy System for treatment of depression provides a method for treating patients with the neuropsychiatric disorder of depression. Patients who are selected for treatment with the VNS Therapy System for treatment of depression are determined to have a specific type of neuropsychiatric disorder (depression), and the VNS Therapy System delivers a predetermined electrical stimulus to the patient's vagus nerve, which modulates the activity of the vagus nerve in a manner to alleviate the symptoms of the patient's neuropsychiatric disorder (depression).

Claim	Claim Language	VNS Therapy System for Treatment of Depression
7	The method of claim 1, wherein the neuropsychiatric disorder being treated is depression, and the predetermined stimulus is an electrical signal in the form of a pulse waveform with signal parameters programmed to increase synchronous activity of the patient's EEG during the patient's waking hours, and to increase the patient's rapid eye movement (REM) activity during sleep.	Claim 1 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for the treatment of depression provides a method for treating depression by delivering a predetermined stimulus as an electrical signal in the form of a pulse waveform with signal parameters programmed to increase synchronous activity of the patient's EEG during the patient's waking hours, and to increase the patient's rapid eye movement (REM) activity during sleep.
8	The method of claim 1, wherein the predetermined stimulus is an electrical signal selected to activate the patient's vagus nerve [sic] to modify the release of serotonin in the patient's brain.	Claim 1 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method for delivering a predetermined electrical signal selected to activate the patient's vagus nerve to modify the release of serotonin in the patient's brain.
9	The method of claim 8, wherein the neuropsychiatric disorder being treated is depression, and including applying the predetermined electrical stimulus to the patient's vagus nerve continually over a relatively long period of time to increase the release of serotonin.	Claim 8 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method for treating the neuropsychiatric disorder of depression, and applies an electrical stimulus to the patient's vagus nerve continually over a relatively long period of time to increase the release of serotonin.
12	The method of claim 1, wherein said stimulus is an electrical signal in the form of a pulse waveform with programmable signal parameters, and is applied to a nerve electrode implanted in the patient's neck on the vagus nerve.	Claim 1 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method for delivering a stimulus that is an electrical signal in the form of a pulse waveform with programmable signal parameters, and is applied to a nerve electrode implanted in the patient's neck on the vagus nerve.

Claim	Claim Language	VNS Therapy System for Treatment of Depression
13	The method of claim 12, wherein said electrical signal is further programmable for any of continuous periodic or intermittent application to the patient's vagus nerve.	Claim 12 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method for delivering an electrical signal that is programmable for any of continuous, periodic, or intermittent application to the patient's vagus nerve.
15	The method of claim 12, wherein the parameter values of the electrical signal including pulse width, output current, frequency, on time and off time, are selectively programmable.	Claim 12 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method for delivering an electrical signal with selectively programmable parameter values for the electrical signal, including pulse width, output current, frequency, including on and off time.

Claim	Claim Language	VNS Therapy System for Treatment of Depression
16	<p>A new use for a neurostimulator device adapted to be implanted in a human patient, in which the device comprises an electrical signal generator which is programmable to generate an electrical output signal having selected signal parameters, and an electrical lead adapted to be connected at a proximal end thereof to the signal generator, the lead including an electrode electrically connected to a distal end of the lead and having a configuration for encompassing a portion of the length of a nerve so that the electrode is adapted to be implanted on the patient's vagus nerve to modulate the electrical activity of the nerve in response to application of the programmed electrical output signal from the signal generator to the lead, the new use of the neurostimulator device comprising the steps of: implanting said electrode on the vagus nerve of the patient, electrically connecting the proximal end of the lead to said signal generator, programming the output signal of the signal generator to constitute a pulse waveform with parameter values of pulse width, output current, frequency, and on and off times selected for therapeutic treatment and control of a neuropsychiatric disorder of the patient among the group of such disorders consisting of schizophrenia, depression, borderline personality disorder.</p>	<p>The VNS Therapy System for treatment of depression involves use of a neurostimulator device adapted to be implanted in a human patient, in which the device comprises an electrical signal generator which is programmable to generate an electrical output signal having selected signal parameters, and an electrical lead adapted to be connected at a proximal end thereof to the signal generator, the lead including an electrode electrically connected to a distal end of the lead and having a configuration for encompassing a portion of the length of a nerve so that the electrode is adapted to be implanted on the patient's vagus nerve to modulate the electrical activity of the nerve in response to application of the programmed electrical output signal from the signal generator to the lead, the new use of the neurostimulator device comprising the steps of: implanting said electrode on the vagus nerve of the patient, electrically connecting the proximal end of the lead to said signal generator, programming the output signal of the signal generator to constitute a pulse waveform with parameter values of pulse width, output current, frequency, and on and off times selected for therapeutic treatment and control of a neuropsychiatric disorder of the patient among the group of such disorders consisting of schizophrenia, depression, borderline personality disorder.</p>

Claim	Claim Language	VNS Therapy System for Treatment of Depression
18	<p>A method for use in advancing the treatment and control of neuropsychiatric disorders, including the steps of providing an electrical lead with a stimulating electrode assembly at its distal end for implantation on a patient's vagus nerve, providing a programmable stimulus generator for generating electrical pulse sequences with selectively variable electrical parameters for selective application to the lead/electrode assembly when implanted on the vagus nerve, incorporating an electrical connector in the stimulus generator to accommodate electrical connection of the proximal end of the electrical lead to the stimulus generator, restricting the programmable ranges of the variable parameters of the electrical pulse sequences to values which in combination will stimulate the vagus nerve and thereby modulate its electrical activity when one or more programmed pulse sequences are applied to the nerve via the lead/electrode assembly, to alleviate symptoms of the particular neuropsychiatric disorder to be treated, adapting the stimulus generator for physician control of the programming, and supplying the stimulus generator and lead/electrode assembly for the treatment and control of neuropsychiatric disorders.</p>	<p>The VNS Therapy System for treatment of depression provides a method for advancing the treatment and control of neuropsychiatric disorders, including the steps of providing an electrical lead with a stimulating electrode assembly at its distal end for implantation on a patient's vagus nerve, providing a programmable stimulus generator for generating electrical pulse sequences with selectively variable electrical parameters for selective application to the lead/electrode assembly when implanted on the vagus nerve, incorporating an electrical connector in the stimulus generator to accommodate electrical connection of the proximal end of the electrical lead to the stimulus generator, restricting the programmable ranges of the variable parameters of the electrical pulse sequences to values which in combination will stimulate the vagus nerve and thereby modulate its electrical activity when one or more programmed pulse sequences are applied to the nerve via the lead/electrode assembly, to alleviate symptoms of the particular neuropsychiatric disorder to be treated, adapting the stimulus generator for physician control of the programming, and supplying the stimulus generator and lead/electrode assembly for the treatment and control of neuropsychiatric disorders.</p>
19	<p>The method of claim 18, wherein the selectively variable electrical parameters include pulse width, amplitude and frequency, sequence duration and intervals.</p>	<p>Claim 19 covers the VNS Therapy System for treatment of depression. The VNS Therapy System for treatment of depression provides a method wherein the selectively variable electrical parameters include pulse width, amplitude and frequency, sequence duration and intervals.</p>

37 C.F.R. § 1.740(a)(10) – Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g)

The relevant dates and information pursuant to 35 U.S.C. § 156(g) that will enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period are as follows:

(A) Investigational Device Exemption (“IDE”) No. G980099 for the NeuroCybernetic Prosthesis (NCP) System for Treatment of Depression was filed with the FDA on April 27, 1998. The NeuroCybernetic Prosthesis (NCP) System is now known as the VNS Therapy System. The cover letter submitted with the IDE is attached as Attachment I.

(B) Premarketing Approval (“PMA”) Supplement No. P970003/S50 for the VNS Therapy System for the Treatment of Depression was filed with the FDA on October 24, 2003. The cover letter submitted with the PMA is attached as Attachment J.

(C) PMA Supplement No. P970003/S50 was approved by the FDA on July 15, 2005. The approval letter from the FDA is attached as Attachment D.

37 C.F.R. § 1.740(a)(11) – Significant Activities Undertaken by the Applicant during the Applicable Regulatory Review Period

The significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to these activities are as follows:

Date	From	Type of Contact	Subject
04/27/98	Cyberonics	Submission	Submitted Original IDE for D-01 study (Attachment I)
05/29/98	FDA	Conditional Approval	FDA conditionally approved application with 16 deficiencies.
06/09/98	Cyberonics	Meeting Minutes	Meeting minutes and slides from 6/4/98 meeting with FDA. (S1)
06/12/98	Cyberonics	Submission	Submitted responses to 5/29/98 deficiencies. (S3)
07/09/98	FDA	Meeting Clarifications	FDA provided 4 clarifications regarding the 6/4/98 meeting.
07/13/98	Cyberonics	Literature Request	Submitted literature requested by FDA.
07/15/98	FDA	Conditional Approval	FDA conditionally approved 6/12/98 deficiency responses (S3) and identified 12 more deficiencies.
07/22/98	FDA	Teleconference	Discussed questions 4 and 2 from 7/15/98 deficiency letter.
08/28/98	Cyberonics	Submission	Submitted responses to 7/15/98 deficiencies. (S4)
09/24/98	FDA	Teleconference	FDA comments on S4 concerning mania; duty cycle/adverse events.
09/28/98	FDA	Unconditional Approval	FDA unconditionally approved depression study.
09/28/98	Cyberonics	Submission	Submitted additional IRB information; Young Mania Rating Scale; exclusion for defibrillators; correct typographical error. (S5)
10/01/98	Cyberonics	Submission	Submitted revised informed consent. (S6)
10/19/98	Cyberonics	Fax	Revised draft meeting agenda for 10/27/98 meeting.
10/26/98	FDA	Teleconference	FDA approved Supplements 5 and 6, no official communication will be sent.
11/10/98	Cyberonics	Submission	Submitted responses to questions from teleconference regarding protocol and IRBs. (S7)
11/13/98	Cyberonics	Meeting Minutes	Submitted meeting minutes for 10/27/98 meeting.
12/15/98	FDA	Unconditional Approval	FDA approved minor changes (S7); study limited to 3 institutions – enrollment of 45 – implant of 30.
01/08/99	Cyberonics	Submission	Submitted IRB approval for New York site. (S8)
01/22/99	Cyberonics	Submission	Submitted request to increase sites and patients; clinical progress report. (S9)
02/05/99	FDA	Teleconference	FDA approval of Supplements 7 and 8; Supplement 9 under review.
02/11/99	Cyberonics	Submission	Submitted software change from 5.0 to 4.4. (S10)
02/24/99	FDA	Unconditional Approval	FDA unconditionally approved Supplement 9 dated 1/22/99.
03/10/99	Cyberonics	Submission	Submitted IRB approval for Baylor. (S11)
03/10/99	Cyberonics	Draft Submission	Submitted draft submission to FDA regarding questions on software, automatic diagnostics, lead test, 90 second ON time. (S12)
03/11/99	FDA	Unconditional Approval	FDA unconditionally approved Supplement 10 dated 2/11/99.

Date	From	Type of Contact	Subject
03/12/99	Cyberonics	Submission	Submitted response to FDA regarding questions on software, automatic diagnostics, lead test, 90 second ON time. (S12)
03/17/99	FDA	Teleconference	FDA approved Supplement 11 (Baylor IRB approval).
03/26/99	FDA	Teleconference	FDA approved Supplement 10 (Software change – 5.0 to 4.4).
04/12/99	FDA	Fax	FDA provided meeting request package SOP.
04/14/99	Cyberonics	Meeting Request	Requested meeting for pre-IDE pivotal study.
05/12/99	Cyberonics	Teleconference	Upcoming D-02 and subsequent submission.
05/14/99	Cyberonics	Submission	Draft protocol submitted for proposed pivotal study.
05/24/99	N/A	Meeting with FDA	Pre-IDE meeting with FDA for pivotal clinical study.
05/28/99	Cyberonics	Meeting Minutes	Meeting minutes submitted for the 5/24/99 meeting with FDA.
06/11/99	Cyberonics	Meeting Minutes	Meeting minutes for teleconference: follow-up questions from 5/24/99 pre-IDE meeting with FDA submitted with 6/30/99 submission.
06/17/99	Cyberonics	Submission	Submitted request for expedited review. (S13)
06/30/99	Cyberonics	Submission	Submitted application for pivotal clinical study (D-02). (S14)
07/07/99	Cyberonics	Submission	Submitted D-01 protocol amendment and requested expansion of D-01 (S15)
07/16/99	FDA	Unconditional Approval	FDA approved request for expedited review (S13).
07/30/99	FDA	Conditional Approval	FDA conditionally approved pivotal clinical study (D-02) subject to ten (10) conditions (S14).
08/06/99	Cyberonics	Submission	Submitted responses that patients in D-01 would re-consent with revised consent form provided in S15. (S16)
08/06/99	FDA	Denial	FDA denied request for D-01 expansion.
08/09/99	Cyberonics	Fax	Discussion of D-01 study expansion; Question on D-02 (S14).
08/13/99	FDA	Teleconference	FDA approved Supplement 16 (re-consent of D-01 patients).
08/13/99	Cyberonics	Meeting Minutes	Meeting minutes submitted with 8/27/99 submission for teleconference with FDA to discuss denial of D-01 expansion and follow-up questions from conditional approval of 6/30/99 submission.
08/18/99	Cyberonics	Submission	Submitted request to expand D-01 study; prognostic factors; D-02 sample size confirmation; justification of additional clinical site. (S18)
08/27/99	Cyberonics	Submission	Submitted response to FDA 7/30/99 deficiencies and discussion about NIMH; D-02 sample size. (S19)
09/17/99	FDA	Conditional Approval	FDA conditionally approved S18 (expanded D-01 study - 5 sites/90 subjects/60 implants).
09/24/99	FDA	Unconditional Approval	FDA unconditionally approved S19 subject to six (6) recommendations.
10/12/99	Cyberonics	Submission	Submitted Annual Progress Report. (S20)
11/03-05/99	FDA	Teleconference	Review of the six (6) recommendations in 9/24/99 letter.
12/09/99	Cyberonics	Submission	Submitted response to 9/24/99 approval letter; final clinical report; request to increase D-02 to 20 sites/275 enrolled; blinded sequential analysis; statistical analysis plan prior to D-02 patient randomization. (S21)

Date	From	Type of Contact	Subject
12/09/99	Cyberonics	Meeting Request	Requested meeting to review investigational plan among other items.
01/12/00	FDA	Unconditional Approval	FDA unconditionally approved 20 sites/275 enrolled/210 implanted subject to seven (7) recommendations.
01/14-25/00	Cyberonics	Teleconference	5 th D-01 study site problematic.
01/25/00	Cyberonics	Meeting Request Withdrawal	Withdrew request for meeting submitted on 12/9/99.
02/18/00	Cyberonics	Teleconference	4 th D-01 site had repeated delays.
02/22/00	FDA	Teleconference	5 th D-01 study site problematic; NIMH issued; discussed myoclonus and obesity.
02/22/00	Cyberonics	Teleconference	Discussed reassignment of clinical sites.
02/24/00	FDA	Teleconference	Discussion of D-01 5 th site and keeping 4 sites instead of 5.
02/25/00	FDA	Teleconference	D-01 study enrollment.
05/19/00	Cyberonics	Submission	Submitted Unanticipated Adverse Device Effect – accidental overdose/seizure. (S23)
05/1, 8, 19, 22/00	FDA	Teleconference	Discussed D-01 and D-02 protocol revisions.
06/19/00	Cyberonics	Submission	Submitted responses to 01/12/00 approval letter regarding recommendations. (S24)
06/20/00	FDA	Teleconference	Discussed close out of adverse event reported 5/16/00.
07/10/00	Cyberonics	Submission	Submitted request to modify long-term follow up visits for D-01 from annually to quarterly one year post implant; minor protocol revisions. (S25)
07/19/00	FDA	Teleconference	Discussed D-02 protocol changes submitted on 06/19/00 and D-01 protocol changes submitted 7/10/00.
07/20/00	FDA	Unconditional Approval	FDA unconditionally approved supplement submitted 06/19/00 (S24) subject to three (3) recommendations.
08/08/00	FDA	Unconditional Approval	FDA unconditionally approved D-01 protocol changes submitted 7/10/00 (S24).
08/10/00	Cyberonics	Submission	Submitted D-02 pivotal study statistical analysis plan. (S26)
08/30/00	FDA	Teleconference	Discussed D-02 statistical analysis plan submitted on 8/10/00.
09/08/00	FDA	Conditional Approval	FDA conditionally approved D-02 statistical analysis plan submitted on 08/10/00 (S26) subject to seven (7) recommendations.
10/16/00	Cyberonics	Submission	Submitted request for 45-day extension to submit Annual Progress Report. (S27)
10/20/00	FDA	Teleconference	FDA approved 45-day extension to submit Annual Progress Report.
12/11/00	Cyberonics	Submission	Submitted responses to 09/08/00 letter recommendations. (S28)
12/19/00	Cyberonics	Submission	Submitted Annual Progress Report. (S29)
01/11/01	FDA	Unconditional Approval	Unconditional approval of D-02 pivotal study statistical analysis plan. (S26) - FDA accepted advisories 1, 3 4, 5 and 7 (S28) submitted on 12/11/00 indicated three (3) addition items for analysis.
02/12/01	FDA	Teleconference	Discussed site visit, update on D-02 study (number of centers and patients enrolled; third-party randomization)

Date	From	Type of Contact	Subject
02/15/01	Cyberonics	Submission	Submitted unanticipated adverse device effect. (S30)
03/06/01	Cyberonics	Submission	Submitted unanticipated adverse device effect. (S31)
03/22/01	FDA	Teleconference	Discussed adverse device effects.
04/05/01	Cyberonics	Teleconference	Discussed reporting events in IDEs.
04/11/01	Cyberonics	Submission	Submitted anticipated adverse event. (S32)
04/11/01	Cyberonics	Submission	Submitted unanticipated adverse device effect. (S33)
04/17/01	Cyberonics	Submission	Submitted protocol amendment to modify the number of long-term follow-up visits (D-02). (S35)
04/18/01	Cyberonics	Submission	Submitted protocol amendment to modify the number of long-term follow-up visits (D-01). (S34)
05/16/01	FDA	Teleconference	Discussed anticipated adverse event reported 4/11/01 (suicide); Discussed the approval of S35 submitted on 4/17/01.
05/17/01	FDA	Unconditional Approval	FDA unconditionally approved S34 submitted on 04/18/01 – modification of informed consent for D-01 for compensation during long-term phase.
05/17/01	FDA	Unconditional Approval	FDA unconditionally approved S35 submitted on 04/17/01 – modification of informed consent for D-02 for compensation during long-term phase.
06/01/01	Cyberonics	Submission	Submitted D-02 protocol changes—requested increase in implant limit. (S36)
06/13/01	FDA	Unconditional Approval	FDA unconditionally approved requested increase in implant limit (S36) submitted on 06/01/01.
06/18/01	Cyberonics	Submission	Submitted responses to 1/11/01 D-02 statistical analysis plan questions. (S37)
07/12/01	Cyberonics	Teleconference	Discussed D-02 event; D-02 implants were completed with 235 implanted.
07/12/01	Cyberonics	Meeting Request	Submitted request for Pre-IDE Meeting for Randomized, Controlled, Long-Term Study (D-08)
07/12/01	Cyberonics	Submission	Submitted unanticipated adverse device effect of 7/12/01. (S38)
07/19/01	FDA	Unconditional Approval	FDA unconditionally approved response to 1/11/01 D-02 statistical analysis plan questions (S37) submitted on 06/18/01 subject to one (1) recommendation.
07/31/01	Cyberonics	Submission	Submitted CRFs requested by FDA for unanticipated adverse device effect reported 07/12/01. (S38)
08/01/01	Cyberonics	Meeting Request	4 questions to be discussed at meeting with FDA.
08/06/01	Cyberonics	Meeting Request	Proposed dates for meeting.
08/15/01	FDA	Request for Information	Requested additional information on 7/12/01 adverse event.
08/27/01	Cyberonics	Submission	Submitted diathermy contraindication—protocol change. (S40)
09/28/01	Cyberonics	Submission	Submitted response to 8/15/01 request for information concerning adverse event. (S41)
09/28/01	Cyberonics	Submission	Submitted response to telephone request for information concerning diathermy. (S42)
09/28/01	FDA	Unconditional Approval	FDA unconditionally approved diathermy contraindication (S40) submitted on 08/27/01.
10/04/01	Cyberonics	Meeting Request	Requested review of D-08; update on D-01/D-02; introduced new VP of Regulatory.

Date	From	Type of Contact	Subject
10/31/01	Cyberonics	Submission	Submitted D-08 Study – discussed 3 aims of conducting the study; discussed D-01/D-02 progress report and future plans for marketing Depression Indication. (S43)
10/31/01	FDA	Teleconference	FDA agreed with IDE supplements S41 and S42 (diathermy responses) – no official letter will be sent.
11/09/01	Cyberonics	Meeting Request	D-08 Meeting Request letters attached; discussed D-08 relationship with D-01/D-02; discussed reason D-08 is not a traditional pilot study and additional meeting details.
12/05/01	FDA	Conditional Approval	FDA conditionally approved D-08 study (S43) with 22 conditions.
01/10/02	Cyberonics	Submission	Submitted request for 60-day extension to submit responses to 12/5/01 questions from FDA. (S44)
01/10/02	Cyberonics	Submission	Submitted request for 45-day extension to submit Annual Report. (S45)
01/16/02	Cyberonics	Email	Discussion of D-01/D-02/D-08 Meeting Minutes.
01/16/02	Cyberonics	Meeting Minutes	Emailed FDA draft D-01/D-02/D-08 meeting minutes and slides.
02/27/02	Cyberonics	Submission	Submitted Annual Progress Report (D-01/D-02 & D-03). (S46)
02/27/02	Cyberonics	Email	Sent slide to FDA for 3/1/02 teleconference to discuss D-02 study results
03/01/02	Cyberonics	Teleconference	D-02 Protocol revisions; dose response discussion; less resistant patients; reblinding; statement made by FDA that “we will review anything you submit”; D-04 discussion; placebo discussion.
03/20/02	Cyberonics	Submission	Submitted request for 2 nd extension (6 months) to submit responses to 12/05/01 deficiency questions. (S47)
03/25/02	Cyberonics	Teleconference	FDA described deficiencies for 2001 Annual Progress Report.
03/29/02	FDA	Deficiency Letter	Deficiency questions on 2001 Annual Progress Report.
04/02/02	Cyberonics	Submission	Submitted Amendment to Annual Progress Report (responses to questions raised during 3/25/02 teleconference).
04/03/02	Cyberonics	Meeting Minutes	Sent draft meeting minutes from 3/1/02 teleconference.
04/17/02	Cyberonics	Meeting Minutes	Sent final meeting minutes from 3/1/02 teleconference and slides.
04/26/02	Cyberonics	Submission	Submitted 6-month progress report (current investigator list). (S49)
04/26/02	Cyberonics	Submission	Withdrawal of D-08 Application. (S48)
05/03/02	Cyberonics	Submission	Submitted responses to 3/29/02 deficiency questions for Annual Progress Report. (S50)
05/28/02	FDA	Acknowledgement Letter	FDA acknowledged withdrawal of D-08 application.
07/22/02	Cyberonics	Submission	Submitted software change (Model 250 Version 4.6). (S51)
08/09/02	FDA	Teleconference	Answered question from S. Hinckley about 4.6 software change.
09/03/02	Cyberonics	Submission	Submitted revised statistical plan for D-02/D-04. (S52)
09/05/02	Cyberonics	Teleconference	FDA requested additional copies of revised statistical plan; discussed meeting date.
09/05/02	Cyberonics	Submission	Submitted 4 desk copies of revised statistical plan.

Date	From	Type of Contact	Subject
09/06/02	Cyberonics	Submission	Submitted CD-ROM copy of revised statistical plan.
09/10/02	FDA	Teleconference	FDA requested clarification of statistical plan.
09/16/02	FDA	Teleconference	FDA requested sample device for OST; discussed review of statistical plan.
10/04/02	FDA	Acknowledgement Letter	FDA acknowledged receipt of statistical plan; FDA recommended changes including new study and D-02/D-04 analysis.
10/09/02	Cyberonics	Teleconference	Discussion of acknowledgement letter and future plans.
10/11/02	Cyberonics	Teleconference	A. Totah called C. Witten, T. Stevens to discuss Pre-PMA meeting and future plans.
10/15/02	Cyberonics	Meeting Cancellation	Cancellation notice to FDA and discussion of rescheduled date.
11/22/02	Cyberonics	Submission	Submitted 45-day extension for 2002 Annual Progress Report.
01/06/03	Cyberonics	Submission	Submitted 2002 Annual Progress Report (S54)
10/24/03	Cyberonics	Submission	Submitted Depression PMA-S (P970003/S50); (Attachment J)
11/14/03	Cyberonics	Submission	Submitted 2003 Annual Progress Report (S56)
12/03/03	Cyberonics	Submission	Submitted Status of Outstanding Items, Templates, Protocol Deviations and Efficacy (P970003/S50/A001)
12/15/03	FDA	Filing Letter	FDA accepted Depression PMA-S (P970003/S50) as fileable
12/18/03	Cyberonics	Submission	Submitted additional statistical information per FDA's request (P970003/S50/A002)
01/26/04	FDA	Pittsburgh Site Inspection 483	Pittsburgh Site received 483 Inspectional Observations (Inspection Dates: 1/8, 9, 12-14, 20, 26/04)
01/28/04	FDA	Substantive Issues Fax	FDA faxed list of 53 substantive issues with Depression PMA-S (P970003/S50)
01/31/04	Cyberonics	Submission	Submitted Amendment to 2003 Annual Progress Report (S57)
02/04/04	Cyberonics/ FDA	100-Day Meeting at FDA Offices	100-Day Meeting to discuss status of Depression PMA-S (P970003/S50) and 53 issues faxed to Cyberonics on 01/28/04
02/16/04	Cyberonics	Submission	Submitted request to prepare Panel Package in parallel with FDA's review of our response (P970003/S50/A003)
03/01/04	FDA	Deficiency Letter	Deficiency Letter for Depression PMA-S (P970003/S50)
03/17/04	Cyberonics	Submission	Response to 03-01-04 Deficiency Letter (P970003/S50/A004)
03/26/04	Cyberonics	Submission	Resubmitted questions 2, 9, 11, and 18 from Deficiency Letter (P970003/S50/A005)
04/02/04	Cyberonics	Submission	Submitted Response to 3-26-04 Email – New Question Q24 (P970003/S50/A006)
04/07/04	Cyberonics	Submission	Submitted Response to 3-31-04 Email – Clarification of Q1 (Suicide) and Q5 (Linear Regress) (P970003/S50/A007)
04/09/04	Cyberonics	Submission	Submitted protocol change for X02 Family (58)
05/12/04	FDA	Deficiency Letter	FDA requested a protocol revision and CRF for re-implant (G980009/S58)
05/17/04	FDA	Depression Study Inspection (D-01, D-02 & D-04)	FDA found no observations for inspection of depression studies D-01, D-02 and D-04 (Inspection Dates: 1/21-23/04; 2/12, 19/04)

Date	From	Type of Contact	Subject
06/15/04	Cyberonics/ FDA	Neurological Devices Advisory Panel Meeting	Attended Neurological Devices Advisory Panel Meeting and presented Depression PMA-S (P970003/S50)
06/23/04	Cyberonics	Submission	Submitted Response to 5/12/04 FDA Letter requesting a protocol revision and CRF for re-implant (S59)
06/25/04	FDA	Telephone	FDA made request for information concerning Message Board for P970003/S50
06/28/04	Cyberonics	E-mail	Clarification e-mail concerning FDA's request of 6/25/04 for Message Board information. Cyberonics promised to send minor amendment by 6/30/04. (P970003/S50)
06/28/04	FDA	E-mail	FDA acknowledged Cyberonics's understanding of FDA's request for information and added an additional request for Message Board records. (P970003/S50)
06/29/04	Cyberonics	E-mail	Cyberonics requested teleconference call with FDA to discuss minor amendment for Message Board and meeting agenda for Friday (7/2/04) teleconference call. (P970003/S50)
06/30/04	Cyberonics	E-mail / teleconference	Clarification of teleconference call on 6/30/04 regarding Message Board records and revision of FDA's request. Cyberonics revised earlier promise and stated that would submit minor amendment during week of 7/5-7/9/04. (P970003/S50)
07/06/04	Cyberonics	Submission	Submitted letter from Skip Cummins to Dr. Celia Witten (P970003/S50/A008)
07/07/04	Cyberonics	E-mail	Cyberonics informed FDA of delivery information for minor amendment concerning Message Board. (P970003/S50/A009)
07/07/04	Cyberonics	Submission	Submitted Response to 6-25-04 Teleconference – Request for Message Board Information (P970003/S50/A009)
07/08/04	Cyberonics	E-mail	Cyberonics informed FDA of delivery for minor amendment of Message Board information. (P970003/S50/A009)
07/08/04	FDA	E-mail	FDA acknowledged 7/8/04 e-mail concerning delivery of minor amendment. (P970003/S50)
07/09/04	Cyberonics	E-mail	Cyberonics informed FDA of alternate contact information as a result of employee vacation. (P970003/S50)
07/26/04	Cyberonics	Telephone	Cyberonics contacted Dr. Pena concerning status of application. He stated that there were no new developments on the application and that inspections were on-going. He would advise if there were any new developments. (P970003/S50)
07/29/04	FDA	Approval Letter	FDA approved G980099/S59 (Response to 5/12/04 FDA Letter requesting a protocol revision and CRF for re-implant)
08/11/04	FDA	Not Approvable Letter	FDA deemed Depression PMA-S (P970003/S50) "not approvable" with deficiencies
08/17/04	FDA	Baltimore Site Inspection 483	Baltimore Site received 483 Inspectional Observations (Inspection Dates: 7/19-23, 26-29/04; 8/5-6, 9-10, 17/04)
09/07/04	Cyberonics	Submission	Submitted Responses to Dr. Yustein's questions regarding Depression Indication Submissoin (P970003/S550/A010)

Date	From	Type of Contact	Subject
09/10/04	Cyberonics	Submission	Submitted Original TIDE Application (S60)
09/15/04	FDA	Inspection of Cyberonics Manufacturing Facility	Cyberonics received 483 Inspection Observations (Inspection Dates: 7/12/04 – 9/15/04)
09/21/04	Cyberonics	Submission	Submitted D-20 Informed Consent and a revised D-20 Clinical Protocol (500 patients at 50 sites to 100 patients at 20 sites) (S61)
09/22/04	FDA	Conditional Approval	FDA conditionally approved G980099/S60 (Treatment Use IDE Application)
09/23/04	Cyberonics	Submission	Submitted Response to 8-11-04 Not Approval Letter (P970003/S50/A011)
10/01/04	Cyberonics	Submission	Response to 9/22/04 Conditional Approval Letter for Treatment Use IDE Application (S62)
10/07/04	Cyberonics	Submission	Submitted Response to 9/15/04 483 Inspection Observations
10/08/04	FDA	Approval Letter	FDA approved G980099/S61 (D-20 Informed Consent and a revised D-20 Clinical Protocol)
10/15/04	FDA	Approval Letter	FDA approved G980099/S62 (Response to 9/22/04 Conditional Approval Letter for Treatment Use IDE Application)
10/27/04	Cyberonics	Submission	Submitted revised TIDE costs; will charge \$15,947 for each devices us in the TIDE (S63)
11/19/04	FDA	Approval Letter	FDA approved G980099/S63 (revised TIDE costs; will charge \$15,947 for each devices us in the TIDE)
12/14/04	Cyberonics	Submission	Submitted 45-day extension for 2004 Annual Progress Report.
12/17/04	FDA	Warning Letter	Baltimore site received Warning Letter for 7/12/04-9/15/04 Manufacturing Facility Inspection
12/22/04	FDA	Warning Letter	Received Warning Letter for 7/19-23, 26-29/04; 8/5-6, 9-10, 17/04 Inspection
12/23/04	Cyberonics	Submission	Submitted 2004 Annual Progress Report (S64)
01/21/05	Cyberonics	Submission	Submitted Response to 12/22/04 Warning Letter
02/02/05	FDA	Approvable Letter	FDE deemed Depression PMA-S (P970003/S50) “approvable” with conditions
03/09/05	FDA	Submission	Response to FDA Approvable Letter
03/09/05-06/01/05	FDA/Cyberonics	Continued Review Process	Continued depression application review and resolution of conditions of approval (Summary of Safety and Effectiveness; Labeling; Postmarket Studies; Warning Letter)
06/01/05	FDA	Inspection Warning Letter Cleared	FDA closed Warning Letter file and issued final report.
06/06/05	FDA	Effectiveness Check of Inspection Warning Letter	FDA informed Cyberonics follow-up inspection required to address conditions of approval. FDA closed follow-up inspection conducted on 6/10/05-6/10/05; report pending.
6/6/05-6/29/05	FDA & Cyberonics	Continued Review Process	Continued depression application review and resolution of conditions of approval (Summary of Safety and Effectiveness; Labeling)
7/15/05	FDA	Approval Letter	(Attachment D)

37 C.F.R. § 1.740(a)(12) – Statement that Patent is Eligible for Extension and the Length of the Extension

PART A: Statement that U.S. Patent 5,299,569 is Eligible for Extension

37 C.F.R. § 1.720 provides that the term of a patent that claims a product, a method of using a product, or a method of manufacturing a product shall be extended if:

1. The term of the patent has not expired before an application for extension is submitted;
2. The term of the patent has never been extended;
3. The application for the extension is submitted by the owner of record of the patent or its agent in accordance with 37 C.F.R. § 1.740;
4. The product has been subject to a regulatory review period before its commercial marketing or use; and
5. The permission for the commercial marketing or use of the product after such regulatory review period is the first commercial marketing or use of the product under the provision of the law under which such regulatory review period occurred.

United States Patent No. 5,299,569 is eligible for extension of patent term because the five requirements of 37 C.F.R. § 1.720 have been satisfied as described below.

1. United States Patent No. 5,299,569 has not expired, and is currently set to expire on May 3, 2011.
2. The term of United States Patent No. 5,299,569 has never been extended.
3. This application for the extension is submitted by the owner of record Cyberonics, Inc. through its agent Howrey, LLP in accordance with 35 U.S.C. § 156(d) in that it is submitted within the 60-day period beginning on the date that the product received permission for marketing under the Federal Food, Drug, and Cosmetic Act on July 15, 2005, and contains the information required by 37 C.F.R. § 1.740.
4. As demonstrated by the letters attached to this Application as Attachments D, I, and J, and as described above in relation to 37 C.F.R. § 1.740(a)(10), the approved product was subject to a

regulatory review period under § 515 of the Federal Food, Drug and Cosmetic Act.

5. The permission for the commercial marketing of the VNS Therapy System for the treatment of depression is the first permitted commercial marketing of the same.

PART B: Calculation of Length of Term Extension

United States Patent No. 5,299,569 is entitled to a term extension of 1,664 days as described below. The length of the term extension is determined by the length of the regulatory review period as determined by 37 C.F.R. § 1.777(c), reduced as appropriate by 37 C.F.R. § 1.777(d)(1) through (d)(6).

(a) The regulatory review period under 37 C.F.R. § 1.777(c) began on April 27, 1998 and ended on July 15, 2005, which is a total of 2,667 days or 7.3 years, which is the sum of (1) and (2) below:

(1) The period under 37 C.F.R. § 1.777(c)(1), which began on the date the clinical investigation on humans involving the device started (April 27, 1998; Attachment I) and ended on the date the application was initially submitted under § 515 of the Federal Food, Drug and Cosmetic Act (October 24, 2003; Attachment J), which is 2,006 days or 5.5 years; and

(2) The period under 37 C.F.R. § 1.777(c)(2), which began on the date the application was initially submitted with respect to the device under § 515 of the Federal Food, Drug, and Cosmetic Act (October 24, 2003; Attachment J) and ended on the date such application was approved (July 15, 2005; Attachment D), which is a total of 661 days or 1.8 years.

(b) The regulatory review period upon which the length of the extension is calculated is the entire regulatory review period as determined by 37 C.F.R. § 1.777(c) above (2,667 days) less:

(1) The number of days in the regulatory review period which were on or before the date the patent issued (April 5, 1994), which is zero (0) days;

(2) The number of days during which the applicant did not act with due diligence, which is zero (0) days;

(3) One half the number of days determined in 37 C.F.R. § 1.777(c)(1) after the patent issued (one half of 2,006 days excluding half days, or 1,003 days). 37 C.F.R. § 1.777(d)(1).

The regulatory review period upon which the length of the extension is calculated is therefore 1,664 days.

(c) The number of days as determined by 37 C.F.R. § 1.777(d)(1) when added to the original term of the patent (currently set to expire on May 3, 2011) would result in the date November 22, 2015. 37 C.F.R. § 1.777(d)(2).

(d) Fourteen (14) years when added to the date of the PMA approval (July 15, 2005) would result in the date July 15, 2019. 37 C.F.R. § 1.777(d)(3).

(e) The earlier date as determined by 37 C.F.R. § 1.777(d)(2) and 37 C.F.R. § 1.777(d)(3) is November 22, 2015. 37 C.F.R. § 1.777(d)(4).

(f) Since U.S. Patent No. 5,299,569 issued after September 24, 1984, the period of patent term extension may not exceed five (5) years. Five years when added to the original expiration date of the patent (May 3, 2011) would result in the date May 3, 2016. 37 C.F.R. § 1.777(d)(5).

(g) The earlier date determined by 37 C.F.R. § 1.777(d)(4) and 37 C.F.R. § 1.777(d)(5) is November 22, 2015.

(h) Therefore, U.S. Patent No. 5,299,569 should be entitled to a patent term extension of 1,664 days and therefore expire on November 22, 2015.

37 C.F.R. § 1.740(a)(13) -- Duty of Disclosure

The applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services

or the Secretary of Agriculture any information that is material to the determination of entitlement to the extension sought for United States Patent No. 5,299,569.

37 C.F.R. § 1.740(a)(14) – Fee

The fee prescribed for this Application is \$1,120. The undersigned attorney authorizes the Commissioner to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 01-2508, referencing Order No. 13637.0003.000000.

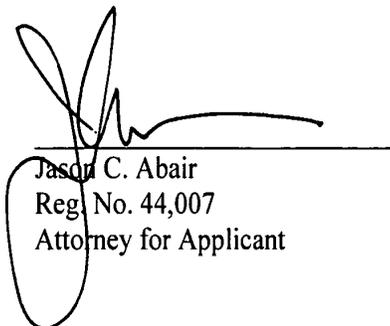
37 C.F.R. § 1.740(a)(15) – Name and Address for Inquiries and Correspondence

All inquiries and correspondence relating to this application for patent term extension are to be directed to Jason C. Abair, Esq., HOWREY, LLP, 1111 Louisiana St., 25th Floor, Houston, Texas 77002; telephone number (713) 787-1595.

37 C.F.R. § 1.740(b) – Certification of Duplicate Papers

The application under this section is accompanied by two additional copies of the application, for a total of three copies.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Jason C. Abair', is written over a horizontal line. The signature is stylized with a large loop at the beginning and a long horizontal stroke at the end.

Jason C. Abair
Reg. No. 44,007
Attorney for Applicant

HOWREY, LLP
1111 Louisiana St., 25th Floor
Houston, Texas 77002
(713) 787-1595

Date: July 18, 2005

Attachments

Attachment A	Assignment
Attachment B	Power of Attorney
Attachment C	VNS Therapy Comparison
Attachment D	Pre-Marketing Approval Letter
Attachment E	Copy of United States Patent No. 5,299,569
Attachment F	Maintenance Fee Payment Receipts
Attachment G	Physician's Manual for the VNS Therapy System for the Treatment of Depression
Attachment H	Patient's Manual for the VNS Therapy System for the Treatment of Depression
Attachment I	Cover Letter for IDE No. G980099
Attachment J	Cover Letter for PMA Supplement No. P970003/S50 for the VNS Therapy System for the Treatment of Depression

A

A S S I G N M E N T

In consideration of our respective employee agreements with CYBERONICS, INC., and of \$1.00, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, we, JOACHIM F. WERNICKE and REESE S. TERRY, JR., respectively residents of League City and Houston, Texas, hereby jointly and severally assign, transfer, and deliver to CYBERONICS, INC., a Delaware corporation having offices at Webster, Texas, U.S.A., its successors and assigns (collectively referred to as "CYBERONICS"), the entire right, title and interest throughout the world to and in our invention(s), made jointly with Jacob Zabara of Philadelphia, Pennsylvania, in TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION, the application for United States patent on the invention(s) we signed on 30 April 1991, 1991, filed in the U.S. Patent and Trademark Office with this Assignment, as well as all continuations and divisions of that application, and all patents granted on that and any other application(s) on the invention(s) in the United States and elsewhere, together with the exclusive right to make application for patents and similar protection, reissues, renewals and extensions on the invention(s) in the U.S. and foreign countries, and we hereby request the U.S. Commissioner of Patents and Trademarks and the corresponding official(s) having the authority to issue patents in any foreign country(ies) to issue patents on the invention(s) to CYBERONICS. We respectively warrant that we have not made any agreement in conflict with this Assignment. We jointly and severally agree that we will promptly sign and deliver such other documents, provide such evidence and other information within our knowledge or belief, and do all other relevant things that CYBERONICS may deem necessary or desirable and request of us or any of us in connection with obtaining or maintaining any of the patents, or in connection with any proceeding, controversy or litigation pertaining to any of the applications or patents, or in order to perfect, protect or enforce CYBERONICS' ownership of the right, title and interest conveyed by this Assignment, or in connection with any other matter relating to or arising out of this Assignment, and that we will do all of these things without need for further payment of money or other consideration to us on the understanding that CYBERONICS will bear all reasonable expenses actually incurred for or in connection with such matters. This Assignment and the obligations we have assumed by signing this document shall be binding on our respective heirs and personal representatives.

Joachim F. Wernicke 30 April 1991
 Joachim F. Wernicke Date

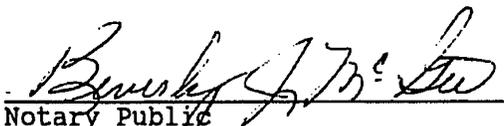
Reese S. Terry, Jr. 30 April 1991
 Reese S. Terry, Jr. Date

NOTARY SEAL

Page 1 of 2

STATE OF TEXAS :
 : ss.
COUNTY OF HARRIS :

On this 30th day of April,
1991, Joachim F. Wernicke and Reese S. Terry, Jr. personally
appeared before me, each of them identified himself to my satisfac-
tion to be an individual named in the foregoing Assignment, and
each signed the document in my presence as being of his free will
and deed.



Notary Public

- NOTARY SEAL

My commission expires 6/25/92

ASSIGNMENT

In consideration of my employee agreements with CYBERONICS, INC., and of \$1.00, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, I, JACOB ZABARA, resident of Miami Beach, Florida, hereby confirm that I have jointly and severally assigned, transferred, and delivered to CYBERONICS, INC., a Delaware corporation having offices in Houston, Texas, U.S.A., its successors and assigns (collectively referred to as "CYBERONICS"), the entire right, title and interest throughout the world to and in my invention(s), made jointly with Joachim F. Wernicke and Reese S. Terry of TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION, the application for United States patent on the invention(s) which issued as U.S. Patent No. 5,299,569, as well as all continuations and divisions of that application, and all patents granted on that and any other application(s) on the invention(s) in the United States and elsewhere, together with the exclusive right to make application for patents and similar protection, reissues, renewals and extensions on the invention(s) in the U.S. and foreign countries.

I hereby request the U.S. Commissioner of Patents and Trademarks and the corresponding official(s) having the authority to issue patents in any foreign country(ies) to issue patents on the invention(s) to CYBERONICS. I respectively warrant that I have not made any agreement in conflict with this Assignment. I agree that I will promptly sign and deliver such other documents, provide such evidence and other information within my knowledge or belief, and do all other relevant things that CYBERONICS may deem necessary or desirable and request me in connection with obtaining or maintaining any of the patents, or in connection with any proceeding, controversy or litigation pertaining to any of the applications or patents, or in order to perfect, protect or enforce CYBERONICS'S ownership of the right, title and interest conveyed by or arising out of this Assignment, and that I will do all of these things without need for further payment of money or other consideration to me on the understanding that CYBERONICS will bear all reasonable expenses actually incurred for or in connection with such matters. This Assignment and the obligations I have assumed by signing this document shall be binding on my respective heirs and personal representatives.

Jacob Zabara

Jacob Zabara

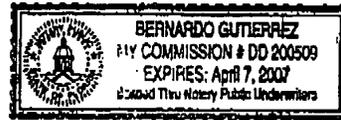
6/13/05

Date

STATE OF FLORIDA :
 :
 COUNTY OF MIDNIGHT : SS.

On this 13 day of JUNE, 2005, Jacob Zabara personally appeared before me, who identified himself to my satisfaction to be an individual named in the foregoing Assignment, and he signed the document in my presence as being of his free will and deed.

Bernardo Gutierrez
Notary Public



Notary Seal

My commission expires APRIL 7 2007

3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent 5,299,569
Issued: April 5, 1994
To: Joachim F. Wernicke, Reese S. Terry, and Jacob Zabara
Assignee: Cyberonics, Inc.
For: TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE
STIMULATION

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

**CORRESPONDENCE ADDRESS
DECLARATION UNDER 37 C.F.R. § 3.73
AND POWER OF ATTORNEY**

Sir:

Please direct all communications as follows:

Jason C. Abair
HOWREY LLP
750 Bering Drive
Houston, TX 77057
(713) 787-1400

The undersigned, being Assignee of the entire interest in the above-identified application by virtue of an Assignment recorded in the United States Patent and Trademark Office as set forth below, hereby revokes any previous Powers of Attorney and appoints the practitioners associated with Customer No. 23369 (Howrey LLP) as its attorneys to transact all business with the U.S. Patent and Trademark Office in connection with the above-identified patent.

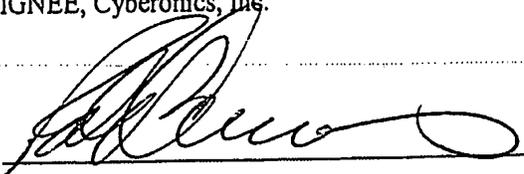
Pursuant to 37 C.F.R. § 3.73, the undersigned has reviewed the evidentiary documents, specifically the Assignment on file for United States Patent 5,299,569, and certifies that to the best of his knowledge and belief, title remains in the name of the Assignee, and that he is empowered to sign this statement on behalf of Assignee.

HOWREY LLP

ASSIGNEE, Cyberonics, Inc.

Date: JUNE 10, 2005

By:



Title: CHAIRMAN ; CEO

ASSIGNMENT:

- Copy of Inventors' Assignments Enclosed with this Power of Attorney
- Previously Recorded:
 - Date:
 - Reel:
 - Frame:

HOWREY LLP

ATTACHMENT C

This information is a compilation of data from patients who responded to treatment after implantation of the VNS Therapy System. The data for patients with epilepsy comes from the data registry of epilepsy patients maintained by Cyberonics. The data for patients with TRD comes from the depression studies that were submitted to the FDA for approval of the VNS Therapy System for TRD.

Patients with Epilepsy Who Responded to Treatment after One Year (n = 1,536)								
	Output Current	Pulse Width	Frequency	On-Time	Off-Time	Magnet Output Current	Magnet Pulse Width	Magnet On-Time
average	1.62	379.19	26.30	25.65	3.47	1.83	419.67	52.88
median	1.50	500.00	30.00	30.00	3.00	1.75	500.00	60.00
mode	1.50	500.00	30.00	30.00	5.00	1.75	500.00	60.00
max	3.50	1000.00	40.00	90.00	180.00	3.50	1000.00	90.00
min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Patients with TRD Who Responded to Treatment after One Year (n = 75)								
	Output Current	Pulse Width	Frequency	On-Time	Off-Time	Magnet Output Current	Magnet Pulse Width	Magnet On-Time
average	0.85	415.20	20.07	25.07	4.07	0.00	268.13	36.40
median	0.75	500.00	20.00	30.00	5.00	0.00	130.00	30.00
mode	0.50	500.00	20.00	30.00	5.00	0.00	130.00	30.00
max	1.75	500.00	30.00	60.00	20.00	0.00	500.00	60.00
min	0.00	130.00	10.00	7.00	0.30	0.00	130.00	30.00



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 15 2005

Ms. Annette Zinn, M.P.H., J.D., RAC
Director and Senior Counsel, Regulatory Affairs
Cyberonics, Inc.
100 Cyberonics Boulevard
Houston, TX 77058

Re: P970003/S50
VNS Therapy System
Filed: October 27, 2003
Amended: December 4 and 19, 2003; February 17, March 18 and 29, April 5 and 8, July 7
and 8, September 8 and 23, 2004; and March 11, and June 28, 2005
Prococode: MUZ

Dear Ms. Zinn:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the VNS Therapy System. This device is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. The PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements outlined in the enclosure, you must conduct the following postapproval studies to further characterize the optimal stimulation dosing and patient selection criteria for the VNS Therapy System for treatment-resistant depression (TRD). The first study is a prospective, multicenter, randomized, double-blind comparison of different output currents in 450 new subjects with TRD. You have agreed to assess the effectiveness responses to differing outputs 16 weeks after the end of a 4-6 week titration period during which concomitant therapies will not be changed. You have also agreed to follow these subjects for at least one year following implantation to further characterize duration of response as well as safety parameters at

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these higher doses. The second study is a prospective, observation registry study of 1000 implanted subjects with TRD with follow-up extending to 5 years after implantation. This study is designed to evaluate long-term patient outcomes as well as predictors of response to therapy. Post approval study progress reports and results will be submitted as a report to the PMA at 6 month intervals. As appropriate, CDRH may request panel review of the postapproval study data. When necessary, the results will be incorporated into the labeling, via a supplement.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

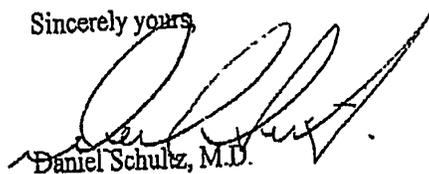
All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

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If you have any questions concerning this approval order, please contact me at (301) 827-7975.

Sincerely yours,



Daniel Schultz, M.D.

Director
Center for Devices and
Radiological Health
Food and Drug Administration

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
 - b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.
2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:
 - a. has not been addressed by the device's labeling; or
 - b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.

The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

ATTACHMENT C

This information is a compilation of data from patients who responded to treatment after implantation of the VNS Therapy System. The data for patients with epilepsy comes from the data registry of epilepsy patients maintained by Cyberonics. The data for patients with TRD comes from the depression studies that were submitted to the FDA for approval of the VNS Therapy System for TRD.

Patients with Epilepsy Who Responded to Treatment after One Year (n = 1,536)								
	Output Current	Pulse Width	Frequency	On-Time	Off-Time	Magnet Output Current	Magnet Pulse Width	Magnet On-Time
average	1.62	379.19	26.30	25.65	3.47	1.83	419.67	52.88
median	1.50	500.00	30.00	30.00	3.00	1.75	500.00	60.00
mode	1.50	500.00	30.00	30.00	5.00	1.75	500.00	60.00
max	3.50	1000.00	40.00	90.00	180.00	3.50	1000.00	90.00
min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Patients with TRD Who Responded to Treatment after One Year (n = 75)								
	Output Current	Pulse Width	Frequency	On-Time	Off-Time	Magnet Output Current	Magnet Pulse Width	Magnet On-Time
average	0.85	415.20	20.07	25.07	4.07	0.00	268.13	36.40
median	0.75	500.00	20.00	30.00	5.00	0.00	130.00	30.00
mode	0.50	500.00	20.00	30.00	5.00	0.00	130.00	30.00
max	1.75	500.00	30.00	60.00	20.00	0.00	500.00	60.00
min	0.00	130.00	10.00	7.00	0.30	0.00	130.00	30.00



US005299569A

United States Patent [19]

[11] Patent Number: **5,299,569**

Wernicke et al.

[45] Date of Patent: **Apr. 5, 1994**

- [54] **TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION**
- [75] Inventors: **Joachim F. Wernicke, League City; Reese S. Terry, Jr., Houston, both of Tex.; Jacob Zabara, Philadelphia, Pa.**
- [73] Assignee: **Cyberonics, Inc., Webster, Tex.**
- [21] Appl. No.: **695,420**
- [22] Filed: **May 3, 1991**
- [51] Int. Cl.⁵ **A61N 1/18**
- [52] U.S. Cl. **607/45; 128/731; 607/62; 607/118**
- [58] Field of Search **128/421, 419 S, 419 C, 128/731**

Assistant Examiner—Scott M. Getzow
Attorney, Agent, or Firm—O'Connor, Cavanagh, Anderson, Westover, Killingsworth & Beshears

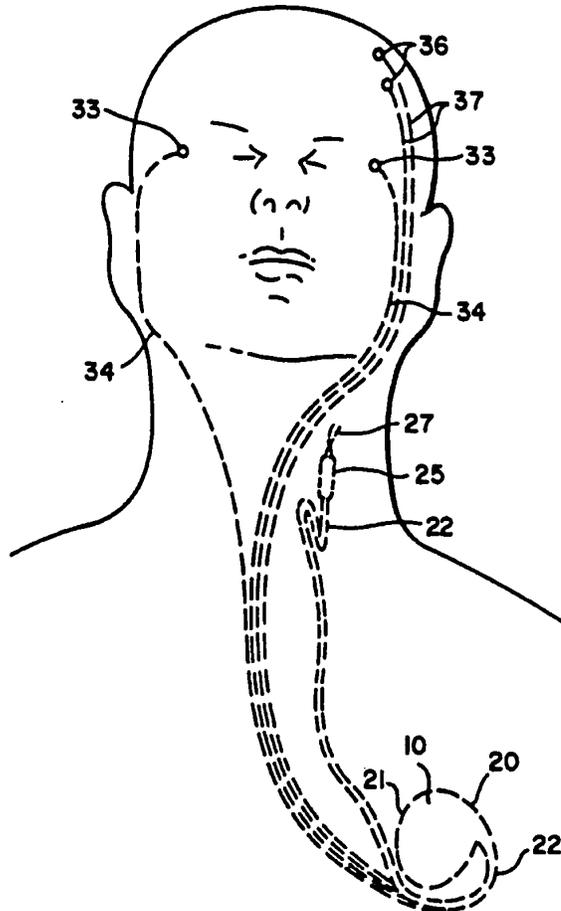
[57] ABSTRACT

Method and apparatus for treating and controlling neuropsychiatric disorders including schizophrenia, depression, and borderline personality disorder by selectively applying a predetermined electrical signal to the patient's vagus nerve for stimulation thereof to alleviate the symptoms of the disorder being treated. The electrical signal may be applied continuously, periodically, or intermittently to the vagus nerve depending, in part, on the nature of the disorder being treated. In certain instances, the electrical signal is applied upon detection of an event indicative of onset of the disorder. In other instances, the electrical signal is selectively applied at will to the vagus nerve, such as by patient activation of the signal generator. Parameter values of the electrical signal including pulse width, output current, frequency, on time and off time, are selectively programmable.

- [56] **References Cited**
- U.S. PATENT DOCUMENTS**
- 3,850,161 11/1974 Liss 128/419 S
- 3,918,461 11/1975 Cooper 128/422
- 4,709,700 12/1987 Hyrman 128/421
- 5,025,807 6/1991 Zabara 128/421

Primary Examiner—William E. Kamm

19 Claims, 2 Drawing Sheets



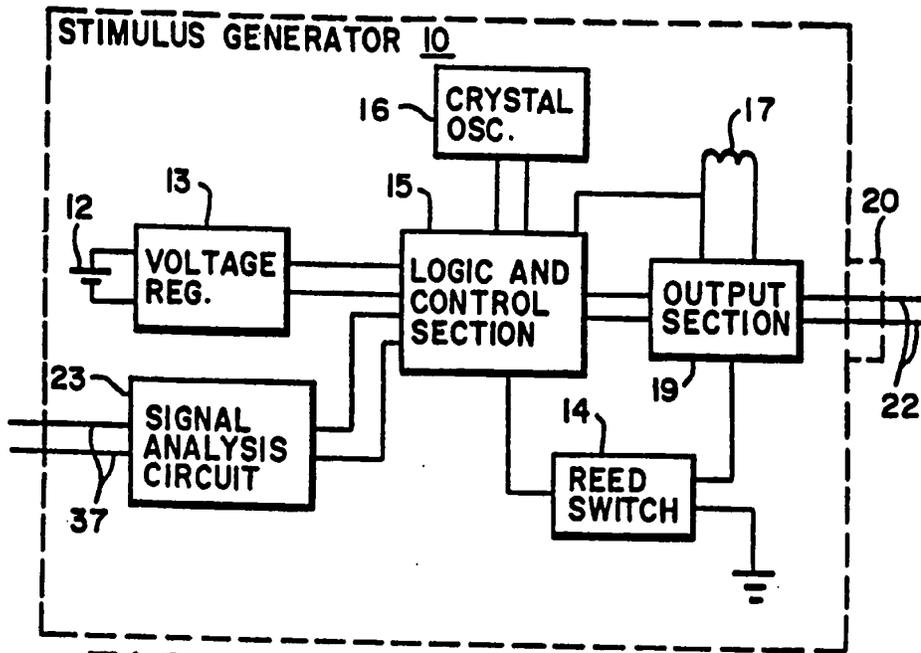


FIG. 1

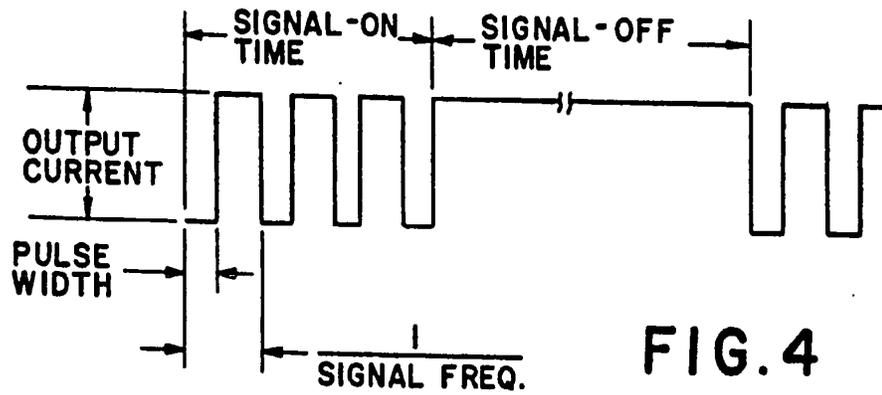


FIG. 4

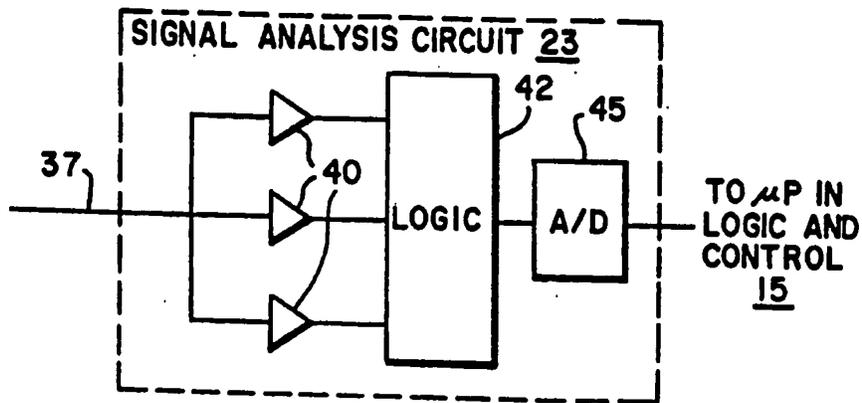


FIG. 5

FIG. 3

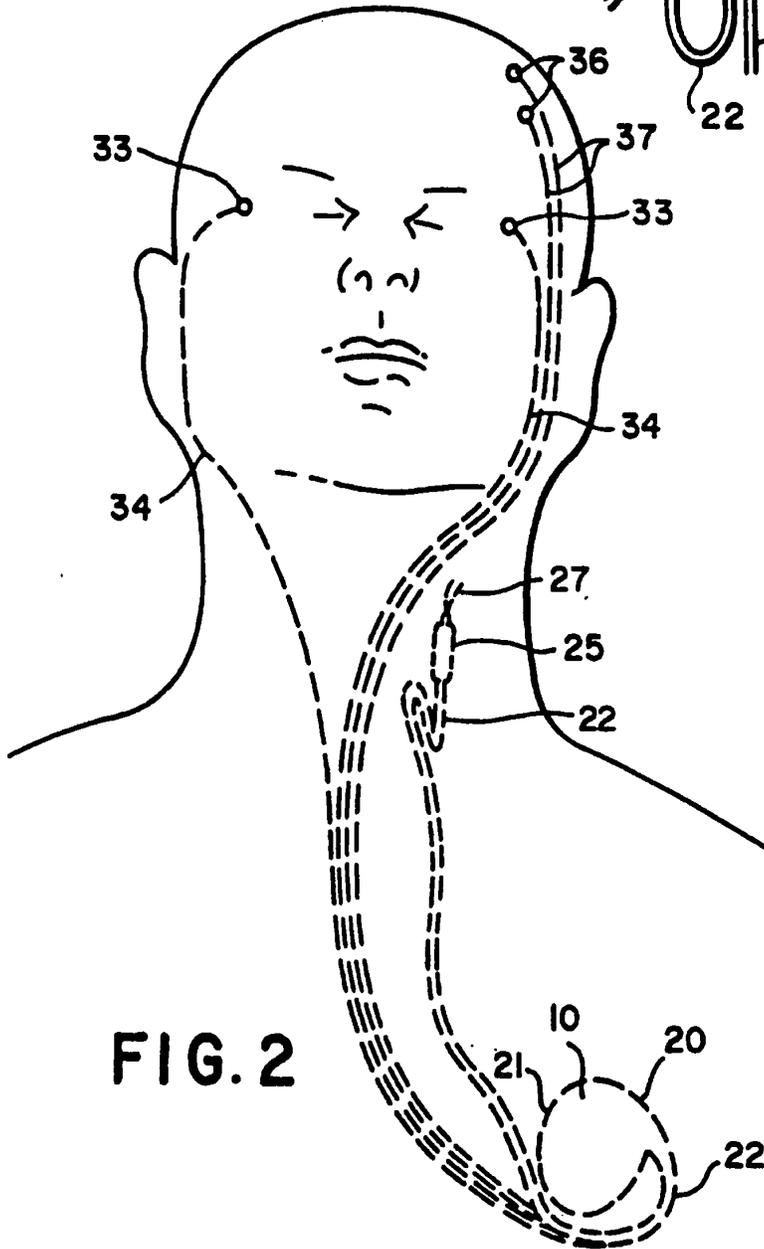
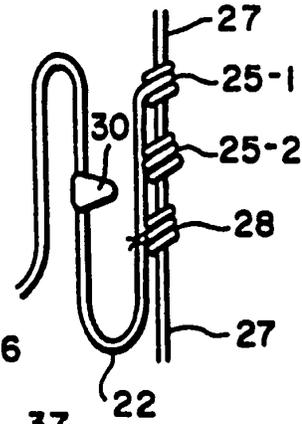


FIG. 2

TREATMENT OF NEUROPSYCHIATRIC DISORDERS BY NERVE STIMULATION

BACKGROUND OF THE INVENTION

The present invention relates generally to methods and apparatus for treating or controlling medical, psychiatric or neurological disorders by application of modulating electrical signals to a selected nerve or nerve bundle of the patient, and more particularly to techniques for treating patients with neuropsychiatric disorders by application of such signals to the vagus nerve, using an implantable neurostimulating device. Specifically, the invention is directed toward treating the symptoms of neuropsychiatric disorders such as schizophrenia, depression, and borderline personality disorder, by selective modulation of vagus nerve activity.

Schizophrenia was initially thought to have only psychological origins. Advances in psychobiology and psychopharmacology have revealed that the illness is primarily organic in nature. Electrophysiologic studies of patients with schizophrenia have supported an organic etiology. Although not entirely consistent, electroencephalogram (EEG) studies have tended to reveal abnormalities in these patients. Also, some parallels have been found between schizophrenia and epilepsy.

In *Psych. Res.* ((1989) 29:419-420, Mueller reported finding increased beta (17.5 Hz) wave activity over the left central-temporal region during acute psychotic episode, whereas before and after the episode the frequency distribution in the EEG was normal. Williamson et al. in *Can. J. Psych.* (1989) 34:680-686, reported that a review of EEG mapping studies revealed that abnormalities exist, with some studies finding asymmetric fast activity while others reported primarily slowing. In *Comprehensive Psych.* (1990) 30(1):34-47, Keshaven et al. reported that sleep EEG studies in schizophrenic patients consistently showed abnormalities, and that although not specific to schizophrenia, patients tended to show impaired sleep continuity and reduced total sleep, but not all patients showed these abnormalities.

Gruzelier et al. reported in *Int. J. Psychophysiol.* (1990) 8:275-282, that in normal subjects the power of the beta II region of the EEG spectrum is decreased in cortical areas associated with specific mental tasks, this focal reduction in power being consistent with the thalamocortical EEG desynchronization response, and being decreased or absent in patients with schizophrenia. In *Psychopathol.* (1989) 22:65-140, Diehl indicated that acute psychotic episodes may be manifestations of temporal lobe epilepsy, and expressed the belief that disorders may exist in the ictal as well as the interictal phase. Kido et al. discussed six patients with seizures followed by schizophrenia-like states, in *Japan J. Psych. Neurol.* (1989) 43:433-438. In *Intern. J. Neuroscience*, Ardilla et al. described three cases in which patients diagnosed as psychotic were actually found to have complex partial status epilepticus.

Turning to depressive disorder, developments in psychobiology and psychopharmacology have provided considerable evidence that major depressive disorder and bipolar depression are biological rather than psychological diseases. Deficiency of brain neurostimulators has been associated with depression. In particular, abnormally low concentrations of serotonin and its metabolites have been found in depressed patients, as

reviewed by Stark et al. in *J. Clin. Psychopharmacol.* (1985) 46[3, Sec.2]:7-13. Several serotonin uptake inhibitors, which increase the amount of serotonin at the synapse have been shown to be effective antidepressants. Serotonin is a neurotransmitter known to be involved in the brain stem projections of the vagus nerve in animals (Kilpatrick et al. in *Eur. J. Pharmacol.* (1989) 159:157-164) and in humans (Reynolds et al. *Eur. J. Pharmacol.* (1989) 174:127-130). It is postulated, then, that increased activity of the vagus nerve would be associated with release of more serotonin in the brain.

The conclusion that depression has a biological basis is also supported by numerous electrophysiological and endocrine studies.

A paper by Pollock et al. in *Biol. Psychiatry* (1990) 27:757-780, reported that a review of studies of the EEG in awake depressed patients reveals that alpha and beta activity are increased compared to controls. Elevations of delta and theta frequency ranges were possibly present as well. It was also felt that increased beta activity may be particularly prominent in patients with coexistent anxiety. Buysee et al. reported in *Arch. Gen. Psych.* (1988) 45:568-575, finding that sleep EEG of patients with primary depression and secondary dementia showed a higher percentage of rapid eye movement (REM) and more phasic REM activity and intensity than patients with primary dementia and secondary depression.

A strong relationship has been found to exist between sleep and depression. One of the most effective treatments for depression is sleep deprivation, which, however, is not a practical long term therapy. As with schizophrenia, a relationship also appears to exist between depression and seizures.

A substantial body of data suggests that anti-convulsant compounds have a spectrum of therapeutic efficacy in a variety of psychiatric syndromes which have not been associated with an epileptoid process. Pathological degrees of neuronal excitability and/or dysregulation may be associated with marked alterations in behavior, which are potentially treatable with anticonvulsant compounds, even in the absence of a concurrent seizure disorder.

The use of electroconvulsive therapy (ECT) to induce seizures is a primary treatment in acute depressive disturbances. ECT appears equal or superior to traditional psychopharmacological treatment modes with tricyclic antidepressants. Although the precise mechanism by which the effect of ECT is achieved is not fully known, it is thought to be related to biochemical changes in the brain resulting from synchronous discharges associated with seizures. Antidepressant drugs may produce similar changes but without inducing seizures.

Certain anticonvulsant agents such as carbamazepine are used in psychiatric disorders. Some studies have indicated dramatic improvement by carbamazepine in affective and schizophrenia-like syndromes associated with epilepsy. Non-epileptic patients with nonspecific EEG abnormalities who suffer from marked psychiatric disorders have also been shown to respond favorably to this drug. In this group, improvements in violent behavior, irritability, emotional lability, depression, agitation, and apathy have been reported. Anticonvulsant compounds thus appear to have an important spectrum of clinical activity in neuropsychiatric syndromes in addi-

tion to their clinical utility in the treatment of epileptic disorders.

Borderline personality disorder is a poorly understood, but recognized psychiatric disorder which seems to have some overlap of schizophrenia and depression. Patients tend to be poorly functional without florid psychosis or overt depression. Lahmeyer et al reported, in *J. Clin. Psych.* (1989) 50(6):217-225, that sleep architecture in patients with borderline personality disorder is disturbed in that REM latency is decreased and REM density is increased. This was found to be particularly true if patients suffered coexisting depression, a history of affective illness or a family history of psychopathology. Sleep abnormalities were reported to appear similar to those seen in affective disorders.

In addressing a therapy involving nerve stimulation to treat such neuropsychiatric disorders, observation should be made of existing knowledge that most nerves in the human body are composed of thousands of fibers, having different sizes designated by groups A, B and C, carrying signals to and from the brain and other parts of the body. The vagus nerve, for example, may have approximately 100,000 fibers (axons) of the three different types, each of which carries such signals. Each axon of that nerve only conducts in one direction, in normal circumstances. The A and B fibers are myelinated, that is, they have a myelin sheath in the form of a substance largely composed of fat. On the other hand, the C fibers are unmyelinated.

Myelinated fibers are typically larger, have faster electrical conduction and much lower electrical stimulation thresholds than the unmyelinated fibers. Along with the relatively small amounts of electrical energy needed to stimulate the myelinated fibers, it is noteworthy that such fibers exhibit a particular strength-duration curve in response to a specific width and amplitude of stimulation pulse.

The A and B fibers are stimulated with relatively narrow pulse widths, from 50 to 200 microseconds (μ s), for example. A fibers exhibit slightly faster electrical conductivities than the B fibers, and slightly lower electrical stimulation thresholds. The C fibers are relatively much smaller, conduct electrical signals very slowly, and have high stimulation thresholds typically requiring wider pulse widths (e.g., 300-1000 μ s) and higher amplitudes for activation. Although the A and B fibers may be selectively stimulated without also stimulating the C fibers, the magnitude and width of the pulse required for stimulating the C fibers would also activate A and B fibers.

Although electrical stimulation of the nerve fiber typically activates neural signals in both directions (bidirectionally), selective unidirectional stimulation is achievable through the use of special nerve electrodes and stimulating waveforms. As noted above, each axon of the vagus nerve normally conducts in only one direction.

In a paper on the effects of vagal stimulation on experimentally induced seizures in rats (*Epilepsia* 1990, 31 (Supp 2): S7-S19), Woodbury has noted that the vagus nerve is composed of somatic and visceral afferents (i.e., inward conducting nerve fibers which convey impulses toward a nerve center such as the brain or spinal cord) and efferents (i.e., outward conducting nerve fibers which convey impulses to an effector to stimulate it and produce activity). The vast majority of vagal nerve fibers are C fibers, and a majority are visceral afferents having cell bodies lying in masses or ganglia in the neck.

The central projections terminate, by and large, in the nucleus of the solitary tract which sends fibers to various regions of the brain (e.g. the hypothalamus, thalamus, and amygdala); others continue to the medial reticular formation of the medulla, the cerebellum, the nucleus cuneatus and other regions.

Woodbury further notes that stimulation of vagal nerve afferent fibers in animals evokes detectable changes of the EEG in all of these regions, and that the nature and extent of these EEG changes depends on the stimulation parameters. Chase, in *Exp Neurol* (1966) 16:36-49, had also observed that vagal activation can affect the EEG activity of certain parts of the brain. The applicants herein postulate that synchronization of the EEG may be produced when high frequency (>70 Hz) weak stimuli activate only the myelinated (A and B) nerve fibers, and that desynchronization of the EEG occurs when intensity of the stimulus is increased to a level that activates the unmyelinated (C) nerve fibers. Woodbury also observes that vagal stimulation can produce widespread inhibitory effects on seizures and certain involuntary movements.

Extra-physiologic electrical stimulation of the vagus nerve has previously been proposed for treatment of epilepsy and various forms of involuntary movement disorders. Specifically, in U.S. Pat. No. 4,702,254 issued Oct. 27, 1987 to J. Zabara (referred to herein as "the '254 patent"), a method and implantable device are disclosed for alleviating or preventing epileptic seizures, characterized by abnormal neural discharge patterns of the brain. The '254 patent describes an implantable neurocybernetic prosthesis (NCP) which utilizes neurocybernetic spectral discrimination by tuning the external current of the NCP generator to the electrochemical properties of a specific group of inhibitory nerves that affect the reticular system of the brain. These nerves are embedded within a bundle of other nerves, and are selectively activated directly or indirectly by the tuning of the NCP to augment states of brain neural discharge to control convulsions or seizures. According to the patent, the spectral discrimination analysis dictates that certain electrical parameters of the NCP pulse generator be selected based on the electrochemical properties of the nerves desired to be activated. The patent further indicates that the optimum sites for application of the NCP generator output to produce the desired effects are the cranial nerves in general, and the vagus nerve in particular.

The NCP disclosed in the '254 patent may be activated either manually or automatically, to provide treatment for the duration of the seizure. Manual activation is performed when the patient experiences the aura at onset of the seizure. Alternatively, automatic activation may be triggered upon detection of instantaneous changes in certain state parameters immediately preceding or at onset of a seizure. Additionally, a prophylactic or preventive mode may be employed in which the NCP is activated periodically to reduce the occurrence and/or the intensity of the seizures. The NCP stimulator of the '254 patent is implanted in the patient's chest and is connected to electrodes installed at the selected point of signal application at the nerve site with the more negative electrode situated closer to the brain and the positive electrode further from the brain, along the vagus nerve.

It is a principal object of the present invention to apply the techniques of selective modulation of vagus nerve electrical activity, using a neurostimulator device

which may be implantable, or used external to the body with only a small portion of the circuitry implanted or with only the nerve electrode(s) and associated lead(s) implanted percutaneously in the body, to the treatment of neuropsychiatric disorders including schizophrenia, depression, and borderline personality disorder.

SUMMARY OF THE INVENTION

The present invention is directed to methods and devices for treating and controlling certain neuropsychiatric disorders by selective stimulation of the vagus nerve (the tenth cranial nerve) in a predetermined manner primarily to synchronize or desynchronize the patient's EEG, depending on the specific nature of the disorder, to alter the serotonin concentration in the brain, and to improve the patient's sleep patterns. In general, a normal EEG displays low voltage and relatively fast activity. Situations do occur in which the EEG activity slows down, such as during sleep, and displays higher voltage, but this is normal.

The apparatus of the invention employs a neurostimulator (preferably but not necessarily implantable) to selectively apply the therapy to treat the specific neuropsychiatric disorders which may include schizophrenia, depression, borderline personality disorder, or other related disorders. The therapy is delivered in a manner to modulate the vagal activity of the patient in a predetermined manner to treat and relieve the symptoms of the disorder, although it would not necessarily be expected to be effective in alleviating the underlying root cause of the disorder. The neurostimulator is programmed by the attending physician to provide the desired therapeutic modality for treatment of the specific neuropsychiatric disorder suffered by the patient.

We have concluded that vagal stimulation can be effective for treating schizophrenia, for example. One observation toward that conclusion is that fast desynchronous (beta) activity and paroxysmal (synchronous) activity of the EEG have both been reported in studies of this disorder. At some stimulation parameters, vagal stimulation will synchronize the EEG, with a resultant beneficial effect on treatment of the disorder where increased beta wave activity is present. A second observation is the apparent relationship between schizophrenia and temporal lobe epilepsy. The temporal lobes are part of the limbic system, which, we postulate, is malfunctioning in patients with schizophrenia. Vagal stimulation can suppress temporal (complex partial) seizures, which are generated in the limbic system. The structures of this system are interconnected, and the beneficial effect of vagal stimulation seen in the temporal lobes may be transmitted to other brain structures, leading to a similar effect on schizophrenia. In this case, the abnormality being treated is a synchronous paroxysmal (epileptiform) discharge, and the therapy is designed to desynchronize the EEG.

Selection among various strategies for vagal modulation to treat the specific neuropsychiatric disorder will depend on a number of factors. These include (i) a consideration of which of the nerve fibers are to be subjected to the modulation; (ii) the modality for achieving synchronization or desynchronization of the EEG; (iii) the modality for effecting a change in the serotonin concentration of the brain; (iv) whether some type of physiologic signal is generated which can be detected and employed to trigger the modulation; and/or (v) whether a "carryover" or refractory period occurs after modulation in which the benefit of the modulation is

maintained. Although these are not all of the factors to be considered for selecting a stimulation strategy for treatment of a particular disorder, nor necessarily listed in order of importance, they are indicative of considerations which may apply in a specific case.

In the treatment, the invention uses different signal parameters and threshold curves to activate the various fibers of the patient's vagus nerve for selective modulation thereof. By appropriately setting pulse width and amplitude of the electrical signal to be delivered by the neurostimulator to the patient's vagus nerve, the nerve fibers can be selectively stimulated, such as A and not B and C; or A and B, but not C; or A, B and C. Various related factors, however, must be considered in the selection process. For example, because the C fibers conduct signals very slowly, they are not highly responsive to techniques of fast stimulation. Therefore, if it were desired to increase desynchronous activity of the EEG by stimulation of the C fibers at 50 Hz, for example, for treatment of a particular neuropsychiatric disorder, it would be prudent to use a short pulse train for the stimulus. This is because the fibers would become refractory to the stimulation within a relatively short time interval and thus incapable of tracking the pattern of a longer train. After a suitable recovery period, another short pulse train may be applied to achieve further treatment. The precise pattern to be used, e.g., the length of the time intervals on and off, will depend upon and be adjusted to the individual patient and the particular disorder being treated.

Furthermore, proper designation of amplitude and frequency range of the applied signals allows tuning of the fibers for EEG synchronization or desynchronization, by which additional control is achieved for the particular disorder to be treated. Desynchronization of the EEG has been found to be achieved by stimulation at frequencies in the range from 20 to 75 Hz at levels above 0.1 volt, but requires signals greater than 3 volts at frequencies above 75 Hz. If the frequency is above 75 Hz and the signal is below 3 volts, EEG synchronization is achieved. The actual voltage required depends on the type and geometry of the electrode and the impedance of the electrode-tissue interface.

According to the invention, the basic stimulation strategy calls for modulating the activity of a number of brain structures, including the limbic system, the reticular formation, and the hippocampus. As described by Rutecki in *Epilepsia* (1990) 31 (Supp. 2): S1-S6, the vagus nerve projects directly or indirectly to these brain structures. Preferably, this strategy is implemented by circadian programming to automatically activate the stimulus generator to continuously, periodically or intermittently generate an electrical signal appropriate for application to the patient's vagus nerve to modulate the activity of the brain structures including limbic system, reticular formation and hippocampus. For example, if epileptiform activity is being treated the modulation is effected to desynchronize the synchronous high voltage slow wave, and increase the background desynchronous activity. In another aspect of the invention, the treatment is carried out by applying the selectively modulating electrical signals to the patient's vagus nerve in response to the occurrence of one or more predetermined detectable events.

In the case of depression, although sleep deprivation is not a practical long term therapy, vagal stimulation can alter sleep state architecture and is a modality that can produce a beneficial antidepressant effect. Also, the

relationship between seizures and depression, and the effectiveness of treating depression (major depressive disorder) with ECT may be useful for the prescription of vagus nerve stimulation. ECT demonstrates the effectiveness of brain electrical stimulation in the therapy of psychiatric disorders, but the electric current delivered to the brain is sufficiently intense to produce seizures in the patients. In contrast, treatment delivered by the neurostimulator according to the method and apparatus of the present invention is inherently safer and more comfortable for the patient than ECT. The output current is considerably smaller and is not applied directly to the brain through the skull. It appears that certain stimulation parameters for the vagus nerve produce synchronization of brain activity which leads to the biochemical changes required to relieve depression, but without causing seizures. Similar biochemical changes may be achieved with antidepressant drugs. Serotonin, one of the neurotransmitters affected by antidepressant drugs, is also involved in mediation of vagal impulses.

It further appears that vagal stimulation can be effective in the treatment of borderline personality disorders, at least because of the abnormalities in sleep architecture attendant with such disorders and the capability of vagal stimulation to alter sleep states.

Broadly, then, the present invention is directed to apparatus and methods which employ a neurostimulator device, preferably implantable, for therapy or treatment of any of several types of neuropsychiatric disorders through nerve stimulation. The modulating signals applied to the vagus nerve may stimulate or inhibit other neural signals to produce excitatory or inhibitory neurotransmitter release, but for purposes of this disclosure both situations are included within the term "stimulating". It should be emphasized that although the preferred nerve site for application of the modulating signals is the vagus nerve, effective treatment may be achieved through application of the stimulus to one or more other nerves, particularly among the cranial nerves, and such treatment is deemed to be within the ambit of the present invention. The invention recognizes and employs specific techniques of vagal stimulation in a therapeutic regimen for treatment of the particular neuropsychiatric disorder.

Accordingly, it is a more specific object of the invention to provide methods and apparatus for treating and controlling neuropsychiatric disorders by applying electrical stimuli to the patient's vagus nerve or other cranial nerve, to activate a specific group of fibers from among all of the fiber groups of the selected nerve(s), and to selectively synchronize or desynchronize the patient's EEG and/or to vary REM activity according to the specific nature of the disorder, and/or to alter brain serotonin concentrations.

Another object of the invention is to provide methods of treating and controlling neuropsychiatric disorders by sensing a symptom of the disorder or the occurrence of a predetermined detectable event and thereafter automatically or manually effecting modulation of vagal activity through the application of preselected stimuli to the patient's vagus nerve to suppress the disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and still further objects, aspects, features and attendant advantages of the present invention will be better understood from a consideration of the ensu-

ing detailed description of a presently preferred embodiment and method thereof, taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a simplified block diagram of an implantable neurostimulator electronics package (stimulus generator) for use (with appropriate parameter settings and ranges) in treating neuropsychiatric disorders according to the present invention;

FIG. 2 is a simplified fragmentary illustration of a preferred embodiment of the stimulus generator and lead/electrode system of the neurostimulator implanted in the patient's body;

FIG. 3 is a detailed fragmentary illustration of the nerve electrode as implanted on the vagal nerve in the neck of the patient for modulating vagal activity;

FIG. 4 is an illustrative idealized electrical output signal waveform of the stimulus generator useful for clarifying relevant parameters of the signal developed by the stimulus generator for application to the nerve; and

FIG. 5 is a simplified block diagram of an EEG signal analysis circuit used in the stimulus generator.

DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENT AND METHOD

Referring now to the drawings, a block diagram of the basic components of the stimulus generator of a neurostimulator and their interrelationship is illustrated in FIG. 1 and further details of location of an implantable version of the device and the associated lead/electrode system are shown in FIGS. 2 and 3. A generally suitable form of neurostimulator for use in the apparatus of the present invention is disclosed in copending U.S. patent application Ser. No. 07/434,985, now U.S. Pat. No. 5,154,172, issued Oct. 13, 1992, to Anthony J. Varrichio et al., titled "Current Source with Programmable Overhead Voltage", filed Nov. 10, 1989 (referred to herein as the '985 application"), assigned to the same assignee as the instant application. The specification of the '985 application is incorporated herein in its entirety by reference, but certain portions of it are summarized in this application for the sake of convenience to the reader.

The neurostimulator utilizes a conventional microprocessor and other standard electrical and electronic components, and in the case of an implanted device, communicates with a programmer and/or monitor located external to the patient's body by asynchronous serial communication for controlling or indicating states of the device. Passwords, handshakes and parity checks are employed for data integrity. The neurostimulator also includes means for conserving energy, which is important in any battery operated device and especially so where the device is implanted for medical treatment of a disorder, and means for providing various safety functions such as preventing accidental reset of the device.

The stimulus generator 10 (FIG. 1) is preferably adapted to be implantable in the patient's body, in a pocket formed by the surgeon just below the skin in the chest as shown in FIG. 2, although a primarily external neurostimulator may alternatively be employed. The neurostimulator also includes implantable stimulating electrodes (described below) together with a lead system 22 for applying the output signal of the stimulus generator to the patient's vagus nerve. Components external to the patient's body include a programming wand for telemetry of parameter changes to the stimulus generator and monitoring signals from the genera-

tor, and a computer and associated software for adjustment of parameters and control of communication between the generator, the programming wand and the computer. The external components of the system are not shown in the drawings.

In conjunction with its microprocessor-based logic and control circuitry, the stimulus generator 10 or other implanted or external circuitry may include detection circuitry for sensing an event indicative of an abnormality to trigger automatic delivery of the stimulating signal. For example, surface or depth electrodes may be implanted to sense specific characteristics of the patient's EEG for triggering the therapy, as will be discussed presently in conjunction with the description of FIGS. 2 and 5. However, this involves complex and delicate electrode/lead implantation procedures as well as the requirement of circuitry for spectral analysis and/or programmable spectral or pattern recognition. Preferably, therefore, the treatment is applied continuously, periodically or intermittently or in accordance with the patient's circadian rhythm. The stimulus generator is designed, implemented and programmed to deliver a selectively patterned stimulating signal to modulate vagal activity in a manner designed to treat the specific neuropsychiatric disorder of interest.

As shown in FIG. 1, stimulus generator 10 includes a battery (or set of batteries) 12, which may be of any reliable long-lasting type conventionally employed for powering implantable medical electronic devices (such as batteries employed in implantable cardiac pacemakers or defibrillators). In the preferred embodiment of the stimulus generator, the battery is a single lithium thionyl chloride cell. The terminals of the cell 12 are connected to the input side of a voltage regulator 13. The regulator smoothes the battery output to produce a clean, steady output voltage, and provides enhancement thereof such as voltage multiplication or division if necessary for a specific application.

Regulator 13 supplies power to logic and control section 15, which includes a microprocessor and controls the programmable functions of the device. Among these programmable functions are output current, output signal frequency, output signal pulse width, output signal on-time, output signal off-time, daily treatment time for continuous or periodic modulation of vagal activity, and output signal-start delay time. Such programmability allows the output signal to be selectively crafted for application to the stimulating electrode set (FIGS. 2 and 3) to obtain the desired modulation of vagal activity for treatment and control of the disorder. Timing signals for the logic and control functions of the generator are provided by a crystal oscillator 16. A magnetically-actuated reed switch 14 may be incorporated in the electronics package to provide the generator with manual activation capability (by use of an external magnet, not shown, placed immediately adjacent to the package or its implant site).

Built-in antenna 17 enables communication between the implanted stimulus generator and the external electronics (including both programming and monitoring devices) to permit the device to receive programming signals for parameter changes, and to transmit telemetry information, from and to the programming wand. Once the system is programmed, it operates continuously at the programmed settings until they are reprogrammed (by the attending physician) by means of the external computer and the programming wand.

Logic and control section 15 of the stimulus generator 10 controls an output circuit or section 19 which generates the programmed signal levels appropriate to the disorder being treated. The output section and its programmed output signal are coupled (directly, capacitively, or inductively) to an electrical connector 20 on the housing 21 of the generator and to lead assembly 22 connected to the stimulating electrodes (FIGS. 2 and 3). If EEG sensing electrodes or eye movement sensing electrodes are to be implanted in the patient for triggering delivery of therapy by the stimulus generator on detection of an event indicative of the neuropsychiatric disorder of interest, a sense signal analysis circuit 23 is provided within the generator housing 21, with connections to the microprocessor in logic and control section 15 and to the sensing electrodes. An exemplary sense signal analysis circuit will be described presently.

Housing 21 in which stimulus generator 10 is encased is hermetically sealed and composed of a material such as titanium which is biologically compatible with the fluids and tissue of the patient's body. Further details of suitable structure and operation of the neurostimulator, beyond those by which the device is adapted to treat the neuropsychiatric disorder as described herein, are available in the '985. application, to which the reader is referred. Although not used in the preferred embodiment, if a detection system is employed with the neurostimulator to detect characteristics of the EEG, or to detect eye movement, by which to initiate the vagal stimulation automatically upon sensing the predetermined event indicative of need for treatment, the signal parameters of the implanted device may be calibrated by telemetry (via the programming wand) to the particular patient and the results then programmed into the microprocessor for the appropriate treatment.

FIG. 2 illustrates the preferred location of implanted generator 10, in case 21 with connector 20, in the patient's chest in a cavity formed by the implanting surgeon just below the skin, much as a pacemaker pulse generator would be implanted. A stimulating nerve electrode set 25 (FIG. 3) is conductively connected to the distal end of insulated electrically conductive lead assembly 22 which is attached at its proximal end to connector 20. Electrode set 25 is a bipolar stimulating electrode, preferably of the type described in U.S. Pat. No. 4,573,481 issued Mar. 4, 1986 to Bullara. The electrode assembly is surgically implanted on the vagus nerve 27 in the patient's neck. The two electrodes 25-1 and 25-2 are wrapped about the vagus nerve, and the assembly is secured to the nerve by a spiral anchoring tether 28 preferably as disclosed in U.S. Pat. No. 4,979,511 issued Dec. 25, 1990 to Reese S. Terry, Jr. and assigned to the same assignee as the instant application. Lead(s) 22 is secured, while retaining the ability to flex with movement of the chest and neck, by a suture connection 30 to nearby tissue.

The open helical design of electrode assembly 25 (described in detail in the above-cited Bullara patent), which is self-sizing and flexible, minimizes mechanical trauma to the nerve and allows body fluid interchange with the nerve. The electrode assembly conforms to the shape of the nerve, providing a low stimulation threshold by allowing a larger stimulation contact area. Structurally, the electrode assembly comprises two ribbons of platinum constituting the electrodes which are individually bonded to the inside surface of each of the first two spiral loops 25-1 and 25-2 of a three-loop helical assembly, and the two lead wires are respectively

welded to the conductive ribbon electrodes. The remainder of each loop is composed of silicone rubber, and the third loop acts as the tether 28 for the electrode assembly. The inner diameter of the helical bipolar electrode assembly may typically be approximately two millimeters (mm), and an individual spiral is about seven mm long (measured along the axis of the nerve).

Eye movement sensing electrodes 33 may be implanted at or near the outer periphery of each eye socket in a suitable location to sense muscle movement or actual eye movement, as shown in FIG. 2, and electrically connected to leads 34 implanted via a catheter or other suitable means (not shown) and extending along the jawline through the neck and chest tissue to the sense signal analysis circuit 23 of stimulus generator 10. Sense electrodes 33 are utilized for rapid eye movement (REM) detection in a pattern indicative of the disorder to be treated, as will be described in greater detail below. Alternatively, or additionally, EEG sense electrodes 36 may be implanted in spaced apart relation through the skull, and connected to leads 37 implanted and extending along the scalp and temple and then along the same path and in the same manner as described above for the eye movement electrode leads. These or other types of sensing electrodes would only be required for alternative embodiments of the invention, since the preferred embodiment utilizes a continuous, periodic or intermittent stimulus signal applied to the vagus nerve (each of which constitutes a form of continual application of the signal), appropriate to treat the particular neuropsychiatric disorder which has been diagnosed in the case of the specific patient under observation.

The stimulus generator may be programmed with an IBM-compatible personal computer (not shown) using programming software of the type copyrighted by the assignee of the instant application with the Register of Copyrights, Library of Congress, or other suitable software based on the description herein, and a programming wand (not shown). The wand and software permit noninvasive communication with the generator after the latter is implanted. The wand is preferably powered by internal batteries, and provided with a "power on" light to indicate sufficient power for communication. Another indicator light is preferably provided to show that data transmission is occurring between the wand and the generator.

The operation of stimulus generator 10 to control and treat the neuropsychiatric disorder of interest will be described with reference to FIG. 4, which illustrates the general nature, in idealized representation, of the output signal waveform delivered by output section 19 of the neurostimulator to electrode assembly 25. This illustration is presented principally for the sake of clarifying terminology, including the parameters of output signal on-time, output signal off-time, output signal frequency, output signal pulse width, and output signal current.

In the treatment of schizophrenia according to the invention, the preferred stimulation strategy is to use circadian programming to desynchronize the EEG during the patient's normal waking hours, and to synchronize the EEG at night to improve sleep. Alternatively, detection strategies such as EEG detection of beta waves over the central temporal region, and/or of abnormal sleep patterns may be employed to trigger the stimulation. In the preferred embodiment and method, the vagal stimulation is continuously, periodically, or intermittently performed during prescribed segments of

the patient's circadian cycle. For example, daytime stimulation may be periodic with a random frequency for the stimulating pulse waveform, with parameter selection for EEG desynchronization; and nighttime stimulation may employ a periodically applied pattern with parameters selected to synchronize the patient's EEG (e.g., at 90 Hz, 1 mA, 0.10 ms for the pulse waveform), alternating with desynchronizing stimuli at predetermined intervals (e.g., 100 minute separation) to produce low voltage fast (REM) activity. Such a regimen of vagal stimulation is programmed into the neurostimulator electronics package.

The schizophrenic patient is generally unable to recognize the symptoms of the disorder, and consequently no provision is made for patient activation of the neurostimulator for treatment of this particular disorder. However, the stimulus generator may be implemented for manual activation by a companion of the patient (using, for example, an external magnet to actuate the reed switch 14, in the implantable device of FIG. 1).

The preferred range of stimulation parameters for treatment of schizophrenia and the typical value of each parameter of the stimulating output signal are as follows:

	Range	Desynch, Typical	Synch, Typical
Pulse Width	0.05-1.5 ms	0.5 ms	0.1 ms
Output Current	0.1-5.0 mA	1.5 mA	1.5 mA
Frequency	5-150 Hz	25 Hz	80 Hz
On Time	5-500 sec	300 sec	30 sec
Off Time	5-500 sec	10 sec	5 sec
Frequency sweep	10-50 Hz		Optional
Random frequency	10-50 Hz		Optional
	Daytime Only		

Another activation modality for daytime stimulation is to program the output of the neurostimulator pulse generator to the maximum amplitude which the patient can tolerate, with cycling on and off for a predetermined period of time followed by a relatively long interval without stimulation.

For treating depression, the preferred stimulation strategy of the invention is to employ circadian programming for night time stimulation to increase REM activity, and increase synchronization of the EEG during the patient's normal waking hours. Alternatively, a strategy may be employed for EEG detection of alpha or beta waveforms, and/or EEG detection and analysis of REM activity during sleep at night, followed by large signal, infrequent stimulation when the neurostimulator generator is activated by the detection circuitry. Here again, such detection may be implemented using surface or depth sensing electrodes and EEG spectral or REM analysis circuitry.

The patient suffering from depression is capable of recognizing the symptoms of the disorder, and therefore may be provided with a neurostimulator which is implemented, in the manner described above, to permit manual activation for delivery of the therapy. In the case of manual activation, the therapy applied preferably would be that normally employed during the patient's waking hours, i.e., to synchronize the EEG. It is unlikely, however, that an antidepressant effect would be achieved quickly, since treatment of depression using drugs begins to take effect in from two to four weeks and is probably related to changes in receptors, and the use of vagal stimulation for depression is likely to pro-

duce a similar result. For that reason, the neurostimulator should be programmed to generate the stimulus for a relatively long period of time in response to manual activation.

As noted earlier herein, the treatment is designed, in part, to increase the activity of the vagus nerve by which to evoke a release of greater amounts of the neurotransmitter serotonin in the patient's brain. This alteration, and specifically an increase, of the serotonin concentration in the brain is the result of an enhancement of the production of this natural antidepressant through vagal modulation.

A preferred range of stimulation parameters to treat depression, and the typical value of each parameter of the stimulus generator programmed output signal are as follows:

	Range	Desynch, Typical	Synch, Typical
Pulse Width	0.05-1.5 ms	0.10 ms	0.5 ms
Output Current	0.1-5.0 mA	1.0 mA	1.5 mA
Frequency	5-150 Hz	90 Hz	20 Hz
On Time	5-500 sec	30 sec	300 sec
Off Time	5-500 sec	30 sec	10 sec
Frequency sweep	10-50 Hz		Optional
Random frequency	10-50 Hz		Optional

The circadian programming may also be set for synchronization of sleep patterns at night (e.g., output stimulating signal of 20 Hz, 500 ms, and 2 mA, cycled at 300 seconds on and 30 seconds off).

An activation modality for daytime stimulation in which the stimulus is applied to the nerve at the maximum amplitude tolerable by the patient, with on/off cycling for a first interval followed by a relatively long second interval without stimulation, similar to a modality described above for treating schizophrenia, may have value for treating depression. It bears some analogy to ECT which has been found effective in cases of depression, and would produce synchronous activity of the EEG for the brief stimulation intervals.

In the treatment of borderline personality disorder, the preferred stimulation strategy is designed to modify the patient's sleep patterns toward a normal pattern. Here, a suitable detection strategy is to employ implanted electrodes to sense muscle movement or actual eye movement during sleep, such as are shown in FIG. 2, and to analyze the detected REM activity; or to perform EEG detection with surface or depth EEG electrodes, followed by spectral analysis of the EEG. Again, however, circadian programming of the output signal for automatic stimulation in continuous, periodic or intermittent patterns is preferred for the sake of avoiding additional invasive procedures. In general, patient activation of the neurostimulation generator is not a viable option for the patient suffering from borderline personality disorder, although here again the provision of manual activation means could be appropriate for use by a companion.

The preferred range of stimulation parameters for treatment of borderline personality disorder and the typical value of each parameter of the programmed stimulation signal are as follows:

	Range	Typical
Pulse Width	0.05-1.5 ms	0.10 ms
Output Current	0.1-5.0 mA	1.0 mA

-continued

	Range	Typical
Frequency	5-150 Hz	90 Hz
On Time	5-1500 sec	30 sec
Off Time	5-1500 sec	10 sec
Frequency sweep	40-100 Hz	Optional
Random frequency	40-100 Hz	Optional

The circadian programming may employ specific patterns at night to modify REM activity for the purpose of increasing REM latency and to decrease REM intensity, tailored for each individual patient. Such a regimen of stimulation is best designed where the patient exhibits historically consistent sleep patterns, and would require defining the stimulation pattern for discrete time block during the sleep period.

If sense electrodes are to be utilized to detect onset of the disorder being treated, the signal analysis circuit 23 is incorporated in the stimulus generator 10 (FIG.

Referring to FIG. 5, where the sense electrodes are EEG electrodes such as 36 and associated leads 37 of FIG. 2, analysis circuit 23 is implemented for EEG detection and analysis. To that end, circuit 23 includes a plurality of parallel active sense signal bandpass filters 40 staged to provide selective filtering in the ranges from 0-2 Hz, 2-4 Hz and 15-20 Hz, for example; a logic circuit 42 to select the output of one filter from among the plurality of filters 40; and an analog/digital (A/D) converter 45. The outputs of the filters are individually sampled by the logic circuit 42, and the sampling rate, averaging time interval, and weighting assigned to each sense signal band, are controlled by the microprocessor in the logic and control section 15 of the stimulus generator 10 (FIG. 1), to detect the EEG pattern. Upon detection of the symptom of interest of the disorder being treated, the processed digital signal is supplied to the microprocessor to trigger application of the stimulating signal to the patient's vagus nerve.

The activation of the analysis circuit 23 and its internal component circuitry need not be continuous, but only periodic such as every few hours, depending on the disorder being treated.

Various features may be incorporated into the neurostimulator for purposes of the safety and comfort of the patient. For example, comfort would be enhanced by programming the output stimulus to ramp up during the first two seconds of stimulation, rather than to be delivered abruptly. Also, the implanted generator may be provided with a clamping circuit to limit the maximum voltage, to 14 volts for example, which is delivered to the vagus nerve. Such a maximum limit is designed to prevent damage to the patient's vagus nerve.

The programmable functions and capabilities of the neurostimulator are designed and implemented to permit noninvasive communication with the stimulus generator after it is implanted, which is useful for both activation and monitoring functions. Beyond the essential functions of the device, the programming software may readily be structured to provide straightforward menu-driven operation, HELP functions, prompts, and messages to facilitate simple and rapid programming while keeping the user fully informed of everything occurring at each step of a sequence. Programming capabilities should include capability to modify the adjustable parameters of the stimulus generator and its output signal, to test device diagnostics, and to store and retrieve telemetered data. It is desirable that when

the implanted unit is interrogated, the present state of the adjustable parameters is displayed on the monitor of external PC so that the programmer may then conveniently change any or all of those parameters at the same time; and, if a particular parameter is selected for change, all permissible values for that parameter are displayed so that the programmer may select an appropriate desired value for entry into the neurostimulator.

Diagnostics testing should be implemented to verify proper operation of the device, and to indicate the existence of problems such as with communication, the battery, or the lead/electrode impedance. A low battery reading, for example, would be indicative of imminent end of life of the battery and need for implantation of a new device. The nerve electrodes are capable of indefinite use absent indication of a problem with them observed on the diagnostics testing.

Although a preferred embodiment of apparatus and certain preferred methods for treating and controlling neuropsychiatric disorders through vagal modulation according to the invention have been described herein, it will be apparent to those skilled in the field from a consideration of the foregoing description that variations and modifications of such embodiments, methods and techniques may be made without departing from the true spirit and scope of the invention. For example, although a totally implantable device is preferred, the electronic energization package may, if desired, be primarily external to the body. Stimulation can be achieved with an RF power device implemented to provide the necessary energy level. The implanted components may be limited to the lead/electrode assembly, a coil and a DC rectifier. Pulses programmed with the desired parameters would be transmitted through the skin with an RF carrier, and the signal thereafter rectified to regenerate a pulsed signal for application as the stimulus to the vagus nerve to modulate vagal activity. This would virtually eliminate the need for battery changes. The disadvantages of such an implementation are that the external transmitter must be carried by the patient, greater power is required for activation, and the output current to the nerve is less stable.

An external stimulus generator may be employed with leads extending percutaneously to the implanted nerve electrode set. The major problem encountered with this technique is the potential for infection, but it is useful to allow short term testing of the patient to determine whether the particular neuropsychiatric disorder suffered by the patient under observation is amenable to successful treatment. If it is, a more permanent implant may be provided.

Accordingly, it is intended that the invention shall be limited only to the extent required by the appended claims and the rules and principles of applicable law.

What is claimed is:

1. A method of treating patients with neuropsychiatric disorders, which includes
 - selecting a patient suffering from a neuropsychiatric disorder,
 - determining the type of neuropsychiatric disorder exhibited by the patient, and
 - selectively applying a predetermined electrical stimulus to the patient's vagus nerve for modulating the electrical activity thereof in a manner to alleviate the symptoms of the neuropsychiatric disorder exhibited by the patient being treated.

2. The method of claim 1, wherein the neuropsychiatric disorder being treated is schizophrenia, and the predetermined stimulus is an electrical signal in the form of a pulse waveform with signal parameters programmed to increase desynchronous activity of the patient's EEG during waking hours, and to increase synchronous activity of the EEG during sleep.

3. The method of claim 1, wherein the neuropsychiatric disorder being treated is one of schizophrenia, depression or a borderline personality disorder, and further including

- detecting an event indicative of onset of the disorder, and

- initiating application of the predetermined electrical stimulus upon such detection.

4. The method of claim 3, wherein the neuropsychiatric disorder being treated is schizophrenia, and the detected event is one of (i) EEG beta waves over the central temporal region and (ii) abnormal sleep patterns, of the patient.

5. The method of claim 3, wherein the neuropsychiatric disorder being treated is depression, and the detected event is one of (i) EEG alpha and beta waves, and (ii) predetermined level of REM activity during sleep, of the patient.

6. The method of claim 3, wherein the neuropsychiatric disorder being treated is borderline personality disorder, and

- the detected event is a predetermined level of REM activity during sleep by the patient.

7. The method of claim 1, wherein the neuropsychiatric disorder being treated in depression, and the predetermined stimulus is an electrical signal in the form of a pulse waveform with signal parameters programmed to increase synchronous activity of the patient's EEG during the patient's waking hours, and to increase the patient's rapid eye movement (REM) activity during sleep.

8. The method of claim 1, wherein the predetermined stimulus is an electrical signal selected to activate the patient's vagus nerve to modify the release of serotonin in the patient's brain.

9. The method of claim 8, wherein the neuropsychiatric disorder being treated is depression, and including applying the predetermined electrical stimulus to the patient's vagus nerve continually over a relatively long period of time to increase the release of serotonin.

10. The method of claim 1, wherein the neuropsychiatric disorders being treated is depression, including manually activating the predetermined stimulus as an electrical signal in the form of a pulse waveform with signal parameters programmed to alleviate symptoms of the depression.

11. The method of claim 1, wherein the neuropsychiatric disorder being treated is borderline personality disorder, and

- the predetermined stimulus is an electrical signal in the form of a pulse waveform with signal parameters programmed to increase the patient's REM latency and decrease REM intensity during sleep.

12. The method of claim 1, wherein said stimulus is an electrical signal in the form of a pulse waveform with programmable signal parameters, and is applied to a nerve electrode implanted in the patient's neck on the vagus nerve.

13. The method of claim 12, wherein said electrical signal is further programmable for any of continuous periodic or intermittent application to the patient's vagus nerve.

14. The method of claim 12, wherein said electrical signal is selectively applied at will to the patient's vagus nerve.

15. The method of claim 12, wherein the parameter values of the electrical signal including pulse width, output current, frequency, on time and off time, are selectively programmable.

16. A new use for a neurostimulator device adapted to be implanted in a human patient, in which the device comprises an electrical signal generator which is programmable to generate an electrical output signal having selected signal parameters, and an electrical lead adapted to be connected at a proximal end thereof to the signal generator, the lead including an electrode electrically connected to a distal end of the lead and having a configuration for encompassing a portion of the length of a nerve so that the electrode is adapted to be implanted on the patient's vagus nerve to modulate the electrical activity of the nerve in response to application of the programmed electrical output signal from the signal generator to the lead, the new use of the neurostimulator device comprising the steps of:

- implanting said electrode on the vagus nerve of the patient,
- electrically connecting the proximal end of the lead to said signal generator,
- programming the output signal of the signal generator to constitute a pulse waveform with parameter values of pulse width, output current, frequency, and on and off times selected for therapeutic treatment and control of a neuropsychiatric disorder of the patient among the group of such disorders consisting of schizophrenia, depression, borderline personality disorder.

17. The new use of the neurostimulator device of claim 16, including:

- detecting an event indicative of onset of the neuropsychiatric disorder being treated, and, in response to such detected event, applying the output signal of the signal generator to the lead, so as to modulate the electrical activity of the vagus nerve to alleviate symptoms of the neuropsychiatric disorder being treated.

18. A method for use in advancing the treatment and control of neuropsychiatric disorders, including the steps of

- providing an electrical lead with a stimulating electrode assembly at its distal end for implantation on a patient's vagus nerve,
- providing a programmable stimulus generator for generating electrical pulse sequences with selectively variable electrical parameters for selective application to the lead/electrode assembly when implanted on the vagus nerve,
- incorporating an electrical connector in the stimulus generator to accommodate electrical connection of the proximal end of the electrical lead to the stimulus generator,
- restricting the programmable ranges of the variable parameters of the electrical pulse sequences to values which in combination will stimulate the vagus nerve and thereby modulate its electrical activity when one or more programmed pulse sequences are applied to the nerve via the lead/electrode assembly, to alleviate symptoms of the particular neuropsychiatric disorder to be treated,
- adapting the stimulus generator for physician control of the programming, and
- supplying the stimulus generator and lead/electrode assembly for the treatment and control of neuropsychiatric disorders.

19. The method of claim 18, wherein the selectively variable electrical parameters include pulse width, amplitude and frequency, sequence duration and intervals.

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Depression Physician's Manual

**VNS Therapy™ Pulse
Model 102 Generator**

and

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

June 2005

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



26-0005-6300/9

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1-D. BRIEF DEVICE DESCRIPTION

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

2-D. INTENDED USE / INDICATIONS

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression* for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments*.

*See glossary for a definition of terms.

3-D. CONTRAINDICATIONS



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



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

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

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

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

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

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

4-D. WARNINGS

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



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



Not curative

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



Unapproved uses

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

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



Worsening depression/suicidality

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

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



Dysfunctional cardiac conduction systems

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



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

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

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

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



Swallowing difficulties

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



Dyspnea or shortness of breath

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



Obstructive sleep apnea

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



Device malfunction

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



MRI

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



Excessive stimulation

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

Excessive stimulation at an excess duty cycle (that is, one that occurs when “ON” time is greater than “OFF” time) has resulted in degenerative nerve damage in laboratory animals. An excess duty cycle can be produced by continuous or frequent magnet activation (> 8 hours), as determined by animal studies. Do not stimulate at these combinations of ranges.



Device manipulation

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

5-D. PRECAUTIONS

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



Appropriate physician training is very important.

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



Use during pregnancy

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

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



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



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

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



Effects on other medical devices

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



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



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

-  **Do not program the VNS Therapy System to an ON or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.** Failure to observe this precaution may result in patient discomfort or adverse events.
-  Do not use frequencies of 5 Hz or below for long-term stimulation. Because these frequencies generate an electromagnetic trigger signal, their use results in excessive battery depletion of the implanted Pulse Generator and, therefore, should be used for short periods of time only.
-  Resetting the Pulse Generator turns the device OFF (output current = 0.0 mA), and all device history information is lost. The device history information should be printed out before resetting.
-  Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.

5.1-D. Sterilization, Storage, and Handling

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

5.2-D. Lead Evaluation and Connection

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

5.3-D. Environmental and Medical Therapy Hazards



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

5.3.1-D. Hospital and Medical Environments



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



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



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

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



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

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



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

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



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

If an MRI should be done, use only a transmit and receive type of head coil. Magnetic and RF fields produced by MRI may change the Pulse Generator settings (change to reset parameters) or activate the device. Stimulation has been shown to cause the adverse events reported in the “Adverse Events” section of this manual. MRI compatibility was demonstrated using a 1.5T General Electric Signa Imager with a Model 100 only. The Model 102 and Model 102R are functionally equivalent to the Model 100. Testing on this imager as performed on a phantom¹ indicated that the following Pulse Generator and MRI procedures can be used safely without adverse events:

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

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

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



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



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



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



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

5.3.2-D. Home Occupational Environments

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



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

5.3.3-D. Cellular Phones

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

5.3.4-D. Other Environmental Hazards



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

5.3.5-D. Programming Software

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

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

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

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

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



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

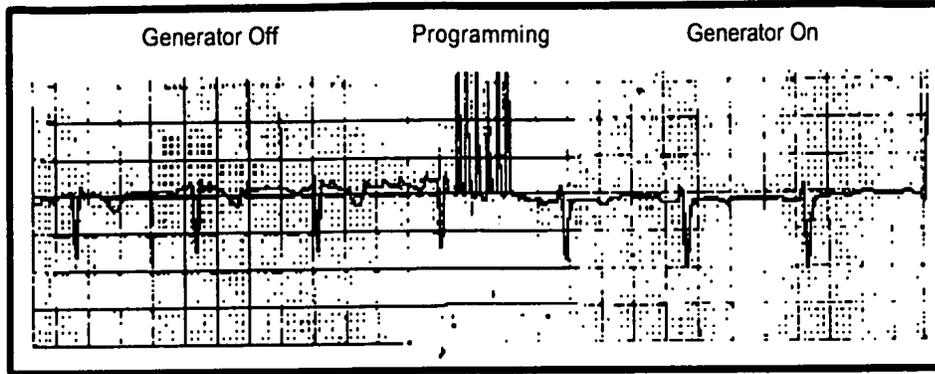


The magnet provided for activation or inhibition of the Pulse Generator may damage **televisions, computer disks, credit cards, and other items** affected by strong magnetic fields.

5.3.7-D. Effects on ECG Monitors

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

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



5.3.8-D. Pulse Generator Disposal



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



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



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

6-D. CLINICAL STUDIES — SAFETY

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

6.1-D. Adverse events

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

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

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

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

6.1.1-D. Discontinuation Due to Adverse Events

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

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

6.2.1-D. Serious Adverse Events (SAEs)

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

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

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

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

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

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

6.2.2-D. Deaths

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

6.2.3-D. Unanticipated Adverse Device Effects

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

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

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

6.3.1-D. Antidepressant Treatments and Manic or Hypomanic Reaction

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

6.3.1.1-D. *Manic Reactions*

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

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

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

Suicidal ideation was analyzed by examining the HRSD₂₄ Item 3 scores. At 12 months of VNS Therapy, 90% of the subjects in the pivotal (D-02) study showed either improvement (56%) or no change (34%) in their Item 3 scores. During the acute D-02 study, 2.6% of the sham subjects and 1.7% of the stimulation subjects increased their Item 3 score by 2 or more points, indicative of an increase in suicidal ideation. During the long-term D-02 phase, 2.8% of the subjects had an increase in their Item 3 score by at least 2 points at 12 months compared to baseline. In a non-randomized control group of subjects treated with standard antidepressant therapies without VNS Therapy (the D-04 study population), 1.9% of the subjects had an increase of at least 2 points. Based on the occurrence of any increase in Item 3 score from baseline to 12 months, 10% of the D-02 subjects had an increase compared to 11% of the D-04 population. Conversely, 27% of the D-02 subjects decreased their score by at least 2 points at 12 months compared to baseline, whereas only 9% of the D-04 subjects did.

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

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

Table D-3. Suicide Attempt and Suicide Rates

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

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

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

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

6.4.1-D. Adverse Events Related to Implantation

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

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

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

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

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

6.4.2-D. Duration of Implant-Related Adverse Events

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

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

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

6.4.3-D. Stimulation-related Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

6.4.5-D. Late-emerging Adverse Events

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

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

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

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

Note: AEs were coded using the COSTART 5 dictionary.

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

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

6.4.6-D. Duration of Stimulation-related Events

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

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

VNS Therapy (N=209)

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

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

6.5-D. Severity of Adverse Events

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

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

6.6-D. VNS Therapy Continuation Rates

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

6.7-D. Device Performance

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

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

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

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

6.8.1-D. Deaths

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

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

6.8.2-D. Serious Injuries

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

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

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

6.8.3-D. Device Malfunctions

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

7-D. CLINICAL STUDIES — EFFECTIVENESS

7.1-D. Feasibility (D-01) Study

The primary efficacy measure in the open-label feasibility (D-01) study was the percent of subjects responding (response was defined as a 50% or greater improvement in the HSRD₂₈ score). Of the 59 subjects with evaluable data, 18 (31%) responded at acute study exit, which was 12 weeks after implantation. Observation of subjects continued. After 1 year of adjunctive VNS Therapy, 25 of 55 subjects (45%) responded, and after 2 years, 18 of 42 (43%) responded. After 1 and 2 years of treatment, 27% and 21% of the subjects, respectively, were in remission (defined as HRSD₂₈ scores less than or equal to 10; . Other measures of depressive symptoms (CGI, MADRS, BDI, IDS-SR) and quality of life (MOS-36) supported the HRSD₂₈ scores.

7.2-D. Pivotal (D-02) Study

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

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

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

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

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

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

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

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

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

7.3.1-D. Comparative Assessments

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

7.3.1.1-D. Concomitant Therapies

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

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

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

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

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

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

* p<0.05.

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

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

7.4.1-D. Pivotal (D-02) study

The primary efficacy variable for both the acute and the long-term phases of the pivotal (D-02) study was the Hamilton Rating Scale for Depression-24 item (HRSD₂₄). For the acute-phase analysis, the HRSD₂₄ response rate (percentage of subjects with a $\geq 50\%$ improvement from baseline to 3 months, acute phase exit) was compared between the treatment and the sham-control groups. For the long-term phase, a linear regression model was used to assess the changes in HRSD₂₄ raw scores. Secondary efficacy analyses included within and between-group comparisons of 1) the Inventory of Depressive Symptomatology-Self Report (IDS-SR), 2) the Clinical Global Impressions (CGI), 3) the Montgomery-Asberg Depression Rating Scale (MADRS), and 4) the Medical Outcome Survey 36-Item Short Form Health Survey (MOS SF-36).

7.4.2-D. Comparative (D-04) Study

The primary efficacy variable for the D-02 and D-04 comparative analysis was the IDS-SR (raw scores). Multiple assessments with the IDS-SR allowed use of a linear regression model for the analysis. The HRSD₂₄ was used as a secondary assessment variable to analyze differences in response rates and raw score changes between subjects in the pivotal (D-02) and comparative (D-04) studies. Subjects in the comparative (D-04) study were assessed with the HRSD₂₄ only at baseline and 12 months.

Secondary analyses included IDS-SR average change, IDS-SR response, IDS-SR remission, IDS-SR sustained response, and HRSD₂₄ remission. Other secondary analyses included the CGI response.

7.4.3-D. Propensity Scores

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

7.4.4-D. Responder Rate

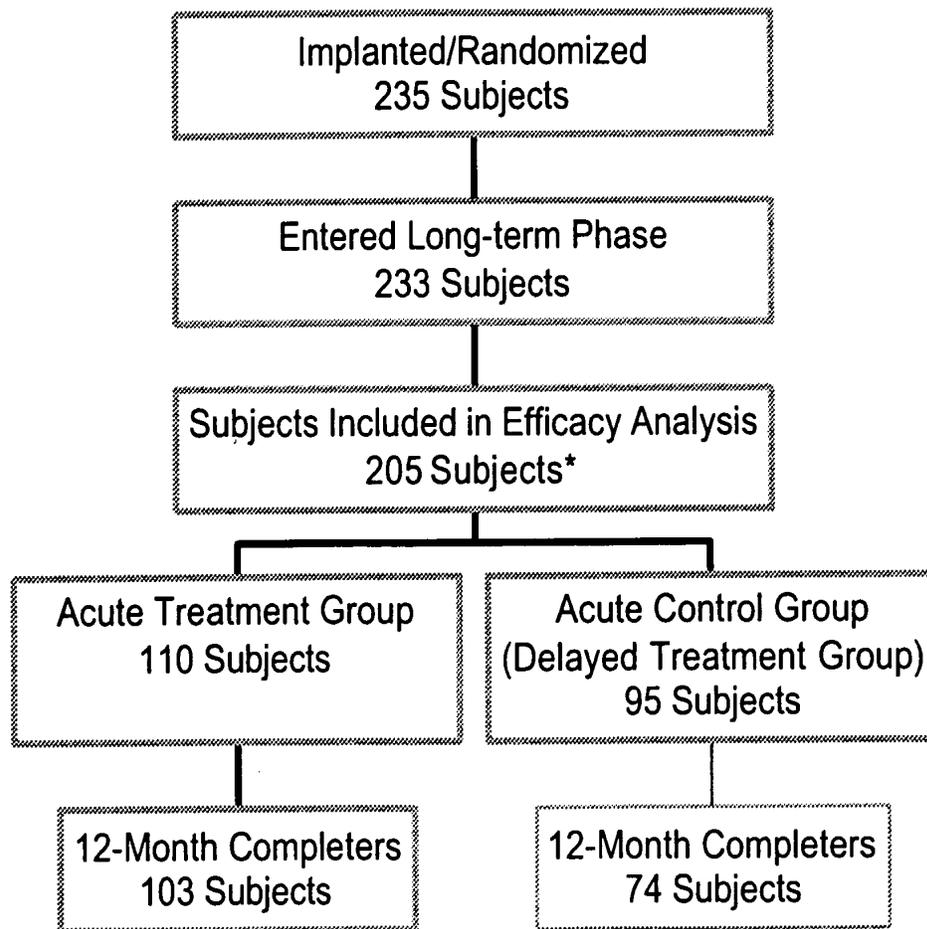
Response was prospectively defined as a $\geq 50\%$ improvement from baseline for the IDS-SR, HRSD₂₄, and MADRS ratings and as a score of much or very much improved for the CGI improvement rating. Remission

(complete response) was prospectively defined as an HRSD₂₄ score of ≤ 9 , a MADRS score of ≤ 10 , or an IDS-SR score ≤ 14 .

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

Figure D-2. Pivotal Study, Long-Term

Flowchart: Pivotal Study, Long-term Phase



*28 subjects did not qualify for Efficacy Analysis:

21 sham-control subjects did not have required HRSD₂₄ score ≥ 18 at acute phase exit

4 subjects did not have long-term phase efficacy assessments

3 subjects did not meet continuation criteria for acute phase

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

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

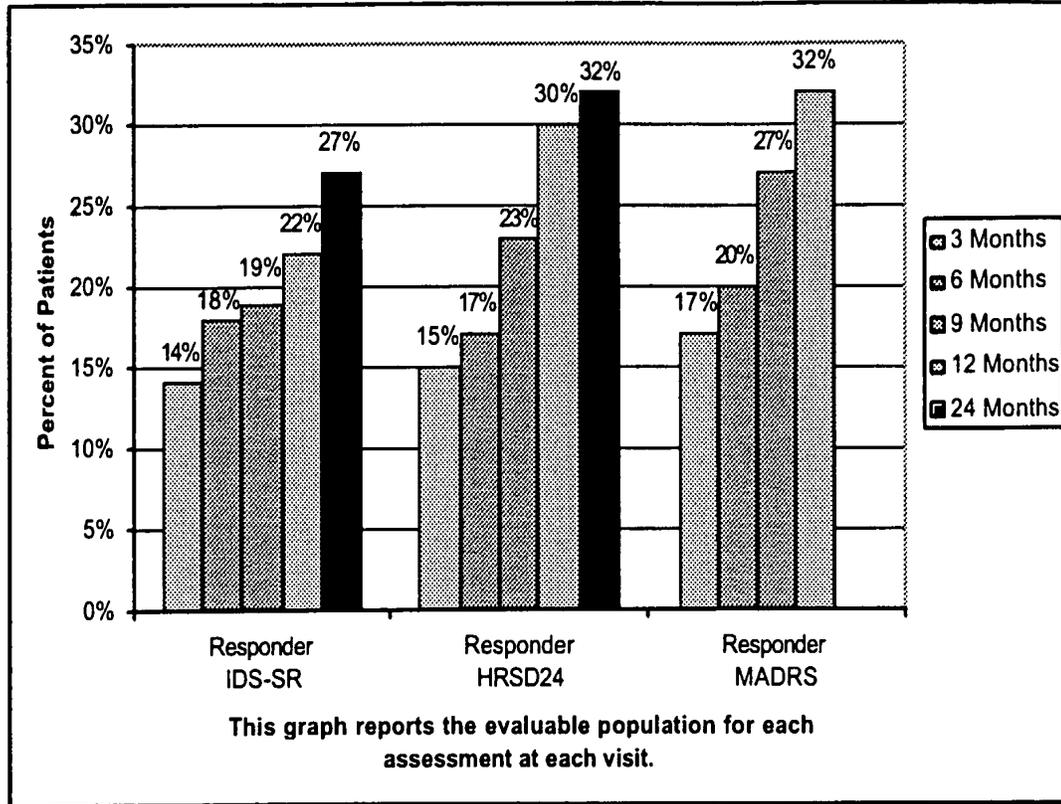
7.5.1-D. Results: Acute phase, pivotal (D-02) study

In the primary efficacy measure, HRSD₂₄ response rate, (the percentage of subjects achieving a $\geq 50\%$ improvement in HRSD₂₄ total score from baseline to acute phase exit), 15% of the treatment group and 10% of the sham-control group were responders ($p=0.238$). Analyses using a secondary efficacy parameter, the IDS-SR, did show a statistically significant advantage for VNS Therapy over sham treatment: 17% response versus 7% response ($p=0.032$) using the last observation carried forward (LOCF) method.

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

During long-term adjunctive VNS Therapy, the D-02 subjects exhibited statistically significant and clinically meaningful improvement. The primary analysis found statistically significant improvement from baseline in HRSD₂₄ scores averaged over 12 months ($p<0.001$). Additionally, clinical significance was shown, using the HRSD₂₄, IDS-SR, MADRS, and CGI (Figure D-3 and Figure D-4, evaluable population, and Table D-14, 12-month completer population).

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

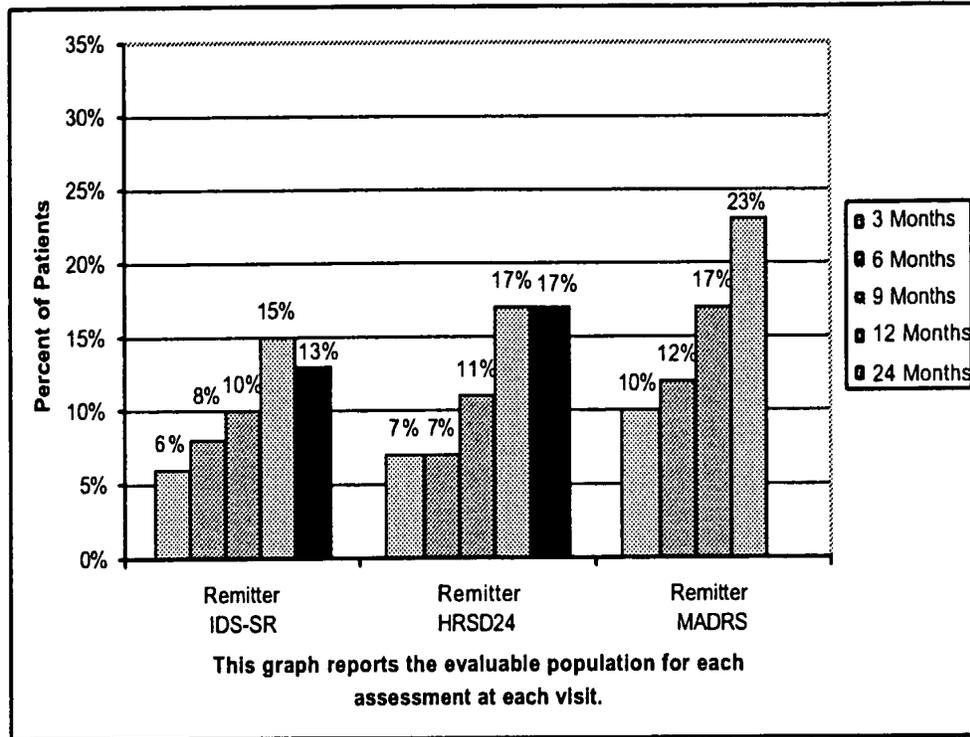


The number of evaluable subjects in each of the above analyses is as follows.

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

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

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



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

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

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

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

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

^b One subject did not have a baseline IDS-SR assessment and several others did not have 12-month assessments, which accounts for the varying Ns in the comparison of HRSD₂₄ with IDS-SR data.

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

7.5.3-D. Quality of Life Assessment

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

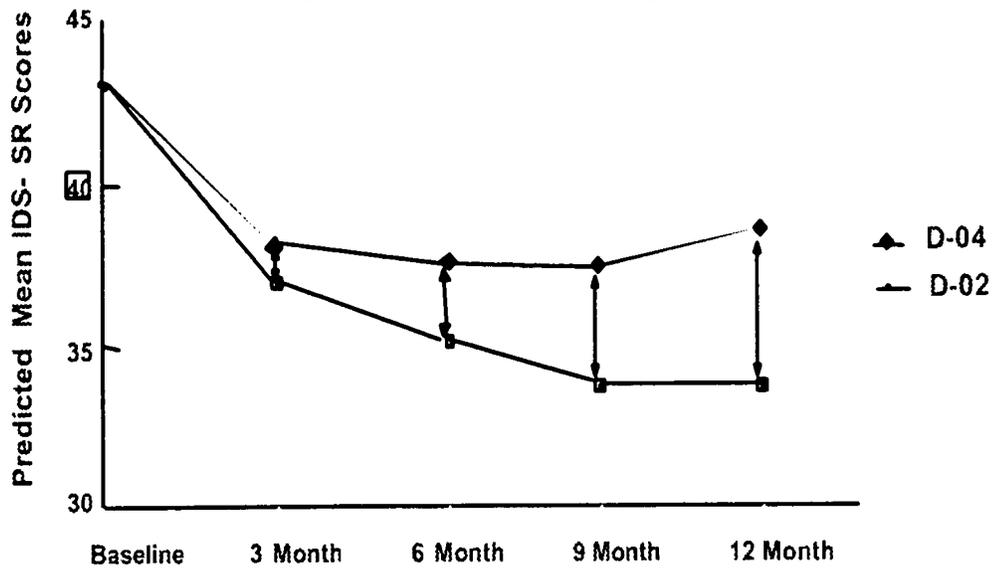
7.6-D. *Results: Comparison of D-02 and D-04 Studies*

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

7.6.1-D. Primary Effectiveness Outcome

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

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



	B/L	3 mos	6 mos	9 mos	12 mos
Mean D04 Scores	43.0 (N=124)	38.1 (N=120)	37.5 (N=119)	37.3 (N=116)	38.5 (N=112)
Mean D02 Scores	43.0 (N=201)	36.9 (N=200)	35.1 (N=195)	33.7 (N=183)	33.7 (N=177)
Predicted Mean Difference	0	-1.2	-2.4	-3.6	-4.8
Actual Mean Difference	-0.9	-4.6	-4.1	-5.0	-6.6

7.6.2-D. Secondary Analyses

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

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

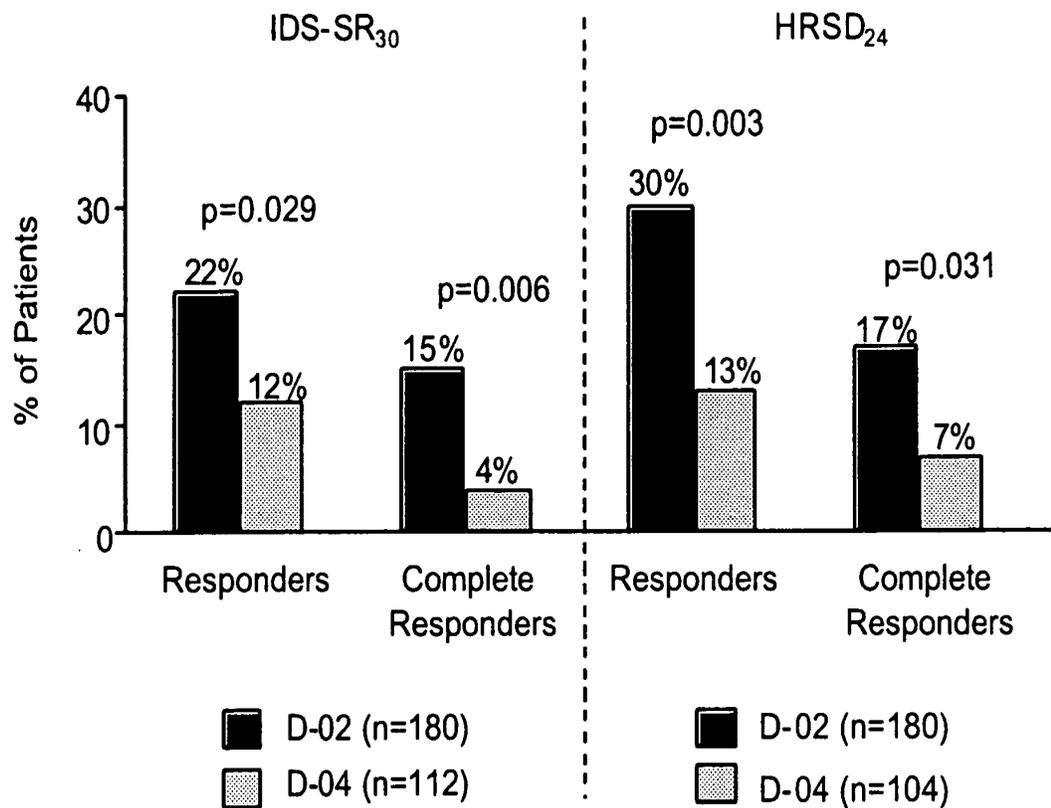
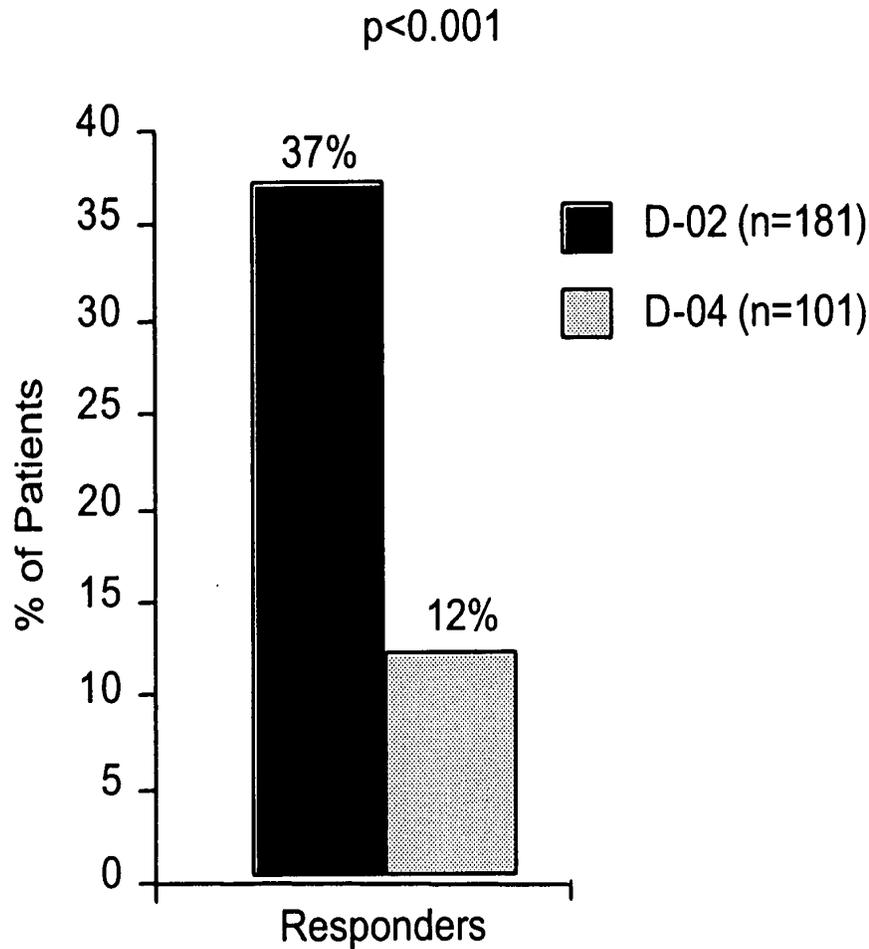


Figure D-7. Secondary Analyses: CGI-I Categorical Outcome at 12 Months (Evaluable Observed Analysis)

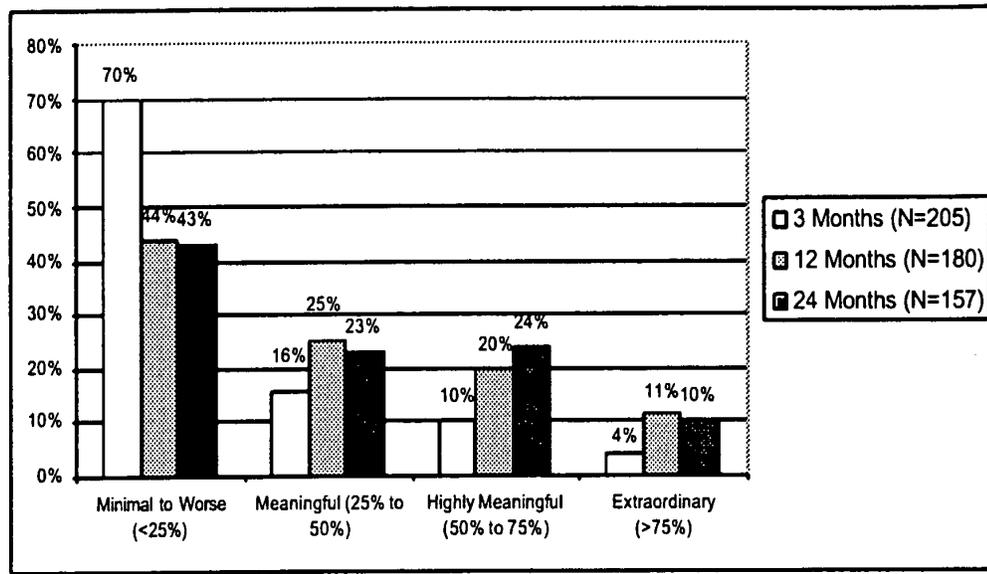


7.7-D. *Clinical Benefit Over Time*

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

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

**Figure D-8. Clinical Benefit after 3, 12 and 24 months;
D-02 Evaluable Population; HRSD₂₄**



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

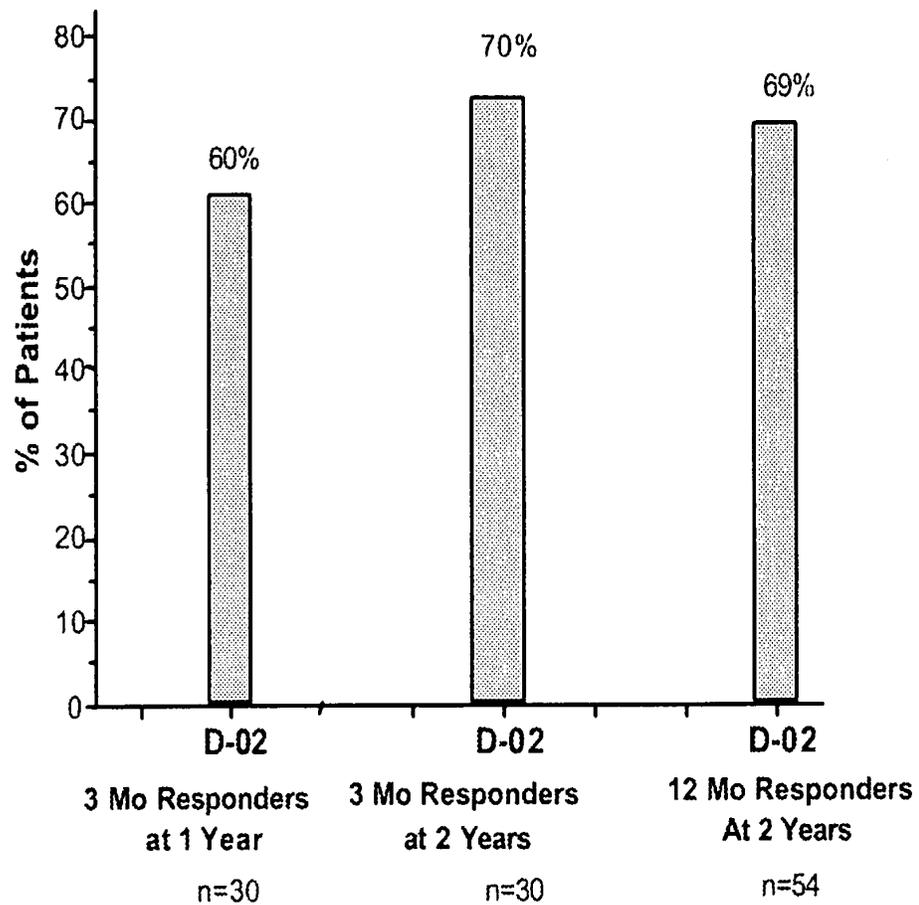
at least a meaningful benefit after 12 months of adjunctive VNS Therapy.

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

7.8-D. Maintaining Response (2 Year Data)

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

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



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

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

7.9.1-D. Electroconvulsive Therapy

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

7.9.2-D. Antidepressant Drugs and Response

Antidepressant drug use was significantly greater among pivotal (D-02) study subjects who were non-responders and comparative (D-04) study subjects overall than among the pivotal (D-02) study subjects who achieved a response ($p < 0.01$). During the 12 months, 77% of the pivotal (D-02) study non-responders and 81% of all comparative (D-04) study subjects either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more. By contrast, only 56% of the pivotal (D-02) study subjects who were responders to VNS Therapy either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more.

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

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

7.9.3-D. Medication Censoring Analyses

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

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

7.10-D. *Bibliography*

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

8-D. INDIVIDUALIZATION OF TREATMENT

Patients should be started on stimulation at a low current output setting (0.25 mA), and the current should be increased gradually to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until a comfortable tolerance level is reached. Physicians should appreciate that some patients will accommodate to stimulation levels over time and should therefore allow further increases (in 0.25 mA steps) in output current, if needed. (See the Model 250 VNS Therapy Software Physician's Manual.) Table D-15 lists the stimulation parameters reported at 12 months of VNS Therapy in the pivotal (D-02) study.

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

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

The magnet output current should be set to 0 mA.

9-D. PATIENT COUNSELING INFORMATION

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

10-D. CONFORMANCE TO STANDARDS

The VNS Therapy System conforms to the following standards:

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

11-D. HOW SUPPLIED

Implantable portions of the VNS Therapy System have been sterilized using ethylene oxide gas (EO), and are supplied in a sterile package for direct introduction into the operating field. A process indicator is included in the package; devices should be implanted only if the indicator is green. An expiration date is marked on the outer package.

If the package has been exposed to extreme temperatures or moisture (see the Sterilization, Storage, and Handling section in the 102/102R Epilepsy Physician's Manual) or if there is any indication of external damage, the package should be left unopened and returned to Cyberonics.

12-D. OPERATOR'S MANUAL

12.1-D. Directions for Use

Please refer to the Directions for Use section under “Operator’s Manual” in the 102/102R Epilepsy Physician’s Manual. The Directions for Use are equivalent for epilepsy and depression with the following exceptions.

- ◆ For patients with depression, the Magnet Mode output current should always be programmed at 0.0 mA, the setting at which the Pulse Generator is shipped from Cyberonics.
- ◆ Use of the Magnet Mode is limited to patients with epilepsy. Patients with epilepsy or their caregivers pass the magnet over the implanted Pulse Generator to activate on-demand delivery of a single train of vagus nerve stimulation and help abort or diminish a seizure.
- ◆ Magnet Mode is not used for patients with depression.

12.2-D. Physician Training/Information

All VNS Therapy System programming should be by or under the supervision of a physician familiar in the use and operation of the Software.

Initial treatment output current (starting new or after Pulse Generator replacement) should be set at the lowest setting (0.25 mA). Subsequent and all future device settings should be made in 0.25 mA increments up to the desired treatment level (see the “Individualization of Treatment” section of this manual).

Physicians implanting the VNS Therapy System should be thoroughly familiar with all associated training materials, including the following:

- ◆ Product labeling for the Pulse Generator, Lead, and accessories, including Physician and Patient Manuals and Directions for Use
- ◆ “Implant Guide for the VNS Therapy System” training manual and other brochures
- ◆ Videotape on the proper implantation technique: “Implantation of the VNS Therapy System”
- ◆ Electrode practice fixture—a device used to practice placing the Lead coil around the left vagus nerve

In the event intolerable adverse events are reported, physicians should consider reducing the output current (mA) as a means of eliminating or reducing the severity of an event. Additionally, physicians should instruct patients or care givers on the application of the magnet to turn the Pulse Generator off (output current 0 mA) if an adverse event becomes intolerable.

12.3-D. Detailed Device Description

Please refer to the Detailed Device Description section under “Operator’s Manual” in the 102/102R Epilepsy Physician’s Manual for a detailed device description.

13-D. CYBERONICS' LIMITED REPLACEMENT WARRANTY

Please refer to the Cyberonics' Limited Replacement Warranty in the 102/102R Epilepsy Physician's Manual.

14-D. TROUBLESHOOTING

Please refer to the Troubleshooting section in the 102/102R Epilepsy Physician's Manual for assistance in troubleshooting the VNS Therapy System.

15-D. INFORMATION AND SUPPORT

If there are questions regarding use of the VNS Therapy System or any of its accessories, please contact Cyberonics:

USA

Cyberonics, Inc.
100 Cyberonics Boulevard
Houston, Texas 77058

Telephone: 281-228-7200

Fax: 281-218-9332

For 24-hour support, please call:

Telephone: 866-882-8804 From US and Canada
281-228-7330 Worldwide

Pager: 713-908-5353 Worldwide-Digital

Messaging

713-827-2518 Worldwide-Answering
Service

Europe

Cyberonics Europe, S.A.
Belgicastraat 9
1930 Zaventem
Belgium

Telephone: +32 2 720 95 93

Fax: +32 2 720 60 53

Internet

www.VNSTherapy.com

16-D. GLOSSARY

ACLS	Advanced Cardiac Life Support
AE (Adverse Event)	Any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency during the course of the study (i.e., any changes from baseline)
ARR	Antidepressant Resistance Rating
Baseline Periods:	
D-02 Acute Phase	Two pre-implantation visits (Visits B1 and B2) for both groups
D-02 Long-Term Phase	For the evaluation of efficacy, the period just before initiation of VNS Therapy; during the long-term phase, the baseline period of subjects who had been assigned to the acute treatment group during the acute phase differed from that of the subjects who had been assigned to the acute sham-control group; because this baseline period is just before treatment initiation for both groups, it is more comparable for analysis purposes
Treatment Group	During the long-term phase, the baseline for the subjects who had been assigned to the acute treatment group during the acute phase was the pre-implantation baseline (B1 & B2)

Delayed Treatment Group (Acute Sham-control Group)	During the long-term phase, the baseline for the subjects who had been assigned to the acute sham-control group during the acute phase was the final two acute study visits, V8 and V9 (acute study exit)
D-04	The visit occurring after obtaining informed consent
BOL	Beginning of Life
CGI (Clinical Global Impressions)	Two 7-point scales completed by the clinical rater to assess the subject's condition regarding the severity of illness (CGI-S) and global improvement (CGI-I); the severity scale ranges from 1 – “normal, not at all ill” to 7 – “among the most extremely ill patients;” the improvement scale ranges from 1 – “very much improved” to 7 – “very much worse;” the CGI was developed by the NIMH to provide a standardized assessment with clinically relevant anchors; it is one of most widely used brief assessment tools in psychiatry.

**Chronic or
Recurrent
Depression**

A current major depressive episode that is of at least two years in duration or a current major depressive episode in a patient with a history of multiple prior episodes of depression.

Clinical Benefit

Degree of improvement in depression as measured by the HRSD₂₄; physician expert consultants to the Sponsor developed this designation

- ◆ extraordinary clinical benefit, at least a 75% reduction from baseline
- ◆ highly meaningful clinical benefit, at least a 50% but less than a 75% reduction from baseline
- ◆ meaningful clinical benefit, at least a 25% but less than a 50% reduction from baseline
- ◆ minimal or no clinical benefit, at least no change or less than a 25% reduction from baseline
- ◆ worsened: increase in HRSD₂₄ compared with baseline

**Complete
Response
(Complete
Responder or
Remitter)**

Subjects who scored less than a pre-defined score were considered to have achieved a complete response; scores representing complete response were an HRSD₂₄ raw score of 9 or less, a MADRS raw score of 10 or less, or an IDS-SR raw score of 14 or less; this corresponds to the concept of remission, where the illness, in this case depression, has few to no residual symptoms present

**D-01, D-02, D-04
Clinical Studies**

Clinical trials conducted in patients with chronic or recurrent treatment-resistant depression. The D-01 study was a long-term, open-label, uncontrolled trial of adjunctive VNS Therapy. The D-02 study included acute and long-term phases. The acute phase was a, double-blind, randomized, sham-controlled trial of adjunctive VNS Therapy; the long-term phase was an open-label, uncontrolled trial of adjunctive VNS Therapy. The D-04 study was a long-term, prospective, observational study of patients with chronic or recurrent treatment-resistant depression who were being treated with standard antidepressant treatments, but not VNS Therapy.

Duty Cycle	Percentage of time during which stimulation occurs; stimulation time (programmed ON time plus 2 seconds of ramp-up time and 2 seconds of ramp-down time) divided by the sum of signal ON and OFF times
EAS	Electronic article surveillance
ECT (Electroconvulsive Therapy)	A treatment for depression and other indications using electrodes on the surface of the head to direct electrical current into the brain to induce a generalized seizure in a patient
EMI	Electromagnetic interference
EOS	End of service
ERI	Elective replacement indicator
Excess Duty Cycle	Duty cycle for which the ON time is greater than the OFF time
Failed Adequate Treatment	Failure to respond to electroconvulsive therapy or an established antidepressant drug administered at an adequate dose for an adequate duration.
FDA	United States Food and Drug Administration

HRSD (Hamilton Rating Scale for Depression)

The HRSD is the most widely used rating scale to assess symptoms of depression; a multi-dimensional, observer-rated scale for assessing overall depression severity; the 28-item version of the scale was administered to subjects in this study; per protocol for the feasibility (D-01) study, all 28 items were used for scoring purposes; per protocol for the pivotal (D-02) study, only the first 24 items were used for scoring purposes

High Lead Impedance

DC-DC Converter Codes greater than four on a device diagnostic test; not a sole determinant of a need for Lead replacement

IDS-SR (Inventory of Depressive Symptomatology Self-Report)

A 30-item patient self-report rating of the symptoms of mood and depression

LIMIT Output Current

Output current other than that which was programmed; not a sole indicator of a device malfunction

LOCF (Last Observation Carried Forward)

This analysis technique uses the last available data point for subsequent time points where data is missing

Long-term Phase	The portion of the pivotal (D-02) study comprising follow-up after the acute portion of the study (after Visit 9); the long-term portion included longitudinal follow-up by a blinded rater; the analysis of the long-term data included a repeated measures within-subjects analysis of changes in depressive symptoms over 12 months of VNS Therapy
MADRS (Montgomery- Asberg Depression Rating Scale)	A 10-item scale completed by the clinical rater for assessing overall depression severity
Magnet Activation	Brief magnet application and removal, which initiates a stimulation
Microcoulomb	Product of current and time, or output current (in mA) multiplied by the pulse width (in msec)
MOS SF-36 (Medical Outcome Survey 36-Item Short Form Health Survey)	A quality of life (QOL) tool that assesses overall QOL and subscales of physical functioning, role functioning-physical, bodily pain, general health perceptions, vitality, social functioning, role functioning-emotional, mental health, and overall change in health

Nominal Parameters	Specific preset parameters available with the software; Cyberonics suggests that the Pulse Generator be set to these parameters when patients are first stimulated (see the Specifications and Product Information section in the 102/102R Epilepsy Physician's Manual for specific nominal parameters)
Output Current	Amount of electrical current delivered in a single pulse of a stimulation, measured in mA
Patient Code	Any three-digit combination assigned by the treating physician; generally programmed at time of implantation; often patient's initials: first, middle, last (or with a hyphen for no known middle initial)
Pulse Width	Duration of a single pulse within a stimulation, measured in μsec
Ramp-down	Gradual decrease over approximately 2 seconds in output current at the end of stimulation greater than 10 Hz in signal frequency
Ramp-up	Gradual increase over approximately 2 seconds in output current at the beginning of stimulation greater than 10 Hz in signal frequency
Remission (Remitter)	See Complete Response

Reset Parameters	Parameters to which the Pulse Generator internally programs when it is reset (see the Specifications and Product Information section in the 102/102R Epilepsy Physician's Manual for specific reset parameters)
Responder	At a given point, a subject with a $\geq 50\%$ reduction in HRSD, MADRS, or IDS-SR scores from baseline or a CGI improvement rating of 1 or 2
SAE (Serious Adverse Event)	Any adverse event that resulted in any of the following outcomes: death, a life threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect or any medical intervention that prevents one of the above; the sponsor also included cancer and pregnancy as SAEs
Signal Frequency	Repetition rate of pulses in a stimulation; measured in number of pulses per second (Hz)
Signal OFF Time	Interval between stimulations when there is no stimulation; measured in minutes
Signal ON Time	Length of time the programmed output current is delivered (not including ramp-up and ramp-down times); measured in seconds

Statistically Significant	Results are considered statistically significant if p-values for the appropriate statistical tests are less than or equal to 0.050
Stimulation Adjustment Period	For the treatment group, a 2-week period between Visit 2 and Visit 4 during the acute portion of the study. For the delayed treatment group, a 2-week period between Visit 9 and Visit 11 at the start of the long-term study. The output current was progressively increased to a comfortably tolerable level during this period. After this period, output current was held constant for an 8-week period unless reduction was necessary for tolerance
Stimulation Parameters	Programmed output current, signal frequency, pulse width, signal ON time, and signal OFF time
Stimulation Time	Therapeutic output of the VNS Therapy Pulse Generator; consists of the signal ON time, plus 2 seconds of ramp-up time and 2 seconds of ramp-down time
Treatment-Emergent	Adverse events that occurred on or after the implant and were not present during the baseline period or events that were present during baseline that worsened in severity after the implant

Treatment Failures

Subjects who, after the randomization procedure, 1) exited the acute study before Visit 9 due to treatment-related adverse events, or a lack of efficacy 2) met the suicide exclusion criteria, 3) attempted suicide resulting in hospitalization of more than 3 days, or 4) developed mania or more than three mood episodes as defined by DSM-IV. Subjects who were treatment failures during the acute study were also considered treatment failures for long-term analysis purposes

UADE (Unanticipated Adverse Device Effect)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application); also, any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients

Vagus Nerve

Either of the pair of tenth cranial nerves arising from the medulla and supplying mainly the viscera, especially with autonomic sensory and motor fibers; in this document, vagus nerve always refers to the *left* vagus nerve

VNS

Vagus Nerve Stimulation

VNS Therapy™

VNS delivered by Cyberonics' VNS Therapy System

Within-Group

A statistical comparison including only subjects in the same group assignment

YMRS (Young Mania Rating Scale)

An 11-item scale completed by the clinical rater to assess the symptoms of mania

Depression

Patient's Manual

H

**For Vagus Nerve Stimulation
with the VNS Therapy™ System**

June 2005

This Patient's Manual is a supplement to the physician's manuals. It is not meant to take the place of advice from your doctor. For a complete discussion of indications for use, contraindications, precautions, warnings, and potential side effects, please talk to your doctor.

Please talk with your doctor about

- ◆ how this device is used
- ◆ how it should not be used
- ◆ safety measures
- ◆ warnings
- ◆ side effects

Your doctor's phone number:



Vagus Nerve Stimulation

REF 26-0005-6000/4

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Useful Terms

These terms are used in this manual.

Adjunctive Therapy — Additional, add-on; VNS is adjunctive therapy, it is added on to other antidepressant treatments

Adverse events — Complications and side effects

Clinical benefit — Categories assigned to describe change in depressive symptoms on Hamilton Rating Scale for Depression-24 Item after VNS Therapy

Meaningful clinical benefit – 25% to 49% improvement in depressive symptoms

Highly meaningful clinical benefit – 50% to 74% improvement in depressive symptoms

Extraordinary clinical benefit – over 75% improvement in depressive symptoms

Clinical studies — Tests of the effectiveness and safety of a therapy on humans

Cyberonics — Company that makes the VNS Therapy System

Electrodes — Part of the VNS Therapy Lead that connects to the vagus nerve

HSRD₂₄ — Standardized test to measure depressive symptoms as reported by the doctor; Hamilton Rating Scale for Depression-24 Item

ISD-SR — Standardized test to measure depressive symptoms as reported by the patient, Inventory of Depressive Symptomatology Self-Report

Lead — VNS Therapy Lead; small wire that connects the VNS Therapy Pulse Generator to the vagus nerve

MADRS — Standardized test to measure depressive symptoms as reported by the doctor, Montgomery -Asberg Depression Rating Scale; commonly used in Europe

Programming Wand — VNS Therapy instrument used to check or change VNS Therapy device and settings

Pulse Generator — VNS Therapy device implanted in the patient's chest; holds the battery and delivers stimulation to the vagus nerve through the VNS Therapy Lead

Reed Switch — This mechanism works like a gate. When the Magnet closes it, the signal (stimulation) cannot pass. The Pulse Generator is temporarily turned OFF.

Remitter — Study participant who was essentially free of depressive symptoms after receiving VNS Therapy; determined by scores of standardized tests; also called complete responder

Responder — Study participant whose depressive symptoms were reduced by 50% or more after receiving VNS Therapy; determined by scores of standardized tests

Stimulate — Send electrical signal; with VNS Therapy, the Pulse Generator sends an electrical signal through the Lead to the vagus nerve, which carries the signal to the brain

Stimulation — The electrical signal that is sent from the Pulse Generator to the brain

Treatment-resistant Depression (TRD) — Depression that has not responded to four or more antidepressant treatments

Vagus nerve — A nerve that extends from the brain through the neck to the major organs (heart, lungs, stomach, etc.) in the torso

Vagus Nerve Stimulation — (VNS) periodic electrical signals sent from the Pulse Generator to the vagus nerve

VNS Therapy — Treatment received from vagus nerve stimulation

VNS Therapy System — All of the parts that provide VNS Therapy: Pulse Generator, Lead, Programming Wand, Computer, Software, and Magnets

1. INTRODUCTION TO VNS THERAPY

Many people have depression. Through the years, doctors and scientists have learned much about depression. They have developed drugs and other treatments. Despite these efforts, some people still have depression. Your doctor has proposed the VNS Therapy™ System for you to reduce the symptoms of your depression because drugs have failed to control them adequately.

The VNS Therapy System sends a mild electrical impulse to a nerve that goes to the brain. This nerve is called the vagus nerve. The treatment is Vagus Nerve Stimulation (VNS) Therapy (VNS Therapy™).

2. THE VNS THERAPY SYSTEM

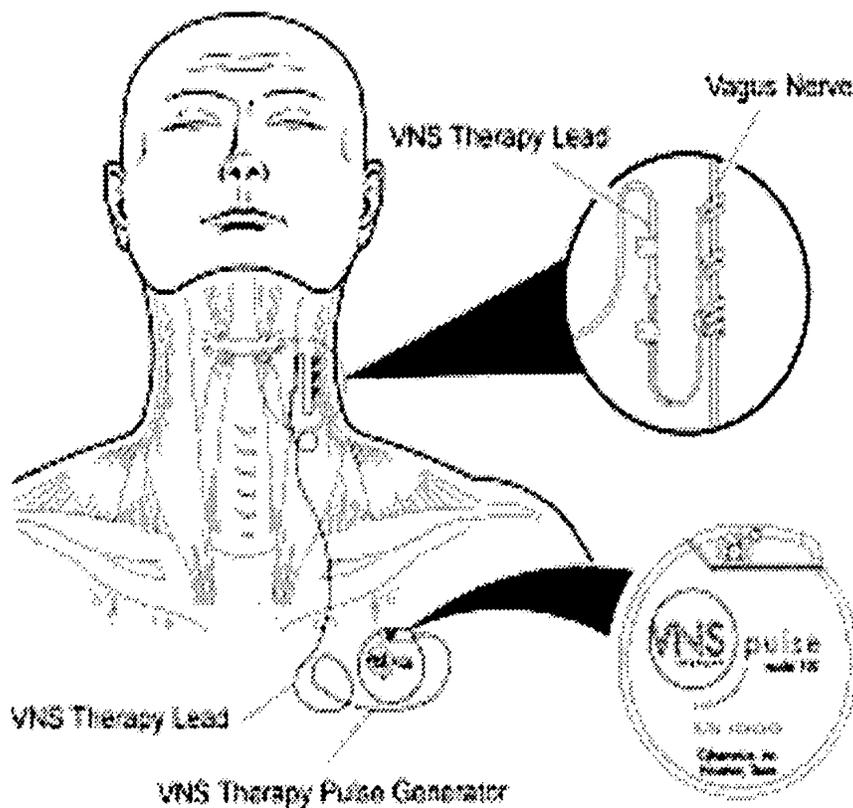
2.1. Parts of the VNS Therapy System

The VNS System has several implantable and nonimplantable parts (see Figure 1 and Figure 2).

2.1.1. Implantable parts

- ◆ VNS Therapy Pulse Generator
- ◆ VNS Therapy Lead

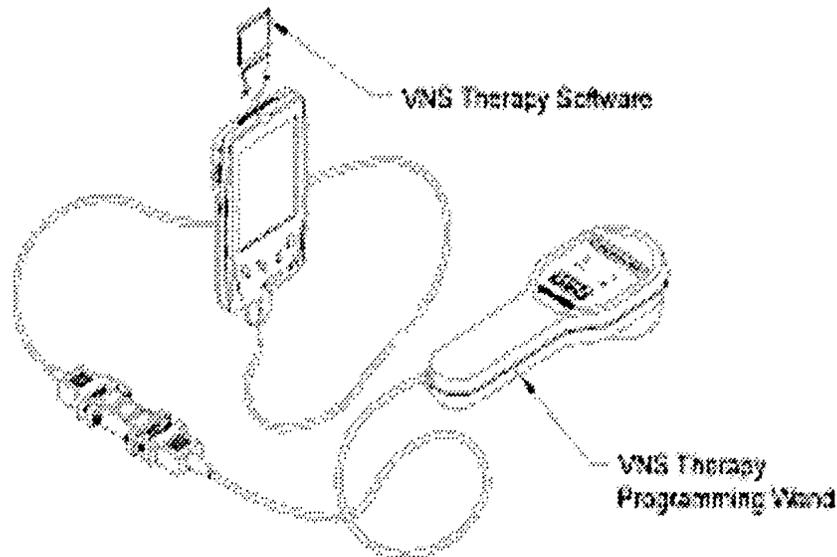
Figure 1. Implantable parts of the VNS Therapy System



2.1.2. Nonimplantable parts

- ◆ VNS Therapy Computer
- ◆ VNS Therapy Programming Software
- ◆ VNS Therapy Programming Wand
- ◆ VNS Therapy Magnets

Figure 2. Nonimplantable parts of the VNS Therapy System



2.1.3. Pulse Generator

The main part is the Pulse Generator, sometimes called a stimulator. Similar to cardiac pacemakers, which have been used since 1958 to control heart problems, the Pulse Generator is computer controlled and battery powered. It sends signals through the electrodes of the Lead to the brain by way of the left vagus nerve.

2.1.4. Placement of the Pulse Generator and Lead

The Pulse Generator is placed under the skin of the upper chest. The Lead connects the Pulse Generator to the vagus nerve. It is surgically attached to the left vagus nerve in the neck. A surgeon implants the Pulse Generator and Lead during an operation that typically lasts about 1 to 2 hours. Later, your doctor sets the Pulse Generator to deliver periodic stimulation 24 hours a day (for example, 30 minutes ON and 5 minutes OFF). At the office, your doctor can read and change stimulation settings with the Computer, Software, and Programming Wand.

2.1.5. Cyberonics Magnet

Cyberonics provides a Magnet for you to stop stimulation if and when you need to (see the “Using Your Cyberonics Magnets” section of this manual).

2.1.6. Stimulation settings

The Pulse Generator has many settings. Your doctor will choose the settings. He or she can change (reprogram) the periodic stimulation at any time with the Programming Wand, Software, and Computer. Most of the time, changing the VNS Therapy System settings is a painless procedure, takes only a few minutes, and can be done in the doctor’s office.

2.1.7. Pulse Generator life

The battery in the Pulse Generator can last from 1 to 16 years.

The lifespan depends on these factors:

- ◆ Pulse Generator model

- ◆ Settings your doctor chooses
- ◆ Interaction of the Lead and vagus nerve over time

When the battery in your Pulse Generator runs out, the Pulse Generator must be replaced in order for you to continue to receive VNS Therapy. This requires an additional surgical procedure. The operation involves anesthesia and generally takes less than an hour to complete. Please refer to the “Battery depletion (running out)” section of this manual for additional information about battery depletion.

3. QUICK REFERENCE GUIDE

This quick guide provides important information about the VNS Therapy System. It will be most useful after you have read the whole manual. A list of frequently asked questions is included at the end of this manual.

When you see this symbol , pay special attention to the important information after it.

After you receive your VNS Therapy System, keep this important information in mind.

- ◆ You should not receive a VNS Therapy System implant if your left vagus nerve has previously been cut.
- ◆ You CANNOT have any short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy anywhere on your body if you have an implanted VNS Therapy System.
- ◆ **Use the Cyberonics Magnet to stop the stimulation** if it becomes painful or irregular (see the “Using Your Cyberonics Magnets” section of this manual).
- ◆ **Call your doctor right away** if any of the following occur:
 - ◆ Your voice is constantly hoarse.
 - ◆ Stimulation becomes painful or irregular.
 - ◆ Stimulation causes any choking, trouble with breathing, trouble with swallowing, or change in heart rate.
 - ◆ You or someone else notices changes in your level of consciousness (for example, you become constantly drowsy).

- ◆ You think that the Pulse Generator may not be stimulating properly or that the VNS Therapy System battery is depleted (stops stimulating).
- ◆ You notice anything new or unusual that you relate to the stimulation.
- ◆ The feeling that you usually have during stimulation becomes stronger or weaker (see the “Complications” section of this manual).
- ◆ Your depressive symptoms increase or suicidality (suicidal thoughts or behavior) increases. See the “Additional Safety Considerations” section of this manual for details.
- ◆ Call your doctor before you have **any medical tests** that might affect, or be affected by, the VNS Therapy System, such as magnetic resonance imaging (MRI) scans (see the “Medical Hazards” section of this manual).
- ◆ Call your doctor before you have **any other medical devices implanted** (see the “Medical Hazards” section of this manual).
- ◆ Tell your doctor at your next visit if you no longer feel the routine stimulation. Your doctor may decide to change your settings.

Cyberonics *cannot* provide health care advice or services. Your source for health questions must always be your doctor.

4. WHO USES VNS THERAPY?

VNS Therapy has been approved for people with chronic or recurrent treatment resistant depression who have failed to respond to four or more adequate treatments. It is *not* right for everyone who has depression. You and your doctor will decide if VNS Therapy is right for you. Your doctor will also decide if you have any other medical conditions that might be affected by VNS Therapy.

4.1. Indications for Use

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

4.2. Contraindications (When VNS Therapy Should Not Be Used)

 **CONTRAINDICATION:** The VNS Therapy System should not be used (is contraindicated) in people who have had the left vagus nerve cut to treat another disorder (a left vagotomy).

 **CONTRAINDICATION:** Inform anyone treating you that you **CANNOT** have any short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (hereafter referred to as “diathermy”) anywhere on your body because you have an implanted VNS Therapy System (sometimes referred to as a “Vagus Nerve Stimulator” or “Vagus Nerve

Stimulation”). **Diagnostic ultrasound is not included in this contraindication.**

Diathermy is a treatment to promote healing or relieve pain. It is provided by special medical equipment (diathermy equipment) in a doctor’s office, dentist’s office, or other healthcare setting.

Energy from diathermy therapy may cause heating of the VNS Therapy System. 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.

Diathermy may also damage parts of your VNS Therapy System. This damage can result in loss of therapy from your VNS Therapy System. More surgery may be required to remove or replace parts of your implanted device.

Injury or damage can occur during diathermy treatment whether your VNS Therapy System is turned “ON” or “OFF.”

5. WARNINGS AND PRECAUTIONS

As with all types of treatment for depression, VNS Therapy carries some risks. Talk to your physician about other risks not covered in this manual that you should know about. Also be sure to ask any questions that you have about any of the following warnings, precautions, side effects, and possible hazards.

5.1. Warnings

Worsening Depression/Suicidality

You will need to be observed closely for clinical worsening and suicidality (suicidal thoughts or behavior), especially at the time of drug or drug dose changes, or VNS Therapy stimulation parameter changes.

Unapproved uses

The safety and efficacy of the VNS Therapy System have not been established for uses outside its approved indications for use. The safety and efficacy of VNS Therapy have *not* been shown for people with these conditions:

- ◆ Acute suicidal thinking or behavior
- ◆ History of schizophrenia, schizoaffective disorder or delusional disorders
- ◆ History of rapid cycling bipolar disorder
- ◆ History of previous therapeutic brain surgery or brain injury
- ◆ Progressive neurological diseases other than epilepsy

- ◆ Heart arrhythmias (irregular heart beats) or other heart abnormalities
- ◆ History of dysautonomias
- ◆ History of lung diseases or disorders, including shortness of breath and asthma
- ◆ History of ulcers (gastric, duodenal, or other)
- ◆ History of vasovagal syncope (fainting)
- ◆ Only one vagus nerve
- ◆ Other concurrent forms of brain stimulation
- ◆ Preexisting hoarseness

 **Swallowing difficulties**

Difficulty swallowing may occur with active stimulation, and aspiration may result from the increased swallowing difficulties.

 **Shortness of breath**

Shortness of breath may occur with active VNS Therapy, especially if you have chronic obstructive pulmonary disease or asthma.

 **Obstructive sleep apnea**

Use of the VNS Therapy device can cause or worsen pre-existing obstructive sleep apnea (episodes where breathing stops for short periods of time while sleeping).

 **Device malfunction**

Device malfunction could cause painful stimulation or direct

current stimulation. Either event could cause nerve damage and other associated problems.



Magnetic resonance imaging (MRI)

You should not have a full body MRI while the VNS Therapy device is in place. Additional surgery may be required to remove the system if full body MRI is required. You should contact your physician before undergoing MRI.



Device removal

Device removal requires an additional surgical procedure. When removing a device, the surgeon may leave part of the Lead behind. This may pose certain risks (see the “**Medical Hazards**” section in this manual).



Device manipulation

Do not manipulate the Pulse Generator and Lead through the skin as this may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

5.2. Precautions



Use during pregnancy

The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy.



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

5.3. Environmental Hazards

Being close to certain types of equipment can affect the Pulse Generator. Move away from or avoid equipment such as transmitting antennas.

5.3.1. Pacemaker Warning signs

Talk to your doctor before going into places with Pacemaker Warning signs.

5.3.2. Small appliances

Properly operating microwave ovens and other small electrical appliances, such as toasters, hair dryers, and electric shavers, should *not* affect the Pulse Generator.

5.3.3. Cellular phones

Cellular phones can affect some implanted cardiac defibrillators and pacemakers. But tests to date show that they do *not* affect the Pulse Generator.

5.3.4. Transmitting devices

Properly operating electrical ignition systems and power transmission lines should *not* affect the Pulse Generator. Sources with high energy levels, such as transmitting antennas, *may interfere* with the device. Move at least 2 meters (6 feet) away from any equipment that interferes with your device.

5.3.5. Antitheft devices, airport security systems, and other metal detectors

Antitheft devices and metal detectors should *not* affect the Pulse Generator or be affected by it. As a precaution, however, move through them at a steady pace; do not linger in the area.

5.3.6. Devices with strong electromagnetic fields

Electrical or electromechanical devices with a strong static or pulsing magnetic field can cause the Pulse Generator to start suddenly. Such devices may include strong magnets, hair clippers, vibrators, and loudspeakers. Keep this type of equipment at least 15 centimeters (6 inches) away from your chest.

If your Pulse Generator stops while you are in a strong electromagnetic field, move away from the source so that the device may return to regular operation.

5.4. Medical Hazards

Medical equipment, procedures, and surgery using certain electrical instruments can affect the VNS Therapy System's operation and sometimes damage the Pulse Generator or Lead.



Make sure that medical personnel know you have a device implanted in your chest.



Always call your doctor before you have any medical tests that may affect, or be affected by, the VNS Therapy System as described below. Precautions may be needed.

5.4.1. Routine diagnostic procedures

Most routine diagnostic procedures, such as diagnostic ultrasound and radiography (x-rays), should *not* affect the VNS Therapy System.

5.4.2. Mammography

Because the Pulse Generator is in your chest, you may need to be specially positioned for a mammogram. Otherwise, the device may be seen as a shadow on the mammogram. It could make a lesion or lump in that area hard or even impossible to detect. Make sure that your doctor and the mammography technician are aware of the implanted device.

5.4.3. Radiation treatment

Treatment with radiation, cobalt machines, and linear accelerators *may* damage the Pulse Generator. Note that no testing has been done to date. The effect of radiation on the device is not known. Talk with your doctor if you plan to have radiation treatment.

5.4.4. Magnetic resonance imaging

If you plan to have **magnetic resonance imaging** (MRI), make sure your doctor has the following information.

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

MRI using the whole body coil is not recommended because it can damage the vagus nerve. Contact your physician before having any MRI performed so that it can be discussed with the MRI personnel.

5.4.5. Other procedures

External cardiac defibrillation and other procedures for heart problems, as well as extracorporeal shockwave lithotripsy, diathermy, and electrocautery, *may damage* the Pulse Generator. If you had any of these procedures and your doctor did not know about it, have the Pulse Generator checked.

While *diagnostic* ultrasound should *not* affect the VNS Therapy System, *therapeutic* ultrasound therapy *could* damage the Pulse Generator or inadvertently harm you.

5.5. Interference with Other Devices

While the Pulse Generator is stimulating or being set or tested, it may briefly interfere with nearby equipment. If this happens, move at least 2 meters (6 feet) away from such equipment.

5.5.1. Radios and hearing aids

The Pulse Generator can interfere with devices operating in the 40 kHz to 100 kHz range. Hearing aids and transistor radios operate in this range. In theory, the Pulse Generator could affect them, but no effects have yet been reported. No detailed testing has been done, so the effects are unknown.

5.5.2. Implanted devices

The Pulse Generator may affect other implanted medical devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems. These could lead to inappropriate responses from the Pulse Generator.

5.5.3. Credit cards and computer discs

The VNS Therapy Magnets are very strong. They *can* damage televisions, computer disks, credit cards, and other items that are affected by strong magnetic fields. Keep your Magnet at least 25 centimeters (10 inches) away from any of these items. **Do not carry or store the Magnets near them.**

6. SIDE EFFECT AND SAFETY PROFILE OF VNS THERAPY OBSERVED IN CLINICAL STUDIES IN DEPRESSED PATIENTS

This section describes the side effects and safety concerns that were observed in the clinical studies that led to the approval of VNS Therapy as an treatment for patients with treatment-resistant depression. The side effects and safety concerns associated both with the surgical implantation procedure for the VNS Therapy System and those related to stimulation of the vagus nerve are discussed. In addition, this section discusses some specific safety considerations for the treatment of patients with depression.

6.1. Overview of Clinical Studies

Safety and effectiveness studies involved a total of 295 men and women who received VNS Therapy along with their usual antidepressant treatments. Sixty of them participated in a pilot study that compared depressive symptoms before and after VNS Therapy. The favorable results from that study prompted a second study. The second study (sometimes referred to as “D-02”) consisted of two “phases” and included people with treatment-resistant depression. In the first phase, which lasted 3 months, half of the 235 patients who were implanted with the device had it turned on while the other half did not. Patients did not know whether the device was on or not. In the second phase of the study (referred to as the “long-term phase of D-02”), all patients had the device turned on after the first 3 months and were followed for at least a full year. Patients in the long-term phase of the study were allowed to have adjustments in the doses of depression medications prescribed and were also allowed to have new medications or ECT prescribed during this time. These

patients were compared to a separate group of 124 people with treatment resistant depression who received antidepressant treatments, but who did not have the device implanted.

6.2. Surgical Implantation Procedure

6.2.1. Side effects that may occur from implantation of the VNS Therapy System

The following is a list of the side effects that were most commonly reported as being related to the surgical implantation of the VNS Therapy System during the D-02 study. The side effects that occurred in at least 3% of the patients in the D-02 study and the percentage of patients who experienced them were as follows:

- ◆ Incision pain (36%)
- ◆ Voice alteration (33%)
- ◆ Incision site reaction (for example, redness, itching, soreness) (29%)
- ◆ Pain around the device generator or leads (23%)
- ◆ Other reactions around the device generator or leads (for example, swelling, tenderness) (14%)
- ◆ Pharyngitis (inflammation of the throat) (13%)
- ◆ Difficulty swallowing (11%)
- ◆ Numbness (11%)
- ◆ Nausea (9%)

- ◆ Shortness of breath (9%)
- ◆ Headache (8%)
- ◆ Neck pain (7%)
- ◆ Pain elsewhere (7%)
- ◆ Increased cough (6%)
- ◆ Paresthesia (tingling sensation) (6%)
- ◆ Infection at the surgical site (4%)
- ◆ Chest pain (3%)
- ◆ Dizziness (3%)
- ◆ Increased tension of the muscles (3%)
- ◆ Vocal cord paralysis (3%)
- ◆ Skin rash (3%)
- ◆ Inability to pass urine (urinary retention) (3%)

Many of these side effects resolved within 30 days, but in some cases the side effects persisted beyond 90 days. Voice alteration was particularly likely to persist for longer than 90 days.

 Implantation of the Lead may cause nerve constriction (squeezing of the nerve). Call your doctor right away if your voice is always hoarse a few days after surgery. (There could be other explanations for this symptom.)

6.2.2. Infrequent surgical side effects

Surgical side effects that were reported in the D-02 study less frequently than those listed above, but by at least 1% of patients, were as follows: allergic reactions, weakness, fever, bleeding, heart palpitations, difficulty sleeping, neck rigidity, loss of appetite, heartburn, vomiting, bruising, swelling, itching, ear pain, ringing in the ears, and tightness in the throat. Additional serious side effects (reported in less than 1% of patients) were: transient heart stoppage (occurred in the operating room), decrease in heart rate (occurred in the recovery room), abnormal thinking (occurred in the post-operative period, thought due to narcotics), aspiration pneumonia (occurred in the post-operative period), and acute kidney failure.

6.2.3. Surgical scars

There are surgical techniques that may minimize surgical scars. Talk to your surgeon if you have specific concerns.

6.3. Stimulation of the Vagus Nerve

Side effects can occur from stimulation of the vagus nerve by the VNS Therapy System. Generally, the side effects become less noticeable over time for most patients. Only 3% of patients discontinued VNS Therapy because of side effects during the first year of treatment in the D-02 study. Sometimes your doctor can lessen the side effects by changing the device settings.

The VNS Therapy System is not a drug. It does not cause drug-related side effects and does not interact with drugs, including antidepressant medications you may be taking.

6.3.1. Side effects that may occur from stimulation of the vagus nerve

Table 1 shows the side effects that were most commonly reported as being related to stimulation of the vagus nerve by the VNS Therapy System during the D-02 study. Side effects reported in at least 3% of the patients are included. Table 1 shows the percentage of patients who had these side effects after 3 months, 12 months, and 24 months of stimulation.

Table 1. Stimulation-Related Side Effects Reported by Greater Than or Equal To 3% of Patients—Study D-02

	Months of Stimulation		
	3	12	24
Voice alteration	59%	54%	52%
Increased cough	24%	7%	4%
Shortness of breath	14%	16%	14%
Neck pain	16%	13%	15%
Difficulty swallowing	13%	5%	5%
Paresthesia (tingling)	11%	4%	4%
Tightness in throat	10%	6%	5%
Pain	6%	6%	5%
Nausea	6%	1%	1%
Pharyngitis (inflammation of the throat)	6%	5%	4%
Headache	5%	3%	3%
Chest pain	4%	2%	2%
Heart palpitations	4%	3%	2%
Difficulty sleeping	4%	1%	1%
Heartburn	3%	2%	2%
Increased muscle tension	3%	4%	3%

While many of the incidences of these side effects resolved over time, some patients continued to report the side effects throughout the study. This was particularly true for voice

alteration, shortness of breath, and neck pain. Some of the side effects caused by stimulation typically occur only during stimulation (the ON time of the stimulation cycle).

6.3.2. Other side effects reported during VNS Therapy

The following is an alphabetical list of additional side effects reported as at least possibly due to vagus nerve stimulation during the 12-month D-02 study: abnormal dreams, abnormal thinking, agitation, amenorrhea (stoppage of menstrual periods), amblyopia (visual disturbance), amnesia, anxiety, arthralgia (joint pain), asthma, colitis, constipation, deafness, diarrhea, dry mouth, emotional lability, eructation (belching), eye pain, flatulence, flu syndrome/viral infection, gastritis, hiccup, hypertension (high blood pressure), hypotension (low blood pressure), increased appetite, laryngitis, migraine, myalgia (muscle ache), myasthenia (muscle weakness), nervousness, postural hypotension (low blood pressure upon standing), rhinitis, sedation, stridor, sweating, syncope (fainting), tachycardia (fast heart beat), tremor, twitching, vasodilatation (flushing), weight gain, weight loss.

6.4. Additional Safety Considerations

6.4.1. Worsening depression

People who have depression can experience waxing and waning of their depressive symptoms even while receiving treatment. During the first phase of the D-02 study when half the patients had their VNS Therapy System turned on and the other half did not, the study doctors reported 12 serious events of worsening depression requiring hospitalization. Four of these events occurred in patients who had their device turned on, and the other

eight occurred in patients who did not have their device turned on. During the long-term phase of the D-02 study (months 3 through 12), study doctors reported 62 additional serious events of worsening depression in 31 patients. If your depression worsens during VNS Therapy, inform your doctor promptly.

6.4.2. Mania

Some patients being treated for depression may experience a manic or hypomanic episode characterized by an abnormal and persistently elevated or irritable mood. Patients with known bipolar disorder (manic depressive illness) are the people most likely to experience this phenomenon. It is believed that effective antidepressant treatments themselves can cause a manic or hypomanic episode. In the D-02 study (through the 12-month long-term phase), six hypomanic or manic episodes were observed. Five of the six patients had a known history of prior hypomanic or manic episodes. One of these events was considered serious enough to require hospitalization; the other five events were either treated with medication or only required observation. If you experience symptoms of an elevated or irritable mood during VNS Therapy, inform your doctor promptly.

6.4.3. Suicides

People with depression may experience the emergence of suicidal thoughts and behavior (suicidality) whether or not they are receiving treatment. In the D-02 study (through the 12-month long-term phase), there were one suicide and seven additional suicide attempts in six patients. If you or someone else notices your depression worsening or indications of suicidality, inform your doctor promptly. Additionally, if you or someone else notices any of the following symptoms, inform your doctor immediately as they may indicate an increased risk of suicide: new or worse anxiety, feeling agitated or restless, panic attacks, difficulty sleeping, new or worse irritability, acting aggressive, being angry or violent, acting on dangerous impulses, an extreme increase in activity and talking, other unusual changes in behavior or mood.

6.4.4. Deaths that occurred during the depression studies

In the D-02 study (through the 12-month long-term phase), there were four deaths. One occurred in a patient who had enrolled in the study but had not yet received a VNS Therapy System implant. The causes of death for the other three patients were as follows: suicide (described above), sudden death of unknown cause, multi-organ system failure.

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

Once a medical device is approved for commercial distribution, the United States Food and Drug Administration (FDA) regulations require certain parties, including manufacturers of medical devices, to report to the FDA deaths and serious injuries to which a device has or may have caused or contributed. The required report is referred to as a medical device report (MDR). The FDA Office of Biometrics and Surveillance analyzed all MDRs submitted for the VNS Therapy System from July 1, 1997 through October 8, 2004. During this period, the VNS Therapy System had a single approved indication, epilepsy. The analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. By the end of the period analyzed, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience (the presence of the implanted device in an individual for a full year equals one “device-year”). **It is important to emphasize that, although the events occurred during treatment with the VNS Therapy System, the submission of an MDR does not necessarily mean the product caused or contributed to the event being reported.**

6.5.1. Deaths

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

- ◆ seizure disorder (152 reports; 29% of total deaths), including sudden unexplained death in epilepsy and status epilepticus (These are recognized risks in patients with epilepsy—the rate of sudden unexplained death in patients treated with VNS Therapy is within the range of the rates reported for similar patients who are treated with antiepileptic drugs without VNS Therapy.)
- ◆ respiratory events (99 reports; 19% of total deaths), including pneumonia, pulmonary edema, reduced oxygen supply to body tissues
- ◆ cardiac events (51 reports; 10% of total deaths), including heart stoppage, heart attack, and irregular heart beat
- ◆ neurovascular events (24 reports; 5% of total deaths), including stroke and brain hemorrhage (bleeding)
- ◆ cancer (19 reports; 3% of total deaths), including brain and colon
- ◆ suicide (9 reports; 2% of total deaths)

6.5.2. Serious injuries

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

- ◆ vagus nerve injury (181 reports) including vocal cord paralysis (109) and hoarseness (71)
- ◆ respiratory injuries (141 reports) including sleep apnea (cessation of breathing during sleep, 33 reports) shortness of breath (50), and aspiration (inhaling foreign matter or stomach contents into the lungs, 14 reports)
- ◆ cardiac events (123 reports) including fast or slow heart rates, palpitations, high or low blood pressure, fainting, and cessation of heart beat
- ◆ pain (81 reports) including chest and neck pain
- ◆ gastrointestinal events (60 reports) including difficulty swallowing (24) and weight loss (24)
- ◆ depression (21 reports)

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

6.5.3. Device malfunctions

A total of 708 device malfunctions were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Some of the most common malfunctions reported were an abnormal lead test (which can be indicative of a poor connection between the lead and vagus nerve or lead and generator or can indicate a broken lead, 351 reports), lead breakage (116), device failure (44), and a shift in device location (20).

7. BENEFITS OF VNS THERAPY

The effectiveness of VNS Therapy in decreasing depressive symptoms was primarily demonstrated by improved scores on standardized tests after 12 months and 24 months of VNS Therapy in the D-02 study. See “Overview of Clinical Studies” in the preceding section for a description of the D-02 study.

7.1. Effectiveness Results From the D-02 Clinical Study

7.1.1. Three-month results

At the end of the first 3 months, the proportion of patients who had at least a 50% reduction in depression symptoms was 15% in the group of patients receiving active stimulation, slightly better than for patients who were not receiving stimulation (10% of these patients had at least a 50% reduction in symptoms). (See Table 2.) This finding suggested that the full effects of VNS Therapy might require more than 3 months of treatment.

7.1.2. One-year results

After 1 year of VNS Therapy, the results showed that 30% of the study patients were responders (at least a 50% improvement in depressive symptoms) and 17% were remitters (minimal to no depressive symptoms). The results from a second rating scale of depression symptoms showed that 22% of the group were responders and 15% were remitters, and the results from a third rating scale showed that 32% were responders and 23% were remitters (see Table 2). It should be noted that about one in four or five people who were implanted with the device during the study were not included in these calculations of success at 12

months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

7.1.3. Two-year results

After 2 years of VNS Therapy, the results showed that 32% of the patients were responders and 17% were remitters. The results from a second rating scale of depression symptoms showed that 27% of the group were responders and 13% were remitters (see Table 2). It should be noted that about one in three people who were implanted with the device during the study were not included in these calculations of success at 24 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

Table 2. Percent of Responders and Remitters After VNS Therapy

Standard-ized Test	HRSD ₂₄		IDS-SR		MADRS	
	Responders	Remitters	Responders	Remitters	Responders	Remitters
3 months	15%	7%	14%	6%	17%	10%
12 months	30%	17%	22%	15%	32%	23%
24 months	32%	17%	27%	13%	N/A	N/A

Responders - $\geq 50\%$ improvement in depressive symptoms.

Remitters – minimal to no depressive symptoms.

7.1.4. Additional categorization of clinical benefit

After 12 months of VNS Therapy, the patients were also assessed to categorize the degree of improvement in their depression symptoms. The amount of improvement was categorized as follows:

Worsened – depressive symptoms worse than when VNS Therapy was started

Minimal to no change – 0% to 24% improvement in depressive symptoms

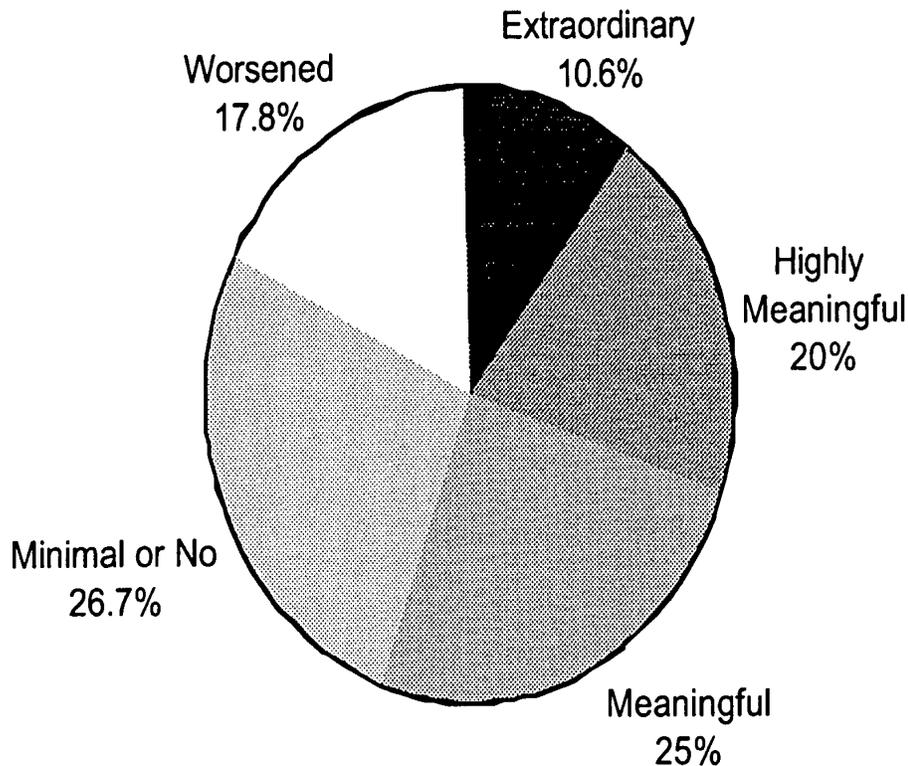
Meaningful clinical benefit – 25% to 49% improvement in depressive symptoms

Highly meaningful clinical benefit – 50% to 74% improvement in depressive symptoms

Extraordinary clinical benefit – over 75% improvement in depressive symptoms

Figure 3 shows the percentage of patients who were in the different categories after 12 months of VNS Therapy. It should be noted that about one in four people who were implanted with the device during the study were not included in these calculations of success at 12 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results shown in the figure.

Figure 3. Categories of Clinical Benefit After 12 Months of VNS Therapy (HRSD₂₄)



7.1.5. Maintenance of benefit over time

Although less than one in three or one in four patients (depending on the rating scale used) appeared to respond to VNS Therapy, most—but not all—of those patients continued to be responders over time. For example, among the 30 patients who were responders on the HRSD₂₄ rating after their first 3 months of VNS Therapy, 60% continued to be responders after one year of VNS Therapy, and 70% were responders after two years of VNS Therapy. Among the 54 patients who were responders after 12 months of VNS Therapy, 69% continued to be responders after two years of VNS Therapy.

7.2. Quality of Life Measurements in the D-02 Clinical Study

In addition to improvements in depressive symptoms, patients who received VNS Therapy for one year in the D-02 study reported improvements in quality of life.

7.3. Expected Rate of Response to VNS Therapy

For patients in whom VNS Therapy is effective, the benefits are not always seen right away. In fact, the 12-week acute studies did not show a significant difference between patients receiving VNS Therapy and those who were not receiving it. Depressive symptoms may improve slowly over the first year of treatment.

7.4. Treatment Continuation Rates

Not all patients continue on VNS Therapy. During the D-02 study, 92% of the patients continued to receive therapy at 12 months and 82% continued to receive therapy at 24 months.

7.5. Limitations of VNS Therapy

VNS Therapy has not been shown to cure depression. It does not work for everyone. For most patients in whom it is effective, improvement in depressive symptoms will be slow (see “Expected Rate of Response to VNS Therapy” above). Some patients may have no change in symptoms with VNS Therapy, and some may actually get worse while receiving VNS Therapy. At present, doctors have no way to predict which patients will respond to VNS Therapy.

8. HAVING THE DEVICE IMPLANTED

VNS Therapy requires surgical placement of the Pulse Generator and Lead by a surgeon. At office visits, your doctor checks the settings and changes them as needed.

8.1. Surgery (Operation)

Surgery lasts from about 1 to 2 hours and typically involves general anesthesia, though local anesthesia is sometimes used. You may stay in the hospital overnight.

The surgeon makes a small incision on the left side of the neck and a second incision below the collarbone in the chest or armpit. The surgeon passes the Lead under the skin between the two incisions. Next the surgeon attaches the Lead to the left vagus nerve in the neck. Then the surgeon attaches the other end of the lead to the Pulse Generator, which is subsequently placed in a “pocket” created at the site of the incision that was made below the collarbone. Finally, the surgeon closes the incisions. See Figure 1.



The operation can be reversed if you and your doctor ever decide to have the VNS Therapy System removed. Removal of the generator and/or lead requires another surgical procedure. Sometimes when a surgeon removes a VNS Therapy System, the surgeon will decide to leave a portion of the Lead behind in order not to risk damaging the vagus nerve. This may pose certain risks (see the “**Medical Hazards**” section of this manual).

8.2. Follow-up After Surgery

The Pulse Generator is usually turned on 2 weeks after it is implanted. (Your doctor will program the Pulse Generator to the proper settings for you.) At that office visit and at subsequent visits, your doctor will check the VNS Therapy System. Your doctor will make sure that it is working well and that the treatment is not uncomfortable for you.

 **Cyberonics recommends that you see your doctor at least once every 6 months. Your doctor will check the VNS Therapy System for safe and effective operation.**

You will be given an Implant and Warranty Registration Card. It has information about your Pulse Generator and Lead.

You will also receive a Patient Emergency Information Card. It has phone numbers to call in case of a device-related emergency.

 **Carry the Patient Emergency Information Card at all times.**

 **Your doctor is your first source for health-related questions and information. Cyberonics *cannot* provide health care advice or services.**

8.3. Antidepressant Medications

Most patients treated with VNS Therapy in the clinical studies also continued to take antidepressant medications. A significant number of patients had new medications added or doses of their old medications increased during the studies.

Your doctor may advise you to continue taking your antidepressant medications after you begin receiving VNS Therapy. Your doctor may also decide to add new medications to your treatment. Always follow your doctor's instructions regarding your medications.

9. THE CYBERONICS MAGNETS

9.1. Handling the Cyberonics Magnets

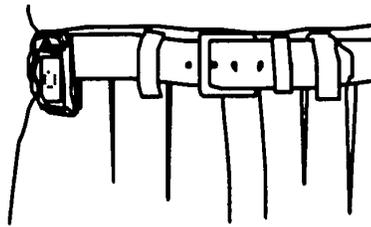
After your operation, your doctor will give you two magnets. You should carry one of the Magnets with you at all times in your pocket, in your purse away from credit cards, or in another convenient place. If you prefer, you can wear them like a watch or a pager (see Figure 4).

If the Magnets are handled carefully, they should last many years.

Figure 4. The Cyberonics Magnets



Cyberonics Magnet
(watch-style)



Cyberonics Magnet
(pager-style)

⚠ Never put or store the Magnets near credit cards, televisions, computers, computer disks, microwave ovens, watches, or other magnets. Keep them at least 10 inches (25 centimeters) away.

⚠ Do not drop the Magnets. They can break if dropped on a hard surface.

⚠ Carry a Magnet with you at all times. Show your family members or caregivers how to use the Magnet.

9.2. Using Your Cyberonics Magnets

Keep a Magnet with you at all times in case you need to turn OFF the Pulse Generator.

The Magnet can be used to stop stimulation temporarily or turn OFF the Pulse Generator:

- ◆ when you plan to sing or speak in public (if stimulation bothers you when you do this)
- ◆ when you are eating (if you have swallowing problems)
- ◆ if stimulation becomes uncomfortable or painful



The correct position for the Magnet may vary from patient to patient. The position depends on how the Pulse Generator is implanted. Find the position that works best for you.

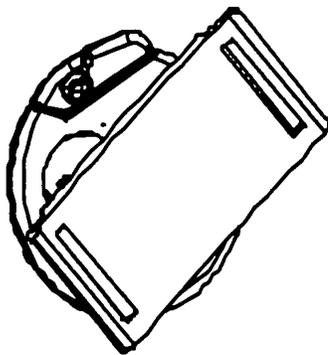
9.2.1. To stop stimulation

1. Put the Magnet over the Pulse Generator (see Figure 5). If the stimulation stays on, move the Magnet around until it stops.

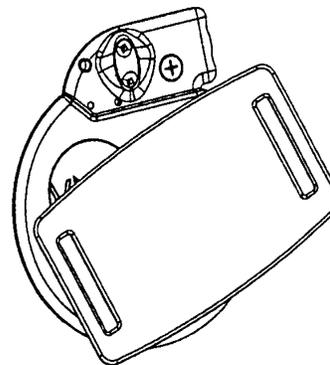
Figure 5. Stopping Stimulation



Model 101



Model 102



Model 102R

- Note:** To show the correct position of the Magnet with the Pulse Generator, the Magnet has been drawn without the belt clip or wristband. The belt clip and wristband use the same Magnet.
2. Leave the Magnet over the Pulse Generator. If needed, tape it to your chest or use an elastic, wrap-around bandage.
 3. If you stopped the stimulation because it was painful or felt unusual, call your doctor right away.

The Pulse Generator will not stimulate while the Magnet is in place, but it will start when the Magnet is removed.

9.3. How the Magnets Work

The VNS Therapy System senses a magnetic field. Holding a Magnet over the Pulse Generator causes a **Reed Switch** inside the Pulse Generator to close. This switch works like a gate. When the Magnet closes it, the signal (stimulation) cannot pass. The Pulse Generator is temporarily turned OFF.

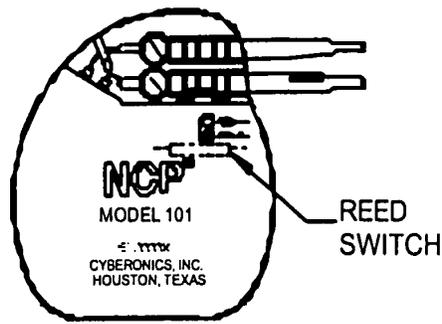
When the Magnet is removed, the switch (gate) opens right away. The VNS Therapy System is turned back ON and can stimulate again.

9.3.1. Finding the Reed Switch

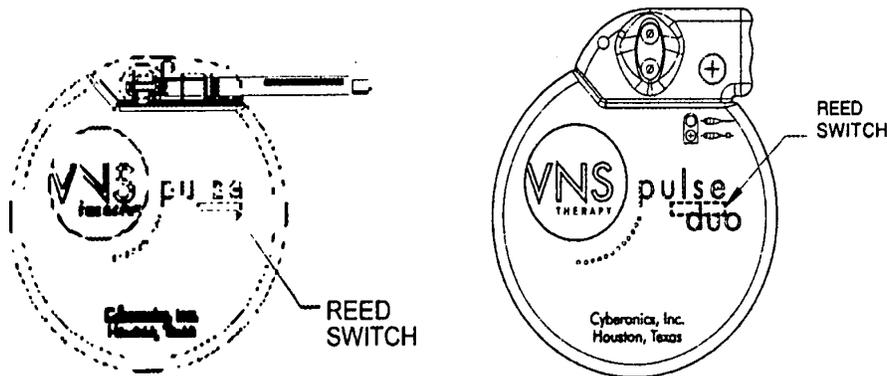
You may need to move the Magnet around to find the Reed Switch and stop stimulation (Figure 6).

The label side of the Magnet should face the Reed Switch. Figure 6 shows the position of the switch.

Figure 6. Reed Switch Position



Model 101



Model 102

Model 102R

9.3.2. Know your Magnets

These tips are also given elsewhere in these instructions. Be sure that you understand them.

- ◆ Use the Magnet only when necessary to turn off stimulation.
- ◆ **With your doctor's permission, it is okay to leave the Magnet in place** for a short while, for example, to sing a song. The Pulse Generator will not stimulate while the Magnet is in place. The stimulation cycle begins again when the Magnet is removed.

- ◆ **If stimulation hurts**, hold the Magnet over the Pulse Generator and keep it there. The stimulation will stop as long as the Magnet is there. If necessary, tape the Magnet in place. Contact your doctor right away.
- ◆ **Always carry the Magnet with you.** If you have pain because of stimulation, you can stop it by placing the Magnet over the Pulse Generator.
- ◆ Keep the Magnets away from credit cards, computer disks, watches, and other items affected by strong magnetic fields.
- ◆ **If you lose one of your Magnets**, you may buy a new one from Cyberonics. A Magnet Order Form is included in your Patient Essentials Kit. You may also buy new Magnets by contacting Cyberonics' Customer Service department (see number on back cover of this manual).
- ◆ And remember—if you are not sure about using the Magnets, ask your doctor to show you how.

 All Magnets can **lose their effectiveness** over time. If you suspect that either of your Magnets is not working, call your doctor.

9.4. Replacing the Cyberonics Magnets

To order a new Magnet, contact Cyberonics' Customer Service department at the number on the back cover of this manual. A Magnet Order Form, with prices, is included in your Patient Essentials Kit.

10. OTHER IMPORTANT INFORMATION ABOUT YOUR VNS THERAPY SYSTEM

10.1. Device Complications

Complications linked to the VNS Therapy System can result from:

- ◆ Surgery
- ◆ Pulse Generator malfunction (not working)
- ◆ Battery depletion (running out)
- ◆ Touching or moving the device through the skin

10.1.1. Surgery

Like a heart pacemaker, the VNS Therapy device is implanted during surgery. One incision is made in the neck to attach the Lead to the vagus nerve, and a second incision is made in the chest for the Pulse Generator. All types of surgery carry some risks. In addition to the risks described in the earlier section of this Manual that summarized the experience from clinical studies, there are potential mechanical complications related to the surgical implantation of the device. The Pulse Generator and/or Lead can—but rarely do—move or come through the skin. Also, the Lead can break or become disconnected from the Pulse Generator.

10.1.2. Pulse Generator malfunction (device not working right)

The Pulse Generator can malfunction, though this is rare. The stimulation from a Pulse Generator that is not working right can cause intense neck pain, hoarseness, choking, or trouble breathing.

 Stimulation from a Pulse Generator that is not working right could damage the vagus nerve and lead to permanent hoarseness or other complications. Malfunction of the Pulse Generator could cause the battery to run out sooner than expected. If you have any of these symptoms, or if stimulation becomes painful, irregular, or nonstop, place the Magnet over the Pulse Generator. Hold it there to stop stimulation (see the “Using Your Cyberonics Magnets” section of this manual). Then call your doctor right away.

10.1.3. Battery depletion (running out)

The battery in your Pulse Generator will normally last between 1 to 16 years, depending on the settings. The Pulse Generator battery will slowly lose its power when it starts to run out. It will begin to stimulate differently. You may sense this change as irregular stimulation. At the end, the stimulation will stop completely.

 **After stimulation stops (when the Pulse Generator battery runs out), you may notice a change in your depressive symptoms. If you think that the Pulse Generator might not be working right, call your doctor.**

When the battery in your Pulse Generator runs out, the Pulse Generator must be replaced in order for you to continue to receive VNS Therapy. This requires an additional surgical procedure. The operation involves anesthesia and generally takes less than an hour to complete.

Replacement or removal of the Lead is a different procedure. It is not required for routine replacement of the Pulse Generator.

10.1.4. Manipulation of the Pulse Generator and Lead

The Pulse Generator is secured into place during surgery, but the device can move slightly. It may be possible to feel the Lead under the skin after surgery. This feeling is normal. It should become less apparent over time (several weeks). Manipulation of the Lead should be prevented at all times.

 **Never move or twist the Pulse Generator or manipulate the Lead. Doing so could damage the Lead or your vagus nerve. It could require that the Pulse Generator and Lead be replaced.**

11. CYBERONICS' PATIENT WARRANTY AND SAFETY LISTING

Government agencies require makers of implantable devices to contact people in case of emergencies related to the device. Cyberonics has a listing of people who have had the Pulse Generator and Lead implanted. The information is kept in confidential files. It is a permanent record of the implantation surgery. Cyberonics will release a file only if required by law.



Please send Cyberonics **a change of address notice** if you move.

12. FREQUENTLY ASKED QUESTIONS

Patients and their family members often ask these questions.

How do most people respond to VNS Therapy? When the device was tested in the clinical trials, depressive symptoms decreased for most patients. Some patients had no change in depressive symptoms and some got worse while receiving VNS Therapy. Among those patients who did improve while receiving VNS Therapy, some did not improve until they had been receiving VNS Therapy for 6 months or longer.

Can I know if I will be helped before I am implanted with the Pulse Generator and Lead? At this time, there is no way to predict what your response will be.

What are the results of the VNS Therapy clinical studies? This Manual provides a summary of important safety and effectiveness results from the clinical studies. Your doctor can give you more information about the clinical (research) studies.

What is the implantation surgery like? You will be given a general or local anesthetic. The operation usually takes 1 to 2 hours. The operation will be done with you as an outpatient (you go home the same day) or you may stay in the hospital overnight. Ask your surgeon to tell you more about the anesthetic, the operation, and the hospital stay so that you will know what to expect.

Are there risks linked with the surgery? Any surgery has some type of risk. It is important that you discuss this question with your surgeon.

Will the scars be noticeable? Each person has different healing and scarring results. You should expect some scarring from surgery. Most people do not think the scarring after surgery is a major concern. If this is a special concern for you, discuss it with your surgeon.

Will people be able to see the implanted device through my skin? The Pulse Generator is shaped like a disk. The Model 101 is 5.4 centimeters (2.1 inches) across and 1 centimeter (0.4 inch) thick; it weighs about 38 grams (1.34 ounces). The Model 102 is 5.2 centimeters (2.0 inches) across and 0.7 centimeter (0.27 inch) thick; it weighs about 25 grams (0.88 ounce). The Model 102R is 5.2 centimeters (2.0 inches) by 5.8 centimeters (2.3 inches) and 0.7 centimeter (0.27 inch) thick, weighing about 27 grams (0.95 ounce). If you have a small frame or are very thin, the device may be visible below your left collarbone.

What happens after the surgery? After surgery (usually 2 weeks later), your doctor will set the treatment settings of your device. If the stimulation feels uncomfortable, your doctor can change it to make you more comfortable. The doctor will use the Programming Wand to check and fine-tune your stimulation settings at subsequent visits.

Will I be able to tell when the stimulator is on? Many people note a change in their voice (often described as hoarseness) or discomfort in the neck (typically mild pain or a tingling sensation) during stimulation. In general, most side effects become less noticeable over time.

What are the side effects of VNS Therapy? The most common side effects reported during VNS Therapy are voice alteration (often described as hoarseness), discomfort in the neck (typically mild pain or a tingling sensation), cough, shortness of breath, difficulty swallowing, and a feeling of tightness in the throat. Often these events only occur when the stimulator is ON. Other less common side effects are discussed in the earlier section of this manual that summarized the experience from clinical studies. In general, most side effects become less noticeable over time.

When should I use the Magnet? Use the Magnet to stop stimulation temporarily or to turn OFF the Pulse Generator when you plan to sing or speak in public (if stimulation bothers you when you do this), when you are eating (if you have swallowing problems), or if stimulation becomes uncomfortable or painful. If you need to use the Magnet for any of these reasons or any other reason, inform your physician.

How does the Magnet work? The Pulse Generator has a sensor (the Reed Switch) that recognizes the Magnet and stops stimulation.

Can any magnet be used? Only the Cyberonics Magnet should be used with your VNS Therapy System. If you lose your Magnet or require extra Magnets, contact your doctor. In an emergency, you may try other strong magnets. The use of other, non-Cyberonics magnets will not harm the VNS Therapy System. But there is no way to know in advance whether a magnet other than the Cyberonics Magnet will work.

What if the Magnet is accidentally kept in place over the Pulse Generator for an extended period? No stimulation will be

delivered while the Magnet is kept over the device. Stimulation will resume only after the Magnet is removed.

Is it possible to stop all stimulation using the Magnet? Yes. To stop stimulation, hold the Magnet over the Pulse Generator and keep it there. Use this method if you have unusual or painful stimulation. Then call your doctor right away. The Magnet will stop all stimulation while it is held in place. You may need to secure the Magnet by taping it over the implanted device.

Who should carry the Magnet? You should carry the Magnet so that it is always with you. You may also want your family members or caregivers to have access to a Cyberonics Magnet.

Is the Magnet an environmental hazard? The Cyberonics Magnet can damage computer disks, credit cards, watches, and other items affected by strong magnetic fields. Keep your Magnet at least 25 centimeters (10 inches) away from any of these items. Do not store Magnets near such items.

Other Questions? If you have other questions about the VNS Therapy System, any of its parts, or VNS Therapy in general, talk to your doctor.

VIA FEDERAL EXPRESS

COPY

April 27, 1998

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
IDE Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

RE: Original IDE Submission
NCP[®] System Treatment of Depression
NeuroCybernetic Prosthesis (NCP[®]) System

Dear Sir/Madam:

Enclosed are three copies of an original Investigational Device Exemption (IDE) submission for the use of the NeuroCybernetic Prosthesis (NCP[®]) System for the treatment of depression. This IDE submission requests approval to begin a pilot or feasibility trial of vagus nerve stimulation indicated for major depressive episodes in either unipolar or bipolar depressive disorder. Cyberonics is the Sponsor of the proposed study and the manufacturer of the NCP[®] System at the addresses given at the bottom of this letter.

Cyberonics submitted a request for a meeting to FDA to discuss this study on March 11, 1998. FDA has not responded to date, and so Cyberonics is withdrawing the meeting request and submitting this IDE. If, after review of this IDE, significant issues require clarification, Cyberonics will request a meeting with FDA.

The investigational device for this study is the same device as that approved in P970003 and therefore, information related to device description and manufacturing information are incorporated herein by reference to P970003 and not reproduced in this original IDE submission.

MANUFACTURING

17448 Highway 3, Suite 100
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(281) 332-1375
Fax: (281) 332-3615

HEADQUARTERS

16511 Space Center Blvd., Suite 600
Houston, TX 77058
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INTERNATIONAL

Cyberonics Europe S.A.
Belgicastraat 2
1930 Zaventem
Belgium
32 2 720 95 93
Fax: 32 2 720 60 53

The FDA facility registration number for the Cyberonics manufacturing facility is 1644487. The device will not be sold during this pilot study.

A claim of categorical exclusion from environmental assessment is made in this submission.

The key contact for this submission is William H Duffel, Ph.D. I can be reached at (281) 228-7223, by pager at (713) 908-5353, or alternatively at whd@cyberonics.com. Mr. Burke Barrett of Cyberonics may be reached at (281) 228-7304 and is an alternate to myself if I am unavailable.

Sincerely,

A handwritten signature in black ink that reads "William H. Duffel, Jr." in a cursive script.

William (Bill) H. Duffel, Jr., Ph.D.
Vice President, Clinical & Regulatory Affairs
Cyberonics, Inc.

CC: Ann H. Costello, Ph.D., D.M.D.

Cyberonics

October 24, 2003

VIA FEDERAL EXPRESS

U. S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

RE: VNS Therapy™ System
PMA Number P970003
Panel-track PMA Supplement
Expedited Review Granted by FDA on July 16, 1999 (See letter attached)

Dear Reviewer:

According to the provisions of 21 CFR 814.39, Cyberonics, Inc. is submitting this Panel-track PMA-Supplement application seeking commercial approval to add the following indication for use statement to the PMA approved VNS Therapy System labeling:

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

Aside from the changes necessary to add the treatment-resistant depression (hereafter referred to as "depression") indication to the VNS Therapy System's labeling, no changes have been made to the commercially approved VNS Therapy manufacturing processes, device system hardware or software and no changes have been made to the programmability or any other aspect of the VNS System. The only proposed changes are to the labeling which are commensurate with the addition of the new indication for depression. The substantive changes include:

- (1) Updating the commercially available VNS Therapy Pulse Model 102 Generator and the VNS Therapy Pulse Duo Model 102R Generator Physicians Manual to add the labeling for the new depression indication for use. The depression-specific labeling has been created following the same format as the primary sections of the commercially approved epilepsy manual and will be appended as a separate section to the currently approved manual. The sections contained within the depression-specific labeling will contain either new information related to the depression indication (such as the Clinical Studies section) or will refer back to the epilepsy portions of the currently approved manual (such as the Device Description section).

- (2) Creating a new depression section of the Patient Essentials Manual based upon the existing manual and will be appended to the back of the manual. This section of the Patient Essentials Manual will be a stand-alone section of the manual and will not refer depression patients back to the Epilepsy section of the Patient Manual.
- (3) In both the physician's and patient's manuals a minor change will be made concerning application of the magnet by the patient to check for battery end of service. This check will be deleted, as the physician will be responsible for monitoring end of service.

PMA Supplement Application

Sponsor: Cyberonics, Inc.
100 Cyberonics Blvd.
Cyberonics Building
Houston, Texas 77058

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Alternate Company Representatives: David Garcia, CQA, RAC
Principle, Regulatory Affairs
Telephone: (281) 228-7265
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david.garcia@cyberonics.com

Device Classification Name: Stimulator, Autonomic Nerve, Implanted for Epilepsy
Code: LYJ

Device Trade Name and Model Numbers: 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™ Tunneler Model 402
VNS Therapy™ Accessory Pack Model 502

Related File Numbers: P970003 - Approved July 16, 1997 (Supplements 1-49)
G980099 - Conditionally approved May 29, 1998,
Unconditionally approved September 28, 1998
G980099 – IDE Supplements 1 – 55

Expedited Review Status On July 16, 1999, FDA granted the PMA Supplement application for the VNS Therapy System for Treatment Resistant Depression expedited review status.

Pre-Submission Meeting Held On September 25, 2003, the Sponsor met with FDA and discussed the proposed structure, analysis plans and timeline of the Panel-track PMA Supplement.

Manufacturing Facility: Cyberonics, Inc.
100 Cyberonics Blvd.
Cyberonics Building
Houston, Texas 77058
Registration #1644487

Description of Application: Cyberonics has completed the pivotal clinical investigation (D-02) of the VNS Therapy System for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant major depressive episode. The D-02 pivotal clinical trial was conducted under IDE Number G980099. The D-02 acute and long-term phase data are being presented in this PMA-Supplement application.

This application also includes a long-term, prospective, multi-center observational study (D-04) that collected depression and health care utilization (not included in the application) outcomes during usual standard of care treatment for treatment-resistant chronic and/or recurrent depression in people who were in a major depressive episode. Since D-04 was an observational study of patients being treated, as usual standard of care, submission of an IDE was not necessary. Therefore, D-04 was run as a non-significant risk study. The data from the D-04 study population was used as a control for the D-02 study population. Data are presented herein that focus on the first 12 months of treatment (stimulation and standard of care) that D-02 subjects received, and compares these results to the treatment (standard of care) that the D-04 subject group received through 12 months without VNS Therapy.

With this submission, Cyberonics Inc. is requesting FDA approval to modify the current PMA approved Physician's Manual for the VNS Therapy System to add the aforementioned proposed indication for use and incorporate information learned during the D-02 pivotal clinical

investigation and D-02/D-04 comparison study to other sections of the Physician's manual commensurate with the inclusion of the new depression indication. A new section behind the current Patient's Manual has also been created for those patients being treated for depression.

PMA Supplement Copies:

- (1) Seven paper copies of the PMA Supplement submission are provided. **(Note: Two copies of CD ROMs containing an electronic copy of the complete paper PMA Supplement submission will be submitted to FDA within the next 7 to 10 days under separate cover. Dr. Pena (FDA Lead Reviewer) agreed with the Sponsor's proposal to allow sufficient time to produce and validate the CD ROMs.);**
- (2) Seven copies of CD ROMs entitled "Patient Interviews." These CD ROMS contain video interviews of treatment resistant depression patients implanted with the VNS Therapy System and are referenced in Vol. 19;
- (3) Two copies of CD-ROMs entitled "RAW SAS Data." These files contain all of the raw data and results (SAS Transport Files) for D-01 Feasibility Study, D-02 Acute Pivotal Study, D-02 Long-Term (LT) Pivotal Study and D-04 Observational Clinical Study. **(Note: Paper Volumes 84 A through 84 D have been included in this submission to assist the FDA reviewer in navigating through the raw data and results presented on the CD-ROMs);**
- (4) Two copies of CD ROMs containing the Summary of Safety and Effectiveness found in Section 3 of this PMA Supplement and;
- (5) Seven copies of the commercially available VNS Therapy surgical implant training procedure on videotapes as referenced in Vol. 18.

Although the final PMA Supplement consists of a total of 87 volumes, it should be noted that much of the information is supportive and may not be critical to all members of the review team. Sections believed to be critical to all reviewers include:

- Volumes 2-4, Sections 9(iii) and 9(iv) – Information Relevant to an Evaluation of the Safety and Effectiveness of the Device.
- Volume 18, Section 11 – Device Labeling
- Volume 19, Section 14 – Clinical Executive Summary and Pivotal D-02 Acute and Long-term and D-02/D-04 Comparison Study (Pivotal Trial Results)

It should be noted that the Clinical Executive Summary (volume 19) was written to provide an overview and orientation for the clinical components of the application. Therefore, it is recommended that the reviewer start their review with the Clinical Executive Summary.

In order to aid the reviewers, the PMA Supplement has been structured in a manner that allows for critical sections of the application to be reviewed independently. For the main clinical reports, an additional customized table of contents is provided directly preceding the reports. These tables of contents are detailed road maps that provide easy reference to all associated volumes (e.g., patient listings). Due to the overall length of this PMA Supplement, the FDA reviewers should familiarize themselves with these tables of contents.

Cyberonics would like to thank FDA for the time and effort already extended by the Agency in support of this application. In particular, we wish to acknowledge the advice given at the pre-PMA submission meeting of September 25, 2003. After that meeting, we attempted to incorporate FDA's comments as completely as possible based on our understanding of the concerns. Recently, on October 15, 2003, we received a draft of FDA minutes/action items from the meeting. A trace matrix providing an explanation of how we are addressing FDA's comments is included in Vol.1 Section 2.

Upon receipt of FDA's minutes, Cyberonics realized that our interpretation of some of the items requested at the meeting differed slightly from FDA's intent. Thus slightly different data presentation may be needed for some of the items in FDA's minutes. Since FDA has informed Cyberonics that they are hopeful that the application will go to the Advisory Board Panel in February of 2004, Cyberonics was very sensitive to the fact that this timeline is contingent on Cyberonics submitting the application as promised in October 2003. Therefore, the decision was made that should minor changes to data presentations be necessary, they would be submitted to the FDA shortly after submission of this application. This plan was discussed during the October 15, 2003 teleconference between FDA and Cyberonics and FDA had no objection.

This letter authorizes the Food and Drug Administration, to include, by reference, information in our approved Pre-Market Approval Application (PMAA) P970003 for the VNS Therapy™ System in support of this PMA-Supplement.

The existence of this PMA-Supplement and the data and other information it contains are confidential.

The Key Contact for this submission is Annette Zinn and the Primary Secondary Contact is Scott Mindrebo. I can be reached at (281) 228-7228 or by email at annette.zinn@cyberonics.com and Scott Mindrebo can be reached at (281) 228-7225 or by email at scott.mindrebo@cyberonics.com. Cyberonics would also like to request that FDA fax a copy of any response regarding this submission to our fax number: 281-228-7517.

Respectfully submitted,



Annette Zinn, M.P.H., J.D., RAC
Director and Senior Counsel, Regulatory Affairs

Approved:



Scott J. Mindrebo
Senior Director, Regulatory Affairs

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