

**SUMMARY OF SAFETY AND
EFFECTIVENESS DATA (SSED)**

Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Vagus Nerve

Device Trade Names: VNS Therapy™ System

VNS Therapy™ Pulse Model 102 Generator

VNS Therapy™ Pulse Duo Model 102R Generator

VNS Therapy™ Programming Wand Model 201

VNS Therapy™ Magnet Model 220

VNS Therapy™ Software Model 250

VNS Therapy™ Lead Model 302

VNS Therapy™ Tunneler Model 402

VNS Therapy™ Accessory Pack Model 502

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Premarket Approval Application (PMA) Number: P970003/S50

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II. 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.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. Contraindications

- The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.
- Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (hereafter referred to as diathermy) on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

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

Testing indicates that diathermy can cause heating of the VNS Therapy System well above temperatures required for tissue destruction. The heating of the VNS Therapy System resulting from diathermy can cause temporary or permanent nerve or tissue or vascular damage. This

damage may result in pain or discomfort, loss of vocal cord function, or even possibly death if there is damage to blood vessels.

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

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

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

B. Warnings and Precautions

See Physician Labeling

IV. DEVICE DESCRIPTION

The VNS Therapy System used for vagus nerve stimulation (VNS), consists of the implantable VNS Therapy Pulse Generator, the VNS Therapy Lead and the external programming system used to change stimulation settings. The lead and the pulse generator make up the implantable portion of the VNS Therapy System. Electrical signals are transmitted from the pulse generator to the vagus nerve by the lead. The software allows a physician to identify, read and change device settings. The pulse generator is surgically placed in the left chest. The lead is then connected to the pulse generator and attached to the left vagus nerve. Patients are provided with magnets that, by placing the magnet over the implanted pulse generator can deactivate (turn OFF) programmed stimulation. Programmed stimulation resumes when the magnet is removed.

A. VNS Therapy™ Pulse Generators (Model 102 and 102R)

The VNS Therapy™ Pulse Generators are implantable, multiprogrammable pulse generators that deliver electrical signals to the vagus nerve. Constant current, capacitively coupled, charge-balanced signals are transmitted from the Generator to the vagus nerve by the lead. The pulse generator is housed in a hermetically sealed titanium case. The pulse generator has a number of programmable settings including pulse width, magnet-activated output current, output current, magnet-activated ON time, signal frequency, magnet-activated pulse width, signal ON time and signal OFF time. The pulse generator has telemetry capability that supplies information about its operating characteristics, such as parameter settings, lead impedance and history of magnet use.

B. VNS Therapy™ Lead Model 302

The lead delivers electrical signals from the pulse generator to the vagus nerve. The lead has two helical electrodes on one end and on the other end a 3.2-millimeter (mm) connector. The lead is insulated with silicone rubber and is non-bifurcated. The lead wire is quadrifilar MP-35N, and the electrode is a platinum ribbon.

C. VNS Therapy™ Tunneler Model 402

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

D. VNS Therapy™ Programming Wand Model 201

The wand is used to activate, program, reprogram and interrogate the pulse generator.

E. VNS Therapy™ Software Model 250

The programming software is a computer program that permits communication with the implanted pulse generator. The programmed parameters and operational status can be interrogated. One or more parameters can be programmed at one time, and the programmed values are verified and displayed.

F. VNS Therapy™ Accessory Pack Model 502

The accessory pack contains replacement components for the VNS Therapy System and includes a hex screwdriver, test resistors and lead tie downs. These are supplied sterile.

G. VNS Therapy™ Magnet Model 220

Cyberonics provides patients two magnets—a watch-style magnet and a pager-style magnet. When a magnet is passed over the pulse generator, the magnetic field causes a reed switch within the pulse generator to close. The magnet is placed over the pulse generator to stop stimulation.

V. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently three major treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode: pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy (including cognitive behavior and interpersonal therapy), and electroconvulsive therapy (ECT). ADDs are the usual first line treatment for depression. Clinical trials have demonstrated efficacy for a number of pharmacologic classes of ADDs. Physicians usually reserve ECT for treatment-resistant cases or when they determine a rapid response to treatment is desirable.

For those patients who do not respond to initial antidepressant treatment, physicians generally use one or more of the following strategies: (1) switching to an alternative first-line ADD, (2) switching to a second-line ADD, (3) adding psychotherapy, a second ADD, or an augmentation agent. Augmentation agents are drugs that are not generally considered to have significant antidepressant activity when administered alone, but they can enhance the effectiveness of an ADD when they are administered in combination with the ADD. Augmentation agents include drugs such as lithium or atypical antipsychotic drugs. Additional options for treatment-resistant patients, especially for patients who fail on the above alternatives, include monoamine oxidase inhibitors and ECT. For treatment-resistant cases that exhibit a marked seasonal pattern, adding phototherapy to pharmacotherapy may also be an option.

VI. MARKETING HISTORY

A. Foreign Marketing History

Since June 1994, the VNS Therapy System has been approved as treatment for epilepsy in all countries of the European Union. In March 2001 CE Mark Approval was granted for the treatment of depression in all European Community (EC) countries. Subsequently, in April 2001 Cyberonics began distribution of the VNS System for the treatment of depression in Canada. The VNS Therapy System has not been withdrawn from marketing in any country outside the United States for any reason, including those related to the safety or effectiveness.

B. U.S. Marketing History

Since July 1997 the VNS Therapy System has been approved for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory partial onset seizures. The VNS Therapy System has not been withdrawn from marketing in the U.S. for any reason related to the safety or effectiveness.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In addition to the normal risks associated with a surgical procedure, complications associated with implantation include, but may not be limited to, vagus nerve damage; skin irritation; pain at the incision site; infection; extrusion or migration of the pulse generator and/or lead dislodgment, disconnection (from pulse generator), breakage (lead), or corrosion; hematoma; fluid accumulation; cyst formation; inflammation; and histotoxic reactions. These phenomena may require device replacement to correct the complication. A pivotal clinical trial of 235 subjects (D-02) was conducted by the sponsor to evaluate the safety and effectiveness of the device for the intended use. The number (and percentage) of subjects reporting an event during the 0-3 month period and during the 9-12 month period is depicted in Table 1 below.

Table 1 – Adverse Events Associated With VNS Therapy at 0-3 Months and 9-12 Months

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%)

VIII. PRE-CLINICAL STUDIES

A. Summary of Non-Clinical Laboratory Studies

1. Pre-Clinical Laboratory and Animal Studies

A summary of these studies can be found in the Summary of Safety and Effectiveness document for P970003 (epilepsy indication). No additional pre-clinical or animal studies were required for this application.

2. Risk Analysis

The commercially available system's risk analysis was re-evaluated for treatment-resistant depression (TRD). Since subjects undergo the same implantation procedure using the same system, no new surgical risks were identified. The sponsor evaluated the potential risks associated with patients who are implanted and are having a TRD episode. The risks associated with this population include suicide attempt/suicide, manic depressive reaction, anxiety, confusion, overdose, and worsening depression. No design related mitigation solutions could be developed.

IX. SUMMARY OF CLINICAL INVESTIGATIONS

Cyberonics has conducted the following studies to support the use of the VNS System in subjects with treatment-resistant depression:

- a feasibility trial (D-01);
- a randomized, sham-controlled 3-month clinical trial (D-02, acute)
- a long-term (12-and 24-month) open-label extension (D-02, long-term); and
- a long-term (12-month) observational study of subjects receiving standard-of-care treatments (D-04) for comparison to D-02 long-term.

1. Feasibility Study D-01

D-01 was an open-label, nonrandomized, single arm, multicenter, 60-patient study of VNS in treatment-resistant major depression. The study included an acute 12-week phase as well as a subsequent long-term follow-up. Patients were required to maintain a stable antidepressant medication regimen during the acute phase of the study.

The most commonly reported treatment-emergent adverse events, regardless of relationship to stimulation (in order of frequency) were: voice alteration (75%), neck pain (32%), depression (27%), headache (27%), dyspnea (23%), dysphagia (18%), increased cough (17%), nausea (15%), dyspepsia (12%), and dizziness (10%). Seventy-seven (77) events in 38 subjects were rated as serious (10 in acute phase and 67 in long-term follow-up) including 34 reports of worsening depression and 12 suicide attempts or overdose.

Fifty-nine of the 60 subjects completed the 12-week acute phase and were available for evaluation of effectiveness. Primary efficacy analysis of the 28-item Hamilton Rating Scale for Depression (HRSD₂₈) at the end of this phase showed 18 (31%) of the 59 evaluable subjects met response criteria ($\geq 50\%$ reduction in score as compared to baseline). In addition, 25 of 55 (45%) were responders after one year, and 18 of 42 (43%) after two years. Furthermore, after one year of stimulation, 13 of the 18 acute responders (72%) maintained their response and 12 of the acute non-responders (29%) became responders. Of the subjects included in the evaluable population, 15%, 27% and 21% reached remission (HRSD₂₈ ≤ 10) at 12 weeks, 1 year, and 2 years, respectively.

2. Pivotal D-02 Study and D-02/D-04 Comparison Study

The acute phase of D-02 was a 12-week, double-blind, randomized, sham treatment-controlled, multi-center, pivotal study where subjects were implanted with the VNS System and randomized to either the treatment (stimulation) group or control (sham) group. Two weeks after surgery, treatment group subjects had the device turned ON and the output current adjusted to a tolerable level during a 2-week period. Sham subjects were treated identically; however, the output current of the device was set at 0.00 mA throughout the acute phase. The treatment group subjects' stimulation parameters remained constant for the remainder of the acute study (8 weeks) but were permitted to be decreased to accommodate for events possibly related to tolerance. During the acute phase of the study, antidepressant medications were to remain unchanged from baseline.

After completion of the 12-week acute phase, subjects could continue in an open-label long-term phase (D-02, long-term), during which time subjects in the treatment group continued VNS therapy and stimulation was initiated for subjects originally in the sham-control group. Sham subjects followed the same treatment schedule that the treatment group received during the acute

phase. Following the acute phase, changes in concomitant treatments (medications and ECT) were permitted.

D-04 was a long-term, observational, prospective study designed to collect data regarding usual standard-of-care (SOC) treatment for TRD in people who were in a major depressive episode at the time of admission. The usual SOC was defined as the treatment strategy the physician and subject chose to follow. Clinical depression assessments and quality of life outcomes were assessed at baseline, 3, 6, 9 and 12 months. D-04 was intended to provide a comparison group for the D-02 long-term analysis. *Safety data were not prospectively collected in D-04.*

a) Inclusion/Exclusion Criteria

D-02 and D-04 Inclusion criteria

- Age 18-80
- In a chronic (≥ 2 years) current major depressive episode (MDE) and/or have had a history of recurrent MDEs (> 4 lifetime episodes, including current) per DSM-IV.
- HRSD₂₄ score ≥ 20 at the acute phase baseline.
- Failed 2-6 mood disorder treatments from different treatment categories as determined by an Antidepressant Resistance Rating (ARR) score of 3 or higher using the modified version of the Antidepressant Treatment History Form)
- Continuation criteria required an HRSD₂₄ score ≥ 18 .
- History of treatment with psychotherapy > 6 weeks without improvement (D02 only)
- Stable medication regimen of not more than 5 medications for at least 4 weeks prior to the baseline visit (D02 only)
- Adequate contraception (D02 only).

Exclusions for both studies included:

- Atypical depression or psychotic symptoms;
- Schizophrenia, schizoaffective disorder, or delusional disorders;
- Rapid cycling; delirium, dementia, amnestic, or other cognitive disorders;
- Not having an acceptable clinical response due to failure with ≥ 7 antidepressant treatments during the current MDE;
- Recent suicide attempts (or suicide risk/plan) within 12 months;
- Recent alcohol or substance dependence or abuse (other than nicotine);
- Other progressive neurological disease, significant CNS disease or injury;
- Current enrollment in another investigational study or using an investigational device;
- History of, or evidence of, significant brain malformation or significant head injury, clinically apparent cerebral vascular events, prior brain surgery such as cingulotomy; or previous implantation with the VNS.
- Myocardial infarction or arrest, general anesthesia within 30 days, ASA III or IV, pacemaker or other implantable stimulator, likely to require MRI or diathermy (D-02 only)

b) Concomitant Mood Disorder Treatments

D-04 subjects were allowed to have mood disorder treatments changed according to the investigator and subject's determination of the best treatment regimen. For the D-02 study, continuation of stable baseline mood disorder treatments was allowed. *Changes* to these treatments were not allowed during the 12-week acute phase but were allowed during the long-term phase, although such changes were discouraged.

c) **D02 and D04 Study Accountability and Subject Population**

D02 Subject Accountability

Of the 235 subjects who were enrolled and randomized in the Acute D-02 study, 2 subjects withdrew during the acute phase (including 1 suicide), 2 additional subjects did not complete the acute study, and 9 were either protocol violations or failed to meet Visit 2 continuation criteria. Therefore, at the end of the acute phase of the D-02 study, 222 subjects were evaluable for effectiveness with 112 from the treatment group and 110 from the sham-control group.

A total of 233 subjects entered the long-term phase of D-02. During this phase, 28 subjects were deemed to be not evaluable for effectiveness for the following reasons:

- No effectiveness data included at any long-term visit 4
- Did not meet acute phase continuation criteria 3
- Did not have acute exit HRSD score ≥ 18 if in sham group 21

A total of 205 subjects were therefore *evaluable* for effectiveness at the end of the D-02 long-term phase study (110 from the original treatment group and 95 from the original sham group) and 209 were evaluable for safety. Of these, 28 did not complete 12 months of follow-up for the following reasons:

- Withdrew before 1 year of stimulation 17
- Reached 1 year but device was ON < 80% of time 6
- Did not have 1 year assessments/records 5

The most common reason cited for early withdrawal was lack of effectiveness. In the end 177 *12-month stimulation completers* (103 from the original stimulation group and 74 from the original sham group) contributed to the effectiveness analysis for the long-term D-02 and D-02/D-04 comparison.

D04 Subject Accountability

For the D04 study, 138 subjects were enrolled. Of these, 11 discontinued and 3 only provided baseline data. As such, 124 subjects were included in the *evaluable* population for this portion of the study. Of these 124, 112 were 12-month *completers* which provided effectiveness data.

D02 and D04 Subject Demographics

Table 2 lists baseline demographics of the evaluable D-02 and D-04 subjects.

Table 2. D02, D04 Comparison of Demographics (Evaluable Subjects)

Parameter	Statistic	D02 (N=205)	D04 (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.

d) Safety Data**Acute Phase Adverse Events****Implantation-Related**

Some acute phase adverse events were noted and judged to be implant-related (due to the surgery). These included the following events (based on N=235): Incision Pain, 84 (36%); Voice Alteration, 78 (33%); Incision Site Reaction 67 (29%); Device Site Pain, 54 (23%); Device Site Reaction, 33 (14%); Pharyngitis, 31 (13%); Dysphagia 26 (11%); Hypesthesia, 25 (11%); Nausea, 20 (9%); Dyspnea, 20 (9%); Neck Pain, 16 (7%); and Increased Cough, 15 (6%).

Stimulation-Related (Device-Related)

Table 3 reports adverse events during the acute randomized phase of D-02 which occurred in the active stimulation group at rates $\geq 3\%$ and were judged at least possibly related to stimulation.

Table 3. Incidence of Treatment-Emergent Adverse Events \geq 3% in Acute Phase of D-02

Event	Treatment (N=119) N (%)	Sham- control (N=116) N (%)
Voice alteration	65 (55%)	3 (3%)
Cough increased	28 (24%)	2 (2%)
Dyspnea	23 (19%)	2 (2%)
Neck pain	19 (16%)	1 (<1%)
Dysphagia	15 (13%)	0
Laryngismus	13 (11%)	0
Paresthesia	12 (10%)	3 (3%)
Pharyngitis	9 (8%)	1 (<1%)
Nausea	8 (7%)	1 (<1%)
Incision Pain	6 (5%)	3 (3%)
Headache	5 (4%)	1 (<1%)
Insomnia	4 (3%)	0
Dyspepsia	4 (3%)	0
Diarrhea	3 (3%)	0
Palpitations	3 (3%)	1 (<1%)
Dizziness	3 (3%)	0
Chest Pain	3 (3%)	1 (<1%)

Duration of Early Adverse Events

For the 7 events which occurred at a frequency \geq 10% in the VNS Therapy group during the acute randomized phase of the study (Table 3), further analysis was performed to determine how long these events persisted in subjects. Table 4 shows a cohort of subjects who reported the 7 most common adverse events during their first 3 months of stimulation and who also had follow-up visits during months 9 through 12. Numbers in the last 3 columns refer to the number (and percentage) of subjects who had the event between months 0-3 (second column) who continued to have the symptom at the latter point.

Table 4. Persistence of Early Stimulation-Related Events Through One Year (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.
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%)

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.

Late-Emerging Adverse Events

New adverse events first reported after the first 3 months of stimulation were assessed by the sponsor. Only event types which were *not* reported by any subjects during the first 3 months were included in this data set. Hence, new reports of voice alteration, neck pain, and the like were not included in this analysis. The new events included syncope (3), gastritis (3), weight gain (3), deafness (2), colitis (2), and 1 of each of the following: stridor, hypotension, speech disorder, back pain, weight loss, arthralgia, myalgia, amblyopia, and viral or flu infection.

Serious Adverse Events (SAE)

A serious adverse event was defined as one that resulted in death, was life-threatening, resulted in or prolonged hospitalization, resulted in a persistent disability, or involved a congenital anomaly. All events were reported regardless of relationship to VNS Therapy.

SAE During Acute Phase of D-02

In the acute D-02 study, there were 30 SAEs in 27 subjects. One death due to suicide occurred in an active stimulation subject. The following SAE occurred more than once.

- Worsening Depression 12 events in 11 subjects (5 treatment, 7 control subjects)
- Site Reaction 2 events in 2 subjects (2 treatment subjects)
- Pneumonia 2 events in 2 subjects (1 treatment, 1 control subject)
- Dehydration 2 events in 2 subjects (1 treatment, 1 control subject)

In addition, the following were reported once in the treatment group alone: asystole, bradycardia, confusion, abnormal thinking, wound infection, and urinary retention. The following SAE were reported once in the control group alone: renal failure, vocal cord paralysis, cholecystitis, voice alteration, and myasthenia.

SAE in the Long-Term Phase of D-02

In the D-02 long-term phase there were 96 SAE . These events are shown in Table 5 below.

Table 5 – Serious Adverse Events in Long-Term D-02

Event	# of Events	# Subjects
Worsening Depression	62	31
Suicide Attempt	7	6
Syncope	4	3
Convulsion	2	2
GI Disorder	2	2
Sudden Unexplained Death	1	1
Chest Pain, Abdominal Pain, Peritonitis, Cholecystitis, Constipation, Dehydration, Dizziness, Drug Dependence, Manic Depression, Somnolence, Abnormal Thinking, Overdose, Accidental Injury, Breast CA, Wound Infection, Surgical Procedure, Enlarged Uterine Fibroid, Cholelithiasis	1 each (18)	18

Deaths

Four deaths were reported. One occurred prior to implantation/stimulation. Two deaths occurred after device implantation and prior to the 12 month follow-up. One was a suicide during the acute phase (in the treatment group) and one was listed as “undetermined” cause. The latter occurred approximately 2-3 months after implantation and stimulation. An additional death occurred after 12 months of follow-up and was due to acute brain injury.

Specific Depression-Related Adverse Events

Mania/Hypomania

The Young Mania Rating Scale (YMRS) was used to detect the emergence of mania in the D-02 study. Three (3) subjects had a manic reaction reported. Another 3 had YMRS > 15 during the long-term phase without an adverse event being reported. Two of the six patients had their event during the acute phase and 5 of the 6 had a prior history of bipolar disorder or mania. One subject’s mania was classified as a serious adverse event.

Worsening Depression

In the acute phase 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 12-month period of stimulation, 62 events were reported in 31 subjects. The number of episodes or worsening depression per patient ranged from 1 to 6. Of note, rates of worsening depression (and other safety endpoints) were not collected during the D04 study for direct comparison. However, the item of “hospitalizations for psychiatric illness” which might be used as a surrogate for worsening depression was captured in D04. The rate of such was 0.237 events per patient-year in the D04 group (n=124 subjects) compared to 0.284 in the 1-year D02 group (n=233 subjects) and 0.314 in the D-02 sham group (n=116 subjects).

Suicidal Ideation and Suicide.

One way in which the sponsor analyzed change in suicidal ideation was to look at Item 3 of the HRSD₂₄ score. During the acute D-02 study, 2.6% of sham subjects and 1.7% of the stimulation subjects increased their Item 3 score by 2 or more points. During the long-term D-02 phase, 2.8% of subjects had increased their Item 3 score by at least 2 points at 12 months versus baseline. In

the D-04 group, this was 1.9%. Conversely, 27% of D-02 subjects decreased their score by at least 2 points at 12 months compared to baseline whereas only 9% of D-04 subjects did.

As noted above, 1 subject committed suicide in the acute phase and 6 attempted suicide during the 12 months of the long-term stimulation phase of D-02 (n=235). One of the 6 subjects noted in the long-term phase attempted suicide twice. Although safety data were not formally collected for the D-04 study, the health care utilization form documented suicide attempts. There were 3 suicide attempts in this group through the first year (n=124).

e) Effectiveness Data

D02 Acute Study

The primary effectiveness endpoint for the randomized, sham-controlled study was an analysis of the percent responders ($\geq 50\%$ decrease in HAM-D (Hamilton) score from baseline to exit) between the 2 groups. In an evaluable patient population, 15.3% (17/111) of the active stimulation group were considered responders as compared to 10.0% of the sham group (11/110). This difference was *not* statistically significant (p=0.238).

Secondary endpoints of the acute phase study assessed changes in other depression scales (IDS-SR, CGI, MADRS, SF-36). The IDS-SR scale revealed a significant difference in the percent responders (17.4% versus 7.5%, p=0.032). None of the other scales (CGI, MADRS, YMRS, SF-36) identified as secondary endpoints, however, showed a statistically significant difference.

After completing the analysis of this acute phase data, an alternate statistical plan for demonstrating effectiveness was employed that included comparison of 12 month results of the D-02 continuation phase to the results of the D-04 observation study (see below).

D02 Long-Term Phase

The primary endpoint for the evaluation of the long-term phase of D-02 was a repeated measures linear regression analysis performed on the raw HAM-D (HRSD₂₄) scores during the first 12 months after initiation of stimulation on the 12 month completer population. This was calculated as the average of the slopes across the 4 quarters with each quarter having equal weight. As a secondary endpoint, similar data was assessed using the IDS-SR scale. These results are shown in Table 6.

Table 6. D-02 Long-Term Primary Effectiveness Results

	N	Slope	p-value
12-Month Completer Population	177		
HAM-D		-0.47/month	<0.001
IDS-SR		-0.55/month	<0.001
12-Month Evaluable Population	205		
HAM-D		-0.45/month	<0.001
IDS-SR		-0.52/month	<0.001
12-Month Intent-to-Treat Population	231		
HAM-D		-0.40/month	<0.001
IDS-SR		-0.45/month	<0.001

Patients were also assessed in terms of response rates as a secondary endpoint. Again, response was defined as a 50% of more improvement in a scale's score at 12 months compared with

baseline. Complete response (or remission) was defined as a score ≤ 9 for HAM-D and ≤ 14 for IDS-SR. These results at 12 months are shown below in Table 7.

Table 7. 12-Month Evaluable Responder and Remission Rates

	Response	Remission
HAM-D	29.8%	17.1%
IDS-SR	21.7%	15.0%

Sustained Response

The evaluable population was assessed over the last 4 visits of the first year (months 9, 10, 11, and 12) to ascertain which subjects were “sustained responders” (defined as ≥ 1 visit with $\geq 50\%$ response and at least an additional 2 visits with $\geq 40\%$ response). Using this definition, 27% (47/177) of the 12-month completer population were considered sustained responders.

To explore whether subjects were receiving benefit that was not fully reflected in these response rates, subjects were assigned to “clinical benefit” categories prospectively defined as extraordinary benefit ($\geq 75\%$ improvement in HRSD₂₄), highly meaningful benefit (50-74%), meaningful benefit (25% -49%), minimal/no benefit (0%-24%), and worsened ($<0\%$). At 12 months, the percentage of evaluable subjects (n=180) in each of these categories was as follows:

- Extraordinary Benefit 10.6%
- Highly Meaningful Benefit 20.0%
- Meaningful Benefit 25.0%
- Minimal or No Benefit 26.7%
- Worse 17.8%

As can be seen after 12 months, 56% of *evaluable* D-02 patients were realizing at least a meaningful clinical benefit. This includes 57 (out of 122) subjects who were originally rated as minimal to worse at 3 months.

For the long-term D-02 subjects who were considered HRSD responders after 12 months of stimulation, data depicting scores over time were further analyzed. Table 8 below describes some long-term response characteristics of these subjects who were regarded as “responders”.

Table 8 – HRSD Responder Characteristics

	Number of Subjects	% of Responders (N=54)
Had \geq 50% of all assessments as responder	31	57.4%
Had \geq 75% of all assessments as responder	9	16.7%
Had last 2 consecutive months as responder	34	63.0%
Had last 3 consecutive months as responder	24	44.4%
Able to reduce/eliminate antidepressant medications	7	13.0%

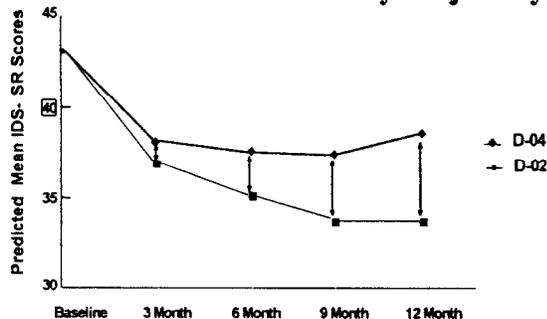
Response by Diagnosis

Separate analyses for both unipolar and bipolar groups were performed and found to show identical results for the evaluable, ITT, or 12 month completer populations. Most of the unipolar analyses retained statistical significance although the bipolar group sample size was too small for most of the outcomes to reach statistical significance.

D02/D04 Comparisons

The efficacy analysis for the D02-D04 comparative analysis was the comparison of the change over time (slope) of the IDS-SR raw scores across 12-months with a repeated measures linear regression model. A statistically significant difference ($p < 0.001$) was demonstrated in the estimated IDS-SR raw scores per month between the D02 and D04 evaluable populations (-0.397 estimated average difference per month). The outcome result is presented graphically in Figure 2 below.

Figure 2. IDS-SR Scores D-02 Versus D-04 Study Subjects by Quarter



	B/L	3 mos	6 mos	9 mos	12 mos
Mean D-04 Scores (N=124)	43.0	38.1 (N=120)	37.5 (N=119)	37.3 (N=116)	38.5 (N=112)
Mean D-02 Scores (N=201)	43.0	36.9 (N=200)	35.1 (N=195)	33.7 (N=183)	33.7 (N=177)

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

Baseline demographic and illness characteristic differences were controlled in the repeated measures linear regression analysis by incorporating the 5-level grouped propensity score. This 5-level grouped propensity score did not contribute to the statistical significance of the outcome

(p = 0.831). Based on this analysis, the observed baseline demographic and illness characteristics did not contribute to the difference in outcome between the D-02 and D-04 populations.

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

IDS-SR and HRSD₂₄ 12-Month Results

Tables 9 and 10 below show results of IDS-SR and HRSD₂₄ evaluations at 12 months for both the D-02 and D-04 long-term evaluable populations.

Table 9. IDS-SR Scores – D-02/D-04 Evaluable Observed Populations

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

Table 10. HRSD₂₄ Scores – D-02/D-04 Comparisons Evaluable Observed Populations

	D-02	D-04	P-Value
N	180	104 ¹	
Baseline Average	27.9	27.8	
12 Month Data			
Average	19.6	22.8	
Median	19.5	23.5	
Average Change	-8.2	-4.9	0.006
LOCF Average Change	-7.4 (N=205)	-4.9 (N=104)	0.040
Median Change	-7.5	-5.0	
Avg. % Change	29.6	16.6	
Median % Change	28.4	15.6	
Response (% of Subjects)	30	13	0.003
LOCF Response (% of Subjects)	27 (N=205)	13 (N=104)	0.011
Complete Response (% Subjects)	17	7	0.031
LOCF Complete Response (%)	16 (N=205)	7 (N=104)	0.059

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

Censored Analysis (D-02 versus D-04 Comparison)

IDS-SR and HRSD₂₄ 12-Month Results after Censoring for Concomitant Treatments

Medication changes and ECT treatments were permitted in D02 subjects following the 12-week acute phase portion of the study. A total of 14 D-02 subjects received ECT during the long-term phase. ECT was used more frequently in non-responders. Four of the 14 subjects were responders, two of which were complete responders; none of the subjects were sustained responders (HRSD₂₄). Only one responder received ECT in proximity to the 12-month visit. Seven (7) D-04 subjects received ECT through 12-months. Two of these 7 were responders at 12-months. To ascertain mood medication changes over the course of the long-term phase, an antidepressant resistance rating (ARR) score was determined for each medication for each subject. More D-02 non-responders (77%) and D-04 subjects (81%) than D-02 responders (56%) added or increased mood medications during the 12 months of VNS Therapy.

An additional post-hoc analysis was performed comparing D02 and D04 subjects after censoring the D02 patients at the first time of a significant addition or change in antidepressant treatment and using the IDS score obtained just prior to this change for all subsequent visits. With this analysis, the difference observed in the estimated IDS-SR raw scores per month between D02 and D04 evaluable populations at 12 months was -0.183 which was not statistically significant ($p=0.052$). In addition, the response rate for the HSRD endpoint decreased from 30% to 19.9%. This censored rate for HSRD was not statistically different from the D04 group response rate (13%, $p=0.118$). Differences in response rates using the IDS-SR scale also were not significant after censoring (18% versus 12%, $p=0.085$)

Sustained Response at 12 Months

As IDS-SR scores were collected only quarterly in the D-04 group, sustained response for comparison of the two groups was defined as a 50% improvement or better at the last two measured quarters (IDS-SR at 9- and 12-months compared to baseline). Statistically significantly more evaluable D-02 subjects (13%) had sustained response than D-04 subjects (4%) [$p = 0.005$] using this definition.

CGI-I (Clinical Global Impression – Improvement)

Thirty-seven percent (37%) of evaluable D-02 subjects were rated as much improved or very much improved at 12 months compared to D-04 subjects (12%; $p < 0.001$).

Other Statistical Analyses of D-02/D-04 Data

An intent-to-treat (ITT) analysis included 231 D-02 subjects and 124 D-04 subjects. The ITT analysis results of the efficacy model were statistically significant ($p < 0.001$). An LOCF analysis uses the last available observation for subsequent time points where data are missing. LOCF analyses were performed on all D-02/D-04 secondary comparisons, and statistical significance was maintained for all comparisons except for the IDS-SR evaluable response rates and HRSD₂₄ evaluable complete response rates; in these latter two analyses, the results were not statistically significant ($p=0.108$ and 0.059 respectively).

Since the D-02 and D-04 studies had some different sites the results were examined from sites that were only involved in both the D-02 and D-04 studies. This examination (using the HRSD₂₄) yielded results similar to the analysis that included all sites (27% HRSD₂₄ 12-month responder rate for D-02 sites that also participated in D-04 vs. 30% for all D-02 sites). A formal statistical analysis was not performed because the decreased sample size would not ensure adequate power.

SUPPLEMENTAL DATA

Although not provided in the original PMA, the sponsor submitted additional information to FDA in a PMA Supplement following the Advisory Panel Meeting. This information is summarized below.

2-Year Response Rates

The sponsor provided 2-year HRSD effectiveness data on 199 subjects including 42 from D-01 (feasibility) and 157 from D-02 (pivotal) representing 75% of the evaluable subjects and 67% of the implanted patients combined from both studies. Table 11 below shows HRSD response and complete response rates at 24 months as well as 3 and 12 months for evaluable subjects.

Table 11. Evaluable D-01 and D-02 HRSD Response Rates 3-24 Months

	D-02	D-01	Combined
3 Months	N=205	N=59	N=264
Responder	30 (14.6%)	18 (31%)	48 (18.2%)
Complete Responder	15 (7.3%)	9 (15%)	24 (9.1%)
12 Months	N=181	N=55	N=236
Responder	54 (29.8%)	25 (45%)	79 (33.5%)
Complete Responder	31 (17.1%)	15 (27%)	46 (19.5%)
24 Months	N=157	N=42	N=199
Responder	51 (32.5%)	18 (43%)	69 (34.7%)
Complete Responder	27 (17.2%)	9 (21%)	36 (18.1%)

The sponsor further evaluated D-02 subjects at 2 years in terms of “clinical benefit” categories based on changes in HRSD scores. This information is included in Table 12 below.

Table 12 – “Clinical Benefit” at 3, 12 and 24 Months for Evaluable D-02 Subjects

	3 Months (N=205)	12 Months (N=180)	24 Months (N=157)
< 25% Improvement (Minimal Benefit)	142 (70%)	80 (44%)	69 (43%)
25-49% Improvement (Meaningful Benefit)	33 (16%)	45 (25%)	36 (23%)
50-74% Improvement (Highly Meaningful Benefit)	21 (10%)	36 (20%)	37 (24%)
>75% Improvement (Extraordinarily Meaningful Benefit)	9 (4%)	19 (11%)	15 (10%)

As can be seen in the table above, at 24 months, 57% of evaluable subjects received at least meaningful benefit and 34% received at least a highly meaningful benefit. In an ITT analysis, however, these percentages are 38% and 23% respectively.

It should be noted that changes and additions in concomitant medications and ECT were allowed from 3 months through this 24 month follow-up and the impact of these changes is unknown.

2-Year Sustained Response

An analysis was also performed to evaluate “2-year sustained response.” Sustained response was defined as 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, respectively). Of the 30 subjects who were 3-month responders, 18 (60%) maintained

responder status at 12 months and 21 (70%) maintained responder status at 24 months. Of the 54 12-month responders, 37 (69%) were also responders at 24 months. Similar rates are seen with IDS data (61%, 57%, and 85% respectively).

New Analysis of Medication Changes

The sponsor performed an additional analysis on antidepressant medications in D-02 subjects. For this analysis, evaluable subjects with an increase in antidepressant medication were compared to subjects who had no increase in antidepressant medication. A total of 48 evaluable subjects had no increase in antidepressant medication while 157 did have an increase over one year of VNS therapy. At 12 months, 50% of the subjects without increase in medications were responders as compared to 23% of the subjects who did have an increase in medications.

2-Year Therapy Continuation Rates

At one year, 98% (59/60) of D-01 subjects and 90% (211/235) of D-02 subjects continued to receive VNS therapy. At 2 years, 87% (52/60) of D-01 subjects and 81% (190/235) of D-02 subjects continued with VNS therapy.

Adverse Event Update

Five (5) new events judged to be related to stimulation were noted between 12 and 24 months that were not reported in the time prior: back pain, cerebral ischemia, hyperventilation, sinusitis, and urinary frequency. The rates of the most common non-serious adverse events after 18 and 24 months of follow-up are shown in Table 13 below.

Table 13. Most Common Adverse Events at 18 and 24 Months

Event	18 Months (N=200)	24 Months (N=184)
Voice Alteration	100 (50%)	95 (51.6%)
Neck Pain	27 (13.5%)	28 (15.2%)
Dyspnea	28 (14.0%)	25 (13.6%)
Laryngismus	9 (4.5%)	10 (5.4%)
Pain	15 (7.5%)	10 (5.4%)
Dysphagia	6 (3.0%)	9 (4.9%)
Increased Cough	14 (7.0%)	8 (4.3%)
Pharyngitis	9 (4.5%)	8 (4.3%)
Paresthesia	6 (3.0%)	7 (3.8%)

No reports of mania were recorded between 12 and 24 months of stimulation.

Serious Adverse Events

Table 14 below depicts the updated number of events of worsening depression and suicide attempts by the quarter in which the event was reported known to the sponsor as of 10/10/03.

Table 14. Worsening Depression and Suicide Attempts per Quarter of Stimulation

Quarter after Start of Stimulation		Number of Events of Worsening Depression	Number of Suicide Attempts
Year 1	1 st	13	2
	2 nd	19	3
	3 rd	13	2
	4 th	14	1
Year 2	5 th	8	1
	6 th	6	0
	7 th	5	1
	8 th	5	0
TOTAL		83	10

The 83 events of worsening depression were reported in 38 subjects and the 10 suicide attempts were reported in 9 subjects.

SAFETY DATA FROM EPILEPSY EXPERIENCE (Studies and Post Marketing Data)

The VNS Device has been approved and marketed in the United States for the treatment of refractory epilepsy since 1997. A summary of safety issues related to that use are provided here.

Therapeutic Side Effects and Tolerability

In the two randomized, double-blind, controlled epilepsy studies the following adverse events were found to occur more frequently acutely, in either High or Low stimulation, than in baseline in at least one of the two studies (E-03 Low Group Rate, E-05 High Group Rate): These results are shown in Table 15 below.

Table 15. Adverse Events in Epilepsy Studies

Event	E-03 Low Group ¹	E-05 High Group ¹
Voice Alteration	38.6%	72.6%
Cough	12.3%	52.6%
Throat Pain	7.0%	42.1%
Pain	Not Reported	33.7%
Dyspnea	10.5%	27.4%
Paresthesia	15.8%	24.2%
Dyspepsia	Not Reported	21.1%
Vomiting	1.8%	17.9%
Infection	3.5%	14.7%

¹High Group defined as receiving therapeutic stimulation

Analysis of Recent MDR Reports Submitted to FDA

An analysis was performed by FDA's Office of Biometrics and Surveillance (OSB) on all medical device reports (MDR) submitted for the VNS Epilepsy indication from July 1, 1997 through October 8, 2004. This analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. It should be noted that during this time, a total of 32,065 VNS Therapy device implants and 80,144 device years of implant experience had occurred.

Submission or an MDR report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer, or product caused or contributed to the events listed.

Deaths

A total of 524 deaths have been reported to FDA. Of these, 102 (20%) were of an “unknown cause.” Of those deaths with a reported cause the following were the most common etiologies:

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

Nine (9) of the deaths were reported from suicide and 39 occurred during sleep.

Serious Injuries

A total of 1,644 serious injuries have been reported by the sponsor. The most frequently reported serious injury was infection (525; 32%). Approximately 40% of these were known to have required device explantation. The second most common serious injury reported was increased seizure activity (324; 20%). Others included:

- vagus nerve injury (181; 11%) including vocal cord paralysis (109) and hoarseness (71);
- respiratory injuries (141; 9%) including sleep apnea (33), dyspnea (50), and aspiration (14);
- cardiac events (123; 8%) including tachycardia, bradycardia, palpitations, hypertension, hypotension, syncope, and asystole;
- pain (81; 5%) including chest and neck pain;
- gastrointestinal events (60; 4%) including dysphagia (24) and weight loss (24);
- depression (21; 1%)

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

Device Malfunctions

A total of 708 device malfunctions have been reported through the MDR system. Some of the most common malfunctions reported were high lead impedance (351), lead breakage (116), device failure (44), and device migration (20).

IX. CONCLUSIONS DRAWN FROM STUDIES

In conclusion, CDRH believes that the PMA applicant has provided reasonable assurance of safety and effectiveness based on valid scientific evidence as required by statute and regulation for the approval of a Class III medical device. CDRH has come to this conclusion because the sponsor has provided data that were systematically collected and analyzed which showed significant improvement from baseline over one and two years for a definable subset of the target population, and comparative data against a reasonably matched control which also showed sustained improvement over time.

X. PANEL RECOMMENDATION

On June 15, 2004, the Neurological Devices Panel, by a vote of 5-2, recommended that the Pre-Market Approval Application (PMA) for the VNS Therapy System for the treatment of chronic or recurrent treatment-resistant depression be found approvable with the following conditions:

1. Patients should have failed four or more trials of traditional treatment modalities for treatment-resistant depression (medications and ECT) prior to use of the device.
2. The device will be implanted by surgeons with appropriate training.
3. Training regarding device electronic programming will be provided for primary care providers.
4. Additional patient labeling for use of the device and identification card be provided.
5. A patient registry to collect clinical data will be established.
6. The physician labeling be revised regarding the following: 12 month open label follow-up, the variable effect of treatment, patient selection, and deletion of imaging claims.

XI. CDRH DECISION

CDRH concurred with the Panel's recommendation of June 15, 2004, and issued a letter to Cyberonics, Inc. on February 2, 2005, advising that its PMA was approvable subject to

1. Submission of complete protocols for two post-market clinical studies:
 - a. A 1-year, randomized dose-ranging study and
 - b. A 5-year observational registry study.
2. Revised physician and patient labeling
3. Resolution of Good Manufacturing Processes (GMP) inspection issues
4. Resolution of Bioresearch monitoring issues

In an amendment received by FDA on March 11, 2005, Cyberonics, Inc. submitted the required data. FDA issued an approval order on July 15, 2005. The applicant's manufacturing facility was inspected on June 10, 2005 and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XII. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.