SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Autonomic Nerve, Implanted for Epilepsy

Device Trade Name: VNS Therapy System

Device Procode: LYJ

Applicant's Name and Address: Cyberonics, Inc.
100 Cyberonics Blvd.
Houston, TX 77058

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970003/S207

Date of FDA Notice of Approval: June 23, 2017

The original PMA (P970003) was approved on July 16, 1997 and is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic medications. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the VNS Therapy System.

II. INDICATIONS FOR USE

The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications.

III. CONTRAINDICATIONS

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

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

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

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

Patients who have implanted Vagus Nerve Stimulators should not be exposed to diathermy treatment.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Cyberonics VNS Therapy System labeling.

V. DEVICE DESCRIPTION

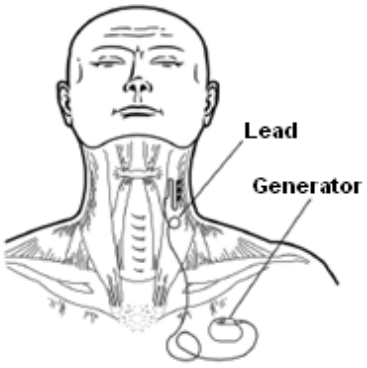
VNS Therapy® System
VNS Therapy® Pulse Model 102 Generator
VNS Therapy® Pulse Duo Model 102R Generator
VNS Therapy® Demipulse®, Model 103 Generator
VNS Therapy® Demipulse® Duo, Model 104 Generator
VNS Therapy® Aspire HC®, Model 105 Generator
VNS Therapy® Aspire SR®, Model 106 Generator
VNS Therapy® Lead Model 302
VNS Therapy® PerenniaDURA®, Lead Model 303
VNS Therapy® PerenniaFLEX®, Lead Model 304
VNS Therapy® Programming Wand Model 201
VNS Therapy® Software Model 250
VNS Therapy® Accessory Pack Model 502

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 (Model102 and l02R)

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 Model502

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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of refractory focal epilepsy in children: antiepileptic drugs (AEDs), responsive neurostimulation, and resective epilepsy surgery. If a child has failed three adequately dosed AEDs, alternative AEDs may be tried alone or in polytherapy. In people with epilepsy for whom medications are not effective or who have unacceptable medication related side effects, responsive neurostimulation or resective neurosurgery may be an option.

Responsive neurostimulation (RNS) therapy is adjunctive to AED therapy and involves the surgical implant of a small, battery-powered device in no more than two areas of the skull in which seizure activity has been identified. Responsive neurostimulation therapy is an adjunctive therapy in reducing the frequency of seizures in individuals 18 year of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and / or secondarily generalized seizures).

Resective neurosurgery for the treatment of epilepsy usually requires removal of removing or disconnecting the part of the brain that is triggering the seizures. In most cases, people who are treated with resective neurosurgery or responsive neurostimulation continue with AED therapy. Surgical approaches include focal brain resections, lobar or

multilobar resections, corpus callosotomy hemispherectomy, and multiple subpial transection.

VII. MARKETING HISTORY

A. US Marketing History

The FDA approved Cyberonics' patented VNS Therapy on July 16, 1997 (P970003) for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory partial onset seizures.

In June 2005 Cyberonics received FDA Approval to begin commercial distribution of the VNS Therapy System for the treatment of depression in the U.S.

B. Foreign Marketing History

Currently, the VNS Therapy System is commercially distributed in all member European Community (EC) countries, Argentina, Australia, Bahrain, Belarus, Brazil, Canada, Chile, China, Colombia, Costa Rica, Ecuador, Egypt, Hong Kong, Iceland, Iran, Iraq Israel, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Libya, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Qatar, Oman, Russia, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Arab Emirates, Uruguay, Venezuela and Yemen.

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

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Device-related serious adverse events have an overall incidence rate/person year of 4.25% in children ages 4-11.

Major device-related adverse events may include:
Flushing (5.3%)
Coughing (15.1%)
Injury (4.4%)
Dysphonia (2.7%)

Dyspnea (0.9%)
Diarrhea (0.9%)
Paresthesia (0.9%)

The following individual adverse events have a statistically significantly greater incidence rate in patients 4-11 years of age when compared to those ages 12-21 years and ages 21 years and older: increased frequency of seizures, infection, fibrosis, new seizure type, increased seizure duration.

For the specific adverse events that occurred in the clinical studies, please see Table 8 in Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical studies (bench and animal) previously submitted to FDA in the Original PMA application (P970003) and supplements continue to support the safety of the commercially available VNS Therapy System for pediatric patients. No additional preclinical studies were required to evaluate the safety of VNS Therapy for the treatment of this age group. The previously approved supplements which support the device and its components are listed below.

VNS Therapy® System (P970003)
VNS Therapy® Pulse Model 102 Generator (P970003/S40)
VNS Therapy® Pulse Duo Model 102R Generator (P970003/S47)
VNS Therapy® Demipulse®, Model 103 Generator (P970003/S76)
VNS Therapy® Demipulse® Duo, Model 104 Generator (P970003/S76)
VNS Therapy® Aspire HC®, Model 105 Generator (P970003/S119)
VNS Therapy® Aspire SR®, Model 106 Generator (P970003/S173)
VNS Therapy® Lead Model 302 (P970003/S40)
VNS Therapy® PerenniaDURA®, Lead Model 303 (P970003/S64)
VNS Therapy® PerenniaFLEX®, Lead Model 304 (P970003/S100)
VNS Therapy® Programming Wand Model 201 (P970003/S16)
VNS Therapy® Software Model 250 (P970003/S183)
VNS Therapy® Accessory Pack Model 502 (P970003/S39)

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant submitted data from four pre-market studies, a post-market study, and a database of clinical use, as listed below, to establish a reasonable assurance of safety and effectiveness of Vagus Nerve stimulation with VNS Therapy System for use in the US for ages 4-11 years, under the IDE submissions for each as indicated. Data from these clinical studies were the basis for the PMA approval decision.

The safety population included all patients 4 years of age and older who underwent implantation with the VNS Therapy System who:

- Participated in the E03, E04, E05, or E06 clinical trials;
- Participated in the Japanese PAS (initial implants only); or
- Had a record in the Cyberonics Post-Market Surveillance database.

Clinical study data from 847 patients were included in the safety population. Of these, 13.8% (n=117) of patients were 4-11 years of age, 23.5% (n=199) of patients were 12-21 years of age, and 62.7% (n=531) were >21 years of age. Post-market surveillance data with information on device relatedness for adverse events were available from 40,926 patients. Of these 18.9% of patients were 4-11 years (n=7,729), 22.9% (n=9,389) of patients were 12-21 years of age, and 58.2% (n=23,808) were >21 years of age.

Patients in the efficacy population included all patients in the safety population with refractory partial onset seizures who had at least 1 seizure recorded at baseline. Patients who were only in the post-market surveillance database were excluded from the efficacy analysis. In total, clinical study data from 663 patients were included in the efficacy analysis. Of these, 582 patients had 12-month efficacy outcome data (n=54 patients 4-11 years, n=126 patients 12-21 years, and n=402 patients >21 years of age).

Pediatric patients under 12 years of age participated in the E04, E06, and Japan PAS. The E03 and E05 studies consisted of patients >12 years of age. Baseline characteristics by age group are reported in Table 1. Both groups had similar rates of prior brain or epilepsy surgery (35.0% of patients 4-11; 34.3% of patients ≥12), however pediatric patients 4-11 years of age in the safety population were more likely to have only generalized seizures (49.6% of patients 4-11; 16.2% of patients ≥12 years). Note that the efficacy evaluation is limited to patients with partial onset seizures.

The studies/sources from which data were submitted are:

- Pre-market data from the E03, E04, and E05 clinical trials (described further below).
- E06: Randomized, parallel group, comparative study to compare the efficacy of VNS Therapy to antiepileptic drug (AED) treatment in reducing the frequency of seizures in children (age 17 or less). The study was initiated in October 2004 and completed in January 2010.
- Japan Post-Approval Study (PAS): Prospective, open label, post-approval study of all consecutive patients treated with VNS Therapy in Japan. Patients were implanted between July 2010 and December 2012.
- Cyberonics Post-Market Surveillance Database: Passively reported adverse events and device tracking data from patients implanted with the VNS Therapy System from November 1988 to September 2015. When assessing device relatedness, post-market data was restricted to reports starting in November 2006 when the post-market coding system was updated to include device relatedness.

The main study was the Japanese PAS, from which there were 30 patients aged 4 – 11 years. The other studies served as prior information to be leveraged within a statistical Bayesian hierarchical model.

The primary efficacy endpoint (of the efficacy analysis in the Japanese PAS) was a 50% reduction in seizures. 14/30 of 4-11 year olds in the Japanese PAS had that level of benefit. The adjusted estimate after leveraging from the other studies was 39% (95% confidence interval (CI): 28%, 52%). The median seizure reduction at 12 months from baseline (combining across all studies) was -24.7% in the 4-11 year age cohort, while the >12 year old cohort had a median reduction of seizure frequency of -40.4%. VNS is not likely to be as effective in children who have previously undergone epilepsy surgery.

Adverse event rate reporting includes information from patients who participated in the E03, E04, E05, or E06 clinical trials; Participated in the Japanese PAS (initial implants only); or had a record in the Cyberonics Post-Market Surveillance database. These sources were used to compare adverse events in the 4-11 years of age group to other age groups. Across these sources, infection rates were significantly higher in the pediatric ages 4-11 year patients in comparison to those 12 and older. For ages 4-11, there were 85 reports in 7729 patients (6.4% of all reports), versus in the ages 12-21, 67 per 9389 patients (3.44% of all reports).

Cardiac and Pulmonary Events, including Sudden Unexpected Death in Epilepsy (SUDEP) events, (from the E03, E04, E05, or E06 clinical trials, the Japanese PAS (initial implants only); or in the Cyberonics Post-Market Surveillance database since 2006), were lower in the 0-4 years of age group and in the 5-9 years of age group compared to other age groups (0.5 and 2.4 respectively, compared to 2.9 for all age groups). This difference was not statistically significant. There was no increased risk of pulmonary events identified in the 4-11 years age group.

Extrusion of the lead was significantly higher in the 4-11 years age group compared to other age groups, with 15/1328 in ages 4-11 years (1.13% of total reports) versus 5 (0.26% of all reports) in ages 12-21.

Two unique age-specific AEs were reported at a higher rate in the 4-11 year group in Study EO4: psychomotor hyperactivity in 3/16 (17.6%) and flushing in 5/16 (29.4%). The rate of psychomotor hyperactivity was no higher than that of the general population at that age.

A. Study Design

The studies/sources from which data were submitted are:

- E03-randomized, controlled
- E04-open label
- E05 – randomized, controlled with high and low stimulation arms (followed by X05, open-label continuation study of all enrolled in the E05 study).
- E06: Randomized, parallel group, comparative study

- Japan Post-Approval Study (PAS): Prospective, open label, post-approval study of all consecutive patients treated with VNS Therapy in Japan. Patients were implanted be- tween July 2010 and December 2012.
- Cyberonics Post-Market Surveillance Database: Passively reported adverse events and device tracking data from patients implanted with the VNS Therapy System from November 1988 to September 2015. When assessing device relatedness, post-market data was restricted to reports starting in November 2006 when the post-market coding system was updated to include device relatedness.

Source study summaries are below; see also Table 1 for an overview of these studies.

Patients were treated between June 1990 and December, 2012. The database for this Panel Track Supplement reflected data collected through December 2012 and included 847 patients. There were 134 investigational sites.

The data were obtained from six studies/sources, which had varying sample sizes and age groups. The main study for the current indication was the Japanese PAS, from which there were 30 patients aged 4 – 11 years. The other studies served as prior information to be leveraged within a statistical Bayesian hierarchical model. The hierarchical model was adjusted for age group (4-11 vs. ≥ 12), as well as study. Several additional models were fit as sensitivity analyses, after which the results were evaluated to be robust to modeling details.

Table 1: Studies Leveraged for Indication in 4-11 Year Old Patients

Study / Source	Study Design	Total # of Subjects	Age Range (years)	Primary Endpoints	Use in this PMA supplement
E-03	Double Blind, Active Control, Parallel, Multicenter, Prospectively Randomized Study	115	13-57 years Ages 4-11: n=0/115	• **Reduction in seizures/day** • **% patients with >50% response** • **Safety**	Historical efficacy: safety
E-04	Open Labeled (Non-Blinded), Longitudinal, Multicenter Study	123	3-63 Ages 4-11: n=17/123	• **Reduction in seizures/day** • **% patients with >50% response** • **Safety**	Historical efficacy: safety
E-05	Assessment of Vagus Nerve Stimulation (VNS) for adjunctive treatment of epilepsy patients who have refractory partial onset seizures with alteration of	199	13-60 (none aged 4-11,n= 35 aged 12-21).	• **Reduction in seizures/day** • **% patients with >50% response** • **Safety**	Historical efficacy: safety

	consciousness.				
XE5	E05 Extension - Long Term Follow-Up Study	199	13-60 (n=57) 4-11 (n=90) aged 12-21)	**Safety:** The primary objective of this study was to demonstrate that treatment with VNS Therapy is safe for use over extended time periods.	Historical efficacy: safety
E-06	Trial to Assess Vagus Nerve Stimulation Therapy vs. Anti-Epileptic Drug (AED) Treatment in Children With Refractory Seizures	39	17 and less: n=43 aged 4-11; n=22 aged 12-17.	• **Reduction in seizures/day** • **% patients with >50% response** • **Safety**	Historical efficacy: safety
JPAS		345	N=57 aged 4-11; n=90 aged 12-21	• **Reduction in seizures/day** • **% patients with >50% response** • **Safety**	Primary
PMS					Safety

Abbreviations: GES=Generalized Epileptic Seizures: JPAS=Japanese PAS: PE=Partial Epilepsy: PMS=Cyberonics Post Market Surveillance: Sz=Seizures: #=number implanted: Use=use for this submission. Historical: used as historical data for Bayesian efficacy analysis. Primary: used as primary data source for Bayesian analysis.

*For efficacy, only PE patients were included.

No core laboratory use, independent evaluators, and/or Data Safety Monitoring Board (DSMB)/Independent Data Monitoring Committee (IDMC) were used as part of these studies.

1. <u>E-03 Clinical Study</u>

Randomized, blinded, parallel, controlled study comparing the effect of two VNS Therapy stimulation paradigms (High and Low) on seizure rates in patients (ages 12-60 years) with refractory partial onset seizures (simple or complex). The study was initiated in June 1990 and completed in July 1993. The primary objective of the study was to demonstrate that stimulation of the vagus nerve reduces the frequency of partial onset seizures. Two weeks after implantation, patients were randomized to the High or Low stimulation group, and the pulse generator was activated. Patients in the High group received a higher frequency, greater pulse width, and higher duty cycle of stimulation compared to the Low group. The randomized treatment period that followed activation of the pulse generator lasted 14 weeks. Following the 14 week randomized treatment phase, the blind was broken and all patients were treated with High parameters during the long term follow-up treatment phase.

The pre-operative state control group was the 12-week baseline seizure frequency. This study's control group received VNS Therapy and therefore was included in the current analysis. The LOW parameters were chosen to provide some sensation to the patient, and thus protect the blinding of the study. Based on data from animal studies, it was hypothesized that this degree of stimulation would not

be effective; however, this could not be verified in humans before the study. (30 seconds on, shorter pulse width, lower frequency stimulation, 90 minute off period). The LOW control group was investigational and not a legally marketed alternative with similar indications for use.

2. E-04 Clinical Study

This was a prospective, open label study of adjunctive VNS Therapy in patients (ages >2 years) with refractory seizures (partial onset or generalized). The study was initiated in September 1991 and completed in June 1996. The primary objective of this study was to demonstrate that stimulation of the vagus nerve reduces the frequency of seizures. Two weeks after implantation, the pulse generator was activated to parameters consistent with the High group from the E03 study. Following activation, patients were followed monthly for the first 3 months, every 3 months for the first year, and every 6 months until study termination. At each visit, safety and efficacy data were collected.

The pre-operative state control group was the 12-week baseline seizure frequency.

3. E-05 Clinical Study

This was a randomized, blinded, parallel, controlled study comparing the effect of two VNS Therapy stimulation paradigms (High and Low) on seizure rates in patients (ages 12-65 years) with refractory partial onset seizures (complex partial or secondarily generalized). The study was initiated in January 1995 and completed in August 1996. The primary objective of this study was to demonstrate that stimulation of the vagus nerve is effective as an adjunctive therapy in reducing the frequency of seizures in epilepsy patients who have medically refractory partial onset seizures with alteration of consciousness. This study was designed to confirm the efficacy and safety of vagus nerve stimulation established in the controlled portion of the E-03 Study. Two weeks after implantation, patients were randomized to the High or Low stimulation group, and the pulse generator was activated. Patients in the High group received a higher frequency, greater pulse width, and higher duty cycle of stimulation compared to the Low group. The randomized treatment period that followed activation of the pulse generator lasted 14 weeks. After the 14 week randomized treatment phase, patients were exited to the open label XE5 study for long-term safety and efficacy monitoring.

The pre-operative state control group was the 12-16 week baseline seizure frequency. This study's control group received VNS Therapy and therefore was included in the current analysis. Placebo-controlled trials of vagus nerve stimulation are difficult because patients can sense stimulation of the vagus nerve. Further, even the lowest levels of stimulation may have a therapeutic effect. To protect the blind and control for the effects of surgery, all patients were implanted with the VNS Therapy System and the LOW group received what is believed to

be a less effective treatment: 30 seconds of shorter pulse width, lower frequency stimulation, followed by a 180 minute OFF period. The treatment HIGH group received what is believed to be a more effective treatment - 30 seconds of longer pulse width, higher frequency stimulation followed by a 5 minute OFF period. The LOW control group was investigational and not a legally marketed alternative with similar indications for use.

4. XE5 Clinical Study

   This was a prospective, open label study of patients who completed the randomized treatment period of the E-05 Study. The study was initiated at the conclusion of the E□05 clinical study and was completed in January 2002; visit 1 of the XE5 study occurred on the same day as the final visit of the E-05 clinical study. The primary objective of this study was to demonstrate that treatment with VNS Therapy is safe for use over extended time periods.

5. E-06 Clinical Study (NCT01118455)

   Randomized, parallel group, comparative study to compare the efficacy of VNS Therapy to antiepileptic drug (AED) treatment in reducing the frequency of seizures in children (age 17 or less). The study was initiated in October 2004 and completed in January 2010. Patients were stratified based on previous therapy history (Early: previously treated with 2 to 5 AEDs; Non-early: previously treated with >5 AEDs). Within each group, subjects were randomized to receive one of the 2 treatments (VNS Therapy treatment or AED treatment). For subjects randomized to the AED arm, a new AED treatment could be initiated and gradually increased to an effective dose in accordance with physician discretion and the manufacturer's suggested guidelines. Subjects randomized to the VNS Therapy treatment arm were implanted with the VNS Therapy System and titrated to tolerable levels as determined by the physician. The study treatment period was 12 months.

   The pre-operative state control group was the 8-week baseline seizure frequency.

   Active alternative treatment control group: This study's alternative treatment control group did not receive VNS Therapy and was therefore not included in the current analysis.

6. Japan Post-Approval Study (PAS)

   Prospective, open label, post-approval study of all consecutive patients treated with VNS Therapy in Japan. The study was mandated by the Pharmaceuticals and Medical Devices Agency (PMDA) to confirm the safety and effectiveness of VNS Therapy after Japan marketing approval in 2010. Patients were implanted between July 2010 and December 2012. Each patient will participate in the study for up to 36 months after the first VNS Therapy stimulation. Data collection occurred pre-

implant, implant, at first stimulation, and 3, 6, 12, 24 and 36 months after first stimulation.

The pre-operative state control group was baseline seizure frequency.

7. Cyberonics Post-Market Surveillance Database

The post-market surveillance database includes passively reported adverse events and implant registration card data from all patients implanted with the VNS Therapy System (includes reports from scientific literature) through September 2015. When assessing device relatedness, post-market data was restricted to reports starting in November 2006 when the post-market coding system was updated to include device relatedness.

8. Clinical Inclusion and Exclusion Criteria

Key enrollment criteria for each of the studies utilized are summarized in Table 2:

Table 2: Key Inclusion and Exclusion Criteria by Study

Criteria	Japan PAS	E-03	E-04	E-05/XE5	E-06
Inclusion					
Age	No stated criterion	12 to 60 years	Age at least two years old. Patients under 12 years old must meet additional criteria[1]	12 to 65 years	Age 17 or less
Seizure Type	Medically refractory partial or generalized onset seizures	Medically refractory partial onset seizures (may become secondarily generalized)	Medically refractory seizures of any type or combination of types	Medically refractory partial onset seizures (may become secondarily generalized)	Refractory seizures
Seizure Count	No stated criterion	At least six seizures per month (average over last three months); no more than 14 days between seizures (average over last 3 months)	At least one seizure per month (average over last 3 months)	At least six partial onset seizures with alteration of consciousness per month; no more than three weeks between such seizures	At least 3 seizures per month (average over 2 months prior to admission), excluding absences; no more than 4 weeks between seizures
Antiepileptic Drug Use	No stated criterion	Seizure activity not adequately controlled by antiepileptic drugs with adequate and stable serum anticonvulsant concentrations (+/- 20% over last three months) Treated with investigational anticonvulsants if a period of five times the half-life of the drug plus two weeks have elapsed	Seizure activity not adequately or appropriately treated by antiepileptic drugs. This may include intolerance to drugs or compelling reasons they should not be taken	Seizure activity not adequately or appropriately treated by antiepileptic drugs as defined by the Investigator based on the patient's history Treated with investigational anticonvulsants if a period of five times the half-life of the drug plus two weeks have elapsed.	Had tried at least 2 appropriate AEDs tested to tolerance or to blood levels at upper end of the target range of which at least 2 had been tolerated at normal dose. Treated with investigational anticonvulsants if a period of five times the half-life of the drug plus two weeks have elapsed. Had at least 3 appropriate AEDs left to try Had current AED medication at an optimal

					dose at baseline
Consent/ Cognition	All patients or legal representative of patient provided informed consent.	Ability to understand consent and required study procedure	Ability to understand the Informed Consent and required study procedure, or be the legal ward of someone who does and will sign the consent.	Ability of parents or caregiver to give accurate seizure counts. Patient or legal guardian to give proper informed consent.	Subject or legal guardian understood study procedures and had voluntarily signed an informed consent in accordance with the institutional policies.
Pregnancy	No stated criterion	Women when using accepted methods of birth control	No stated criterion	Females of childbearing age using acceptable methods of birth control (abstinence was considered acceptable)	Females of childbearing age using acceptable methods of birth control (abstinence was considered acceptable)
Exclusion					
Medical History	Cases in which expected neurosurgery is expected to be successful	Medical condition likely to deteriorate or result in hospitalization within the next year Prior cervical vagotomy Progressive neurological disease Pregnancy	Medical condition likely to deteriorate resulting in hospitalization within the next year Prior cervical vagotomy	Medical condition to deteriorate or result in hospitalization within the next year Prior cervical vagotomy Progressive neurological disease Pregnancy Cardiac or pulmonary disease under treatment Active peptic ulcer Prior enrollment in other vagus nerve stimulation studies Prior treatment of epilepsy with cerebellar or thalamic stimulation Prior therapeutic brain	Unstable medical condition likely to precipitate seizures and make it difficult to evaluate efficacy Prior cervical vagotomy Progressive neurological disease Pregnancy History of non-compliance for seizure diary completion Active peptic ulcer Prior enrollment in other vagus nerve stimulation studies Receiving or likely to receive short-wave diathermy, microwave

				surgery for epilepsy Treated with another investigational device	diathermy, or therapeutic ultrasound diathermy after implantation Likely to require whole body magnetic resonance imaging (MRI) after VNS Therapy System Implantation Currently using another investigational device or drug
Antiepileptic Drug Use	No stated criterion	Taking more than three anticonvulsants	No stated criterion	Taking either no AED or more than three AEDs on a daily basis. Use of AED (unless pre-approved by the contract research organization (CRO) medical monitor or Sponsor).	Tried less than 2 AEDs tested to tolerance or to blood levels at upper end of the target range of which at least 2 had been tolerated at normal doses in the subject's lifetime
Seizure History	No stated criterion	No stated criterion	No stated criterion	History of pseudoseizures Two or more episodes of status epilepticus in the past 12 months.	No stated criterion

[1] 1) During the last five years (or over lifetime if younger), at least three anticonvulsants must have been tried (alone or in combination) to control seizures
2) The Investigator and the family must have been of the opinion (and Investigator must so document in the chart) that seizures and/or drug side effects were detrimental to the patient
3) Admission must first have been discussed with Cyberonics staff and approval was given on a case-by-case basis. The purpose of this condition was to provide investigators and the families with all current information, such that the best risk/benefit decision could be made for the patient

9. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at three months, six months, nine months, and 1 year for most studies (see Table 3) postoperatively.

Table 3 describes the follow-up schedule for each study protocol, listing the evaluations performed both preoperatively and postoperatively, as well as the key timepoints. For purposes of this PMA, the relevant evaluations were seizure frequency, AED log, adverse events and device malfunctions and device programming parameters. All endpoints were collected at 12 months except for the XE5 study which was the longer term follow-up for the E05 study and collected data at 15 months. For all studies, subjects comprised both the control and intent to treat (ITT) groups. The control group was considered the seizure frequency measured at baseline, after which, subjects were implanted and received VNS Therapy in the ITT group. No subgroups or other populations were studied in conjunction with these protocols.

Table 3: Data Collection Schedule by Study

Timing	Screening*	Implant	First Stimulation	3 M	6 M	9 M	12 M/ (15 M)
Seizure Frequency							
Japanese PAS	X	X	X	X	X		X
E03	X	X	X	X†	X	X	X
E04	X	X	X	X	X	X	X
E05/XE5	X	X	X	X†	X	X	X/(15M)
E06	X				X		X
Anti-Epilepsy Drug (AED) Log							
Japanese PAS	X		X	X	X		X
E03	X	X	X	X†	X	X	X
E04	X	X	X	X	X	X	X
E05/XE5	X	X	X	X†	X	X	X/(15M)
E06	X	X	X	X	X	X	X
Adverse Events/ Device Malfunction							
Japanese PAS		X	X	X	X		X
E03		X	X	X†	X	X	X
E04		X	X	X	X	X	X
E05/XE5		X	X	X†	X	X	X
E06		X	X	X	X	X	X
Device Parameters							

Timing	Screening*	Implant	First Stimulation	3 M	6 M	9 M	12 M/ (15 M)
Japanese PAS		X	X	X	X		X
E03		X	X	X†	X	X	X
E04		X	X	X	X	X	X

**At screening, demographics and medical history were taken for each study, along with other measures, depending upon study.
†3 months marked the end of the blinded, randomized acute phase of E-03 and E-05; subsequent time points were open-label. Long term follow-up data for patients in the E-05
clinical trial were collected under the XE5 protocol.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

10. Clinical Endpoints

The primary safety endpoint was the incidence rate of device-related treatment emergent adverse events through 12 months of treatment. Pooling data across all studies listed in Table 1, adverse event rates for patients 4-11 years were compared to that of patients 12-21 years (comparable with respect to physiological development) via a 95% confidence interval for the incidence rate ratio. Adverse events with statistically significant incidence rate ratios greater than 1 indicate that the incidence rate for patients 4-11 years of age is greater than the incidence rate for patients 12-21 years of age.

The primary effectiveness endpoint is the proportion of patients 4-11 years of age in the Japan PAS with at least a 50% reduction in the frequency of seizures following 12 months of treatment. The pre-established efficacy threshold was set to a 30% responder rate with a corresponding 10% uncertainty margin. A Bayesian hierarchical model was used to model the 12-month rates for each study, allowing the Japanese PAS to borrow strength from the other study results.

B. Accountability of PMA Cohort

At the time of database lock, 847 clinical study patients enrolled in the PMA study, of which 805 patients (95%) are available for analysis at the completion of the study (E-03, E-04, E-05, E-06, and Japan PAS studies) at the 12 month post-operative visit (final visit evaluated for safety and effectiveness as the basis for the PMA submission) . Of the 847 in the safety population, 176 were removed from analysis due to having only generalized seizures, 2 were removed for having no baseline seizures, and 6 were removed due to missing or unreliable baseline data, leaving 663 for the efficacy evaluation. Of the 663 patients included in the efficacy population (demographics and baseline), 582 patients (88%) had 12-month efficacy outcome data (n=54 patients 4-11 years and n=528 patients ≥12 years of age) (Table 4). For the patients in the efficacy population, 31 exited the study early and 50 did not collect seizure data at the 12-month visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an epilepsy study performed in the US. The incidence and prevalence of refractory seizure disorders in children in Japan is 63 per 100,000 and 3.4 per 1,000, respectively, which compares similarly to the US population. Demographics are shown in Table 4 and Table 5 below.

Table 4: Demographics and Baseline Characteristics by Component Study

	E-03	E-04	E-05	E-06	Japan	Overall
Gender [n (%)]						
N	115	123	199	65	345	847
% Female	37.4% (43/115)	45.5% (56/123)	53.3% (106/199)	49.2% (32/65)	40.0% (138/345)	44.3% (375/847)
Age (years)						
N	115	123	199	65	345	847
Average ± SD (Range)	33.3 ± 8.5 (13.3-56.7)	24.2 ± 11.6 (4.7-63.4)	33.9 ± 10.5 (14.0-60.9)	11.0 ± 3.4 (4.0-17.5)	26.3 ± 14.1 (4.3-73.0)	27.6 ± 13.2 (4.0-73.0)
Age at Epilepsy Onset (years)						
N	113	123	197	65	338	836
Average ± SD (Range)	11.9 ± 9.4 (0.0-45.0)	6.1 ± 7.1 (0.0-36.0)	11.1 ± 10.5 (0.0-50.0)	2.7 ± 2.9 (0.0-13.4)	9.7 ± 11.7 (0.0-63.7)	9.2 ± 10.4 (0.0-63.7)
Time to VNS since Diagnosis (years)						
N	113	123	197	65	338	836
Average ± SD (Range)	21.8 ± 9.1 (5.2-47.5)	18.0±9.7 (2.6-48.4)	22.8 ± 11.1 (1.3-51.9)	8.4 ± 3.5 (1.7-17.3)	16.4 ± 11.0 (0.1-61.0)	18.2 ±10.9 (0.1-61.0)
Prior Brain or Epilepsy Surgery						
N	113	122	199	65	345	844
% Prior Surgery	31.0% (35/113)	32.0% (39/122)	22.6% (45/199)	6.2% (4/65)	48.4% (167/345)	34.4% (290/844)
Baseline Seizure Type						
N	115	123	199	65	345	847
Partial	100% (115/115)	78.0% (96/123)	100.0% (199/199)	56.9% (37/65)	64.3% (222/345)	79.0% (669/847)
Generalized only	0% (0/115)	22.0% (27/123)	0% (0/199)	43.1% (28/65)	35.1% (121/345)	20.8% (176/847)
0 baseline seizures	0% (0/115)	0% (0/123)	0% (0/199)	0% (0/65)	0.6% (2/345)	0.2% (2/847)
Baseline Number of AEDs by Study						
N	109	111	198	65	345	828
Average ± SD (Range)	2.0 ± 0.8 (0-4)	2.0 ± 0.9 (1-5)	2.1 ± 0.7 (1-3)	2.2 ± 0.9 (1-4)	3.4 ± 1.1 (0-7)	2.6 ± 1.1 (0-7)

Table 5: Demographics (Safety Population)

	4-11 years	≥12 years	Overall
Gender [n (%)]			
N	117	730	847
% Female	45.3% (53/117)	44.1% (322/730)	44.3% (375/847)
Age (years)			
N	117	730	847
Average ± SD (Range)	8.4 ± 2.2 (4.0-11.9)	30.6 ± 11.5 (12.0-73.0)	27.6 ± 13.2 (4.0-73.0)
Age at Epilepsy Onset (years)			
N	117	719	836
Average ± SD (Range)	1.7 ± 1.9 (0.0-7.8)	10.5 ± 10.6 (0.0-63.7)	9.2 ± 10.4 (0.0-63.7)
Time to VNS since Diagnosis (years)			
N	117	719	836
Average ± SD (Range)	6.7 ± 2.5 (1.2-11.6)	20.1 ± 10.6 (0.1-61.0)	18.2 ±10.9 (0.1-61.0)
Prior Brain or Epilepsy Surgery			
N	117	727	844
% Prior Surgery	35.0% (41/117)	34.3% (249/727)	34.4% (290/844)
Epilepsy Etiology			
N	117	730	847
Known	46.2% (54/117)	40.4% (295/730)	41.2% (349/847)
Baseline Seizure Type			
N	117	730	847
Partial onset	49.6% (58/117)	83.7% (611/730)	79.0% (669/847)
Generalized only	49.6% (58/117)	16.2% (118/730)	20.8% (176/847)
zero baseline seizures	0.9% (1/117)	0.1% (1/730)	0.2% (2/847)

Key: SD=standard deviation.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the following cohorts: all patients ages 4 and older who underwent VNS implant and who: participated in the E03, E04, E05, or E06 trial or: Participated in the Japanese PAS (initial implants only) or: had a record in the Cyberonics Post-Market Surveillance database. Study data from 847 patients was available for the 12 month evaluation. The key safety outcomes for this study are presented below in Table 6 and Table 7.

Based on the clinical data, the overall incidence rate of device related treatment emergent adverse events was not different for patients 4-11 years of age compared

to patients 12-21 years of age (Incidence Rate Ratio (IRR): 0.44, 95% CI: 0.20, 1.04). There were no device-related treatment emergent adverse events that had a statistically higher incidence rate in the 4-11 year age group when compared to 12-21 year age group. Two adverse events, myalgia and paresthesia, had statistically lower incidence rates in the 4-11 age group when compared to the 12-21 age group.

Table 6: Device-Related, Treatment-Emergent Adverse Events by Age

Device-Related, Treatment-Emergent Adverse Events by Age based on Clinical Data (overall and statistically significant differences)					
Adverse Event	**4-11 years (N=117 patients, 113 person years)**		**12-21 years (N=199 patients, 194 person years)**		**Incidence Rate Ratio* (IRR) (95% CI)**
	Number of AE Reports	**Incidence Rate/PY (95% CI)**	**Number of AE Reports**	**Incidence Rate/PY (95% CI)**	
Overall rate	**75**	**66.6% (32.2%-145%)**	**293**	**151% (109%-207%)**	**0.44 (0.20-1.04)**
Statistically Significant Difference in Incidence Rates (IRR <1)					
Myalgia	1	0.9% (0.0%-5.4%)	11	5.7% (0.0%-33.8%)	0.16 (0.00-0.90)
Paraesthesia	1	0.9% (0.0%-5.1%)	23	11.9% (5.8%-22.1%)	0.07 (0.00-0.79

Based on post-market surveillance data, the overall incidence rate of device related treatment emergent adverse events was lower for patients 4-11 years of age compared to patients 12-21 years of age (IRR: 0.82, 95% CI: 0.77, 0.88) (Table 3). Infection and extrusion of lead had a statistically greater incidence rate in patients 4-11 years of age. Younger patients may have a greater risk for wound infection when compared to adolescent and adult patients; therefore, the importance of monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be stressed.

Adverse effects that occurred in the PMA clinical study:

Based on the clinical data, the overall incidence rate of device related treatment emergent adverse events was not different for patients 4-11 years of age compared to patients 12-21 years of age (Incidence Rate Ratio (IRR): 0.44, 95% CI: 0.20, 1.04). There were no device-related treatment emergent adverse events that had a statistically higher incidence rate in the 4-11 year age group when compared to 12-21 year age group. Two adverse events, myalgia and paresthesia, had statistically lower incidence rates in the 4-11 age group when compared to the 12-21 age group.

Fifty percent of patients experienced the most common side effect associated with stimulation, hoarseness (voice alteration). Depending on device settings, this can be severe to barely perceptible. Hoarseness is reported to occur primarily during the ON period of stimulation.

Table 7: Device-Related, Treatment-Emergent Adverse Events by Age Based on Post-Market Data

Device-Related, Treatment-Emergent Adverse Events by Age based on Post-Market Data (overall and statistically significant differences)							
Adverse Event	**4-11 years (N=7,729 patients, 31,220 person years)**			**12-21 years (N=9,389 patients, 37,647 person years)**			**Incidence Rate Ratio (95% CI)**
	Number of AE Reports	**Incidence Rate / Person Year (95% CI)**	**% of Total Reports**	**Number of AE Reports**	**Incidence Rate/ Person Year (95% CI)**	**% of Total Reports**	
Overall	1328	4.25% (4.03%, 4.49%)	100%	1948	5.17% (4.95%, 5.41%)	100%	0.82 (0.77, 0.88)
Statistically Significant Difference in Incidence Rates (IRR >1)							
Infection	8	0.27% (0.22%,	6.40%	6	0.18% (0.14%,	3.44%	1.53 (1.11,
Extrusion of Lead	1	0.05% (0.03%,	1.13%	5	0.01% (0.00%,	0.26%	3.62 (1.31,
Statistically Significant Difference in Incidence Rates (IRR <1)							
Painful Stimulation	8	0.27% (0.21%,	6.25%	20	0.53% (0.46%,	10.27	0.50 (0.39,
Pain	6	0.19% (0.15%,	4.52%	15	0.40% (0.34%,	7.70%	0.48 (0.36,
Voice Alteration	6	0.21% (0.16%,	4.97%	12	0.32% (0.27%,	6.26%	0.65 (0.48,
Stimulation Not Perceived	3 7	0.12% (0.08%, 0.16%)	2.79%	9 9	0.26% (0.21%, 0.32%)	5.08%	0.45 (0.31, 0.66)
Coughing	4	0.15% (0.11%,	3.54%	8	0.23% (0.19%,	4.52%	0.64 (0.45,
Migration of Generator	1 2	0.04% (0.02%, 0.07%)	0.90%	4 8	0.13% (0.09%, 0.17%)	2.46%	0.30 (0.16, 0.57)
Dysphagia	1	0.04% (0.02%,	1.05%	4	0.11% (0.08%,	2.05%	0.42 (0.23,
Cognitive Changes	1	0.05% (0.03%,	1.20%	3	0.09% (0.06%,	1.80%	0.55 (0.31,
Erratic Stimulation Perceived	4	0.01% (0.00%, 0.03%)	0.30%	1 5	0.04% (0.02%, 0.07%)	0.77%	0.32 (0.11, 0.97)
Continuous Stimulation Perceived	3	0.01% (0.00%, 0.03%)	0.23%	1 3	0.03% (0.02%, 0.06%)	0.67%	0.28 (0.08, 0.98)
Syncope	1	0.00% (0.00%,	0.08%	1	0.03% (0.01%,	0.56%	0.11 (0.01,

The following individual adverse events have a statistically significantly greater incidence rate in patients 4-11 years of age and comprise >1%: increased seizures, infection, fibrosis, new seizure type, increased seizure duration. Excessive drooling was identified in the 4-11 years of age group. This is particularly important in this group as they may have disorders that increase their oromotor apraxia and are more prone to difficulty handling secretions. Reduced appetite was seen as an increased risk in children aged 4-11 years. Weight loss was increased in the age 12-21 year group but not in the 4-11 year group.

Cardiac Events including SUDEP were lower in the 0-4 years of age group and in the 5-9 years of age group compared to other age groups (0.5 and 2.4 respectively, compared to 2.9 for all age groups).

Table 8 lists all adverse events for all age groups, and age subsets, across all studies. The post-market surveillance database includes passively reported adverse events and implant registration card data from all patients implanted with the VNS Therapy System (includes reports from scientific literature) through September 2015. When assessing device relatedness, post-market data was restricted to reports starting in November 2006 when the post-market coding system was updated to include device relatedness.

Table 8: All post-market Adverse Events, Nov 2006-Sept 2015, by Age Group

	Age 4-11		Age 12+		All Ages
Patient Adverse Event	Count	Rate / PY	Count	Rate / PY	Rate / PY
Overall	2226	7.1%	15759	11.9%	11.0%
Increased Seizures	457	1.46%	1821	1.38%	1.39%
Painful Stimulation	102	0.33%	1706	1.29%	1.11%
Pain	109	0.35%	1568	1.19%	1.03%
Voice Alteration	90	0.29%	1052	0.80%	0.70%
Coughing	72	0.23%	648	0.49%	0.44%
Infection	194	0.62%	430	0.33%	0.38%
Stimulation Not Perceived	45	0.14%	522	0.40%	0.35%
Dyspnea	36	0.12%	452	0.34%	0.30%
Dysphagia	32	0.10%	452	0.34%	0.30%
Muscle Spasm	36	0.12%	349	0.26%	0.24%
Lack of Efficacy - Epilepsy	56	0.18%	281	0.21%	0.21%
Magnet Activations Not Aborting Seizures	65	0.21%	270	0.20%	0.21%
Death	43	0.14%	281	0.21%	0.20%
Migration of Generator	17	0.05%	295	0.22%	0.19%
Lack of Efficacy	56	0.18%	226	0.17%	0.17%
Dissatisfaction, Patient	12	0.04%	218	0.17%	0.14%
Vocal Cord Paralysis	11	0.04%	192	0.15%	0.12%
Swelling	25	0.08%	172	0.13%	0.12%
Headache	6	0.02%	186	0.14%	0.12%
Increased Seizure Intensity	32	0.10%	154	0.12%	0.11%
Cognitive Changes	36	0.12%	147	0.11%	0.11%
Vomiting	29	0.09%	144	0.11%	0.11%
SUDEP	20	0.06%	145	0.11%	0.10%

2. Effectiveness Results

For the primary effectiveness endpoint, a Bayesian hierarchical model was fit to the study-specific 12-month responder rates shown in Table 8 accounting for age group (4-11 vs. 12+ years). The model allowed the Japanese PAS rate in the 4-11 age group to borrow from all data from all other studies. An additional term for age group was used in the model in case the 4-11 year old group performed differently from the 12+ age group. Using this model, the estimated 12 month responder rate for patients 4-11 years of age with partial onset seizures in the Japan PAS was 39% (95% credible interval: 28%, 52%). Since the entire 95% credible interval is greater than 20%, the primary efficacy endpoint was met. In addition, the Bayesian hierarchical model estimate for the population responder rate for patients 4-11 years of age (regardless of study) is 37% (95% credible interval: 26%, 48%). Table 9 contains the individual study estimates, including the frequency estimates, or raw proportions, that do not borrow across studies.

Table 9: Fifty-Percent Responder Rates at 12 months

50% Response Rates at 12 Months						
Study	**Age Group**	**Responders**	**Frequentist Estimate**	**95% Exact Binomial CI**	**Bayesian Estimate**	**95% Credible Interval**
E-03	12+	32/102	31%	23-41%	35%	28-43%
E-04	4-11	1/5	20%	1-72%	36%	23-50%
E-04	12+	18/64	28%	18-41%	35%	27-44%
E-05	12+	67/163	41%	33-49%	41%	34-47%
E-06	4-11	4/19	21%	6-46%	34%	23-47%
E-06	12+	6/18	33%	13-59%	39%	28-49%
Japan	**4-11**	**14/30**	**47%**	**28-66%**	**39%**	**28-52%**
Japan	12+	101/181	56%	48-63%	50%	44-57%
Overall	4-11	19/54	35%	23-49%	37%	26-48%
Overall	12+	224/528	42%	38-47%	39%	33-46%

Median Percentage Change in Seizure Frequency By Age Group

A secondary effectiveness endpoint was median percent reduction in seizure frequency from baseline to 12 months. A comparison of the median percent reduction by age group is reported in Table 10 (pooling across studies). There was no statistically significant difference in the median percent seizure reduction between patients 4-11 years of age (-24.7%) and patients >12 years of age (-40.4%) (p=0.142). Individual estimates of the median percent change by study and age group are presented in Table 11.

Table 10: Median Percent Change in Seizure Frequency at 12 Months by Age Group

Median percent change in seizure frequency at 12 months, by age group		
Age group	**4-11 years**	**>12 years**
N	54	528
Median	-24.7%	-40.4%
95% CI	-45.1% to 0%	-45.6 to -33.3%
	p-value, Mann-Whitney	0.142

Table 11: Median Percent Change at 12 Months by Study and Age Group

Age Group	Study	Raw Median % Change in Seizure Frequency	95% CI (Mann-Whitney)
Pediatrics (4-11 years)	E-04	+6.3%	-63.9%, +320%
	E-06	-2.4%	-27.9%, 70.0%
	Japan	-38.6%	-75.2%, -16.3%
Adolescents (12-21 years)	E-03	-37.7%	-62.4%, -24.2%
	E-04	-24.5%	-39.3%, -0.8%
	E-05	-36.1%	-53.2%, -11.3%
	E-06	-19.2%	-42.8%, +33.3%
	Japan	-50.0%	-63.3%, -22.2%
Adults (22+ years)	E-03	-30.2%	-38.4%, -21.9%
	E-04	-25.9%	-39.2%, +6.3%
	E-05	-44.3%	-48.8%, -34.5%
	Japan	-60.0%	-62.5%, -43.2%

The follow-up necessary for the primary endpoint evaluation was 12 months.

Furthermore, data from the primary study in this submission was from three years of follow-up. The duration of effect was not statistically.

Most patients did not have a change in the dose or number of anti-epilepsy drugs (AEDs) used although some were able to discontinue medications and a small number had an increase in AEDs. The reduction in the number of medications was also not officially statistically analysed.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

- Assessment of Adverse Events related to Age and/or Growth:
  All clinical study and post-market adverse event data from November 2006 through September 2015 were compared to determine if adverse event occurrence or severity was associated with patient age, and if any necessary updates should be made to device labeling should the indication for use be expanded to pediatric patients 4-11 years of age. The analysis concluded that

expanding the indications for using VNS Therapy in children 4-11 years of age in the United States would not increase the risk of adverse events that were selected based on biological plausibility for causal relationships with various factors that may change by age and growth patterns.

- Role of previous brain or epilepsy surgery on responder rates:
  Patients without a previous surgery have a slightly better responder rate. This sensitivity analysis supports a robustness of effect; Japanese patients 4-11 years with no previous surgery have an estimated responder rate of 41% (95% credible interval: 29-54%), and Japanese pediatric patients with previous surgery have an estimated responder rate of 37% (95% credible interval: 25-50%). Again, the lower bound of the 95% credible interval exceeds the threshold of 20%.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the effectiveness of the proposed device in children aged 4 to 11 years old. Because of the difficulty in enrolling children aged 4 to 11 years old, prior studies on adults and adolescents were used to permit inference about the indicated age group.

Data from patients aged 12 and over in the E-03, E-04, E-05, E-06, and Japanese PAS studies) were used to partially extrapolate to patients aged 4 – 11 in the U.S. A limited amount of data from patients aged 4-11 was also available and leveraged from the prior studies. A description of the prior studies is provided in Section X. Table 9 shows the number of patients per age group and study used for extrapolation, along with the 12-month responder rates (both raw and estimated using a Bayesian hierarchical model).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study E-06 included 19 investigators and the Japanese PAS included 46 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Studies E03, E04, and E05:
Cyberonics completed due diligence to find investigator financial disclosure information for the E-03, E-04, and E-05 studies. We were not able to obtain individual investigator financial disclosures because these studies all completed prior to the Financial Disclosure by Clinical Investigators regulation (21 CFR part 54)

which became effective on February 2, 1999. The sponsor is not aware of any financial conflict of interest with these investigators.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The Guideline Development Subcommittee of the American Academy of Neurology published a report titled Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy (Morris GL, Gloss D et al. 2013). The authors reviewed available literature using MEDLINE, EMBASE, and Web of Science (1996 – February 2012). 216 articles were selected for review. In that review, fourteen controlled trials designated as Class III, (well-defined natural history controls or patients serving as own controls in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement), were included in the efficacy analysis. Based on a pooled analysis of 481 patients aged 2 to 25 years, with both partial and generalized seizures, the responder rate (50% seizure frequency reduction) was 55% (95% CI 51%–59%) and the pooled seizure freedom rate was 7% (95% CI 5%–10%). The overall recommendation was that VNS may be considered as adjunctive treatment for children with partial or generalized epilepsy.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Pooling across all studies, 35% (19/54) of children aged 4 – 11 years had a 50% or greater reduction in the number of seizures by 12 months. The Bayesian model-based estimate of the population rate for this age group is 37% (95% credible interval: 26-48%).

Following 12 months of treatment with Vagus Nerve Stimulation (VNS) Therapy, pediatric patients 4-11 years of age had a median percent change (reduction) in seizure frequency of -24.7%. This level of seizure reduction is of meaningful benefit to patients, as well as to caregivers. Typically, in the population studied, the alternative is brain surgery, which carries a high risk generally including the risk of anesthesia, as well as the risks of infection, intracranial and intracerebral hemorrhage; surgery may not be more effective.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

Most patients tolerated the Vagus Nerve Stimulator placement and stimulation. Risks included Pain in 0.19% infection in 0.27%, Painful stimulation 0.27%, Voice Alteration 0.21%, and Coughing: 0.15%. Most of these risks can be managed with changes in the stimulation parameters, or wound care in the case of infection. The stimulator should also be turned off during feeding in order to avoid risk of choking.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above.

Pooling across all studies, 35% (19/54) of children aged 4 – 11 years had a 50% or greater reduction in the number of seizures by 12 months. The Bayesian model-based estimate of the population rate for this age group is 37% (95% credible interval: 26-48%). Following 12 months of treatment with Vagus Nerve Stimulation (VNS) Therapy, pediatric patients 4-11 years of age had a median percent change in seizure frequency of -24.7%. Both 1) the seizure episode, and 2) the post-ictal period, are disabling to patients. The Post-ictal period can last hours or even a day, and include confusion, difficulty using limbs (Todd's paralysis), and somnolence. The patients in these studies had refractory epilepsy, with an average of 30 seizures a month. This number of seizures would result in having no ability to attend school and have a significant impact on ADLs as well. It also would create significant caregiver burden. Therefore, a reduction in the number of seizures in this population is highly valuable.

Most patients tolerated the Vagus Nerve Stimulator placement and stimulation. Risks included Pain in 0.19% 4.52%, infection in 0.27%, Painful stimulation 0.27%, Voice Alteration 0.21%, and Coughing: 0.15%. Most of these risks can be managed with changes in the stimulation parameters, or wound care in the case of infection.

The data was robust for the purposes of this study, and detailed safety and efficacy data were available for analysis. Longitudinal follow-up was appropriate. The results of the studies/sources analysed and presented for consideration are believed to be generalizable to the population of patients for whom this therapy would be made available, that is, the population of pediatric patients who have severe (average of 50 seizures per month) refractory (failed three or more Anti-Epileptic drugs) epilepsy. Of those children with epilepsy, approximately 25% continue to experience poor seizure control even with anti-epileptic drug therapy.

There is no official definition of refractory epilepsy: the American Academy of Neurology recommends that failure of an adequate trial of three anti-epileptic drugs would qualify a patient as being considered refractory. Per French (2006) the issue of designation of refractory is complicated by the fact that 1) there is no widely accepted definition of refractory 2) patients may respond to treatment and later become refractory and 3) patients who have been considered refractory may remit. For patients with refractory epilepsy, the symptoms can be severe. There is a range of seizure frequency, with many seizures per day occurring in some patients, and others,

who have a seizure only several times a year. Those who seize at least daily would be considered to have severe disease with significant physical, cognitive, and social impairment as a result. These patients would be willing to tolerate a higher amount of risk. Note that the proposed device is for use in children ages 4-11 years, and those children, especially of younger age or with underlying brain abnormalities leading to cognitive impairment are not able to make risk benefit decisions, and the parents would be making the decision on behalf of the child. A reduction of seizure frequency has a significant benefit to patients as well as caregivers.

Epilepsy that is refractory to treatment is a serious disorder that is disabling to patients. Children with refractory epilepsy are severely disabled, due to not only the seizures themselves (ictal) but also the time after they have seized (post-ictal) which can include hours of confusion, motor incoordination, and even paralysis. This impairs the child's normal ability to attend school and participate in social and family events, and impairs social and cognitive development. There are few options for children with refractory epilepsy currently, other than invasive surgery, which may itself be ineffective.

For patients who are refractory, besides VNS, surgery is an option. Surgical approaches include focal brain resections, lobar or multilobar resections, corpus callosotomy hemispherectomy, and multiple subpial transection.

VNS is not likely to be as effective in children who have previously undergone epilepsy surgery. Children between the ages of 4-11 years are at increased risk of manipulating the lead, which increases the risk of lead breakage; therefore, children with VNS should be monitored closely for any such behaviors after undergoing implantation for VNS. Children may have greater risk for wound infection than adults due to behaviors more common in children. Extra vigilance in monitoring for occurrence of site infection in children should be undertaken. Because children with epilepsy in the age group 4-11 years are more likely to have motor dysfunction including oromotor apraxia, the device should be turned off during feeding.

The technology is not novel; Vagus Nerve stimulation has been available commercially since 1997 as an adjunctive therapy in reducing the frequency of seizures in adult and adolescents over 12 years of age with medically refractory partial onset seizures.

1. Patient Perspectives.
This submission did not include specific information on patient perspectives for this device.

Overall, the acceptability of the rates of benefit and risk are acceptable considering the severity of the refractory and disabling seizure frequency of these children. In conclusion, given the available information above, the data support that for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and

older with partial onset seizures that are refractory to antiepileptic medications the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The results of the extrapolation study demonstrate that VNS Therapy is a safe and effective treatment for the reduction of partial onset seizures in pediatric patients 4-11 years of age with refractory epilepsy. Based on the Bayesian hierarchical model, the 12 month responder rate for pediatric patients 4-11 years of age with partial onset seizures in the Japan PAS is 39% (95% credible interval: 28%-52%). There were no unanticipated adverse device effects observed in pediatric patients 4-11 years of age. However, infection and extrusion of lead had a statistically greater incidence rate in patients 4-11 years of age. Younger patients may have a greater risk for wound infection when compared to adolescent and adult patients; therefore, the importance of monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be stressed. Otherwise overall, treatment-emergent adverse events in patients 4-11 years of age were consistent with patients ≥12 years of age treated with VNS Therapy and no new risks were identified.

XIV. CDRH DECISION

CDRH issued an approval order on June 23, 12017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

French, Jacqueline A. "Refractory epilepsy: one size does not fit all." *Epilepsy Currents* 6.6 (2006): 177-180.