

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable multi-programmable quadripolar deep brain stimulation system for epilepsy

Device Trade Name: Medtronic DBS System for Epilepsy, consisting of:

Model 37601 Activa PC Neurostimulator
Model 3387S DBS Lead Kit
Model 3389S DBS Lead Kit
Model 37086 DBS Extension Kit
Model 8840 N'Vision Programmer
Model 8870 Software Application Card
Model 37441 Intercept Patient Programmer
Model 37022 External Neurostimulator
Model 3353/3354 Lead Frame Kit
Accessories

Device Procode: MBX

Applicant's Name and Address: Medtronic, Inc.
Medtronic Neuromodulation
7000 Central Ave., N.E.
Minneapolis, MN 55432

Date(s) of Panel Recommendation: March 12, 2010

Premarket Approval Application (PMA) Number: P960009/S219

Date of FDA Notice of Approval: April 27, 2018

II. INDICATIONS FOR USE

The original PMA (P960009) for Medtronic's Deep Brain Stimulator (DBS) System was approved on July 31, 1997 and is indicated for unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with Essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=211&applicant=&tradename=&productcode=&pmanumber=P960009&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&ivdproducts=off&combinationproducts=off&decisiondatefrom=&decisiondateto=08%2F14%2F2015

With the exception of the Intercept Model 37441 Patient Programmer, all components of the Medtronic DBS System for Epilepsy are approved as part of the Activa PC Neurostimulation System (P960009/S052). The Activa PC Neurostimulation System includes Activa Parkinson's Control Therapy and Activa Tremor Control Therapy. Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic Activa Parkinson's Control Therapy is indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication. Unilateral thalamic stimulation by the Medtronic Activa Tremor Control System is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with Essential Tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. The current supplement was submitted to expand the indication for the Medtronic DBS System for Epilepsy.

The Medtronic DBS System for Epilepsy is indicated for the following:

Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

III. CONTRAINDICATIONS

Implantation of a DBS system is contraindicated for:

Diathermy - Patients exposed to diathermy. Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

Diathermy can also damage the neurostimulation system components, resulting in loss of therapy and requiring additional surgery for system explantation and replacement. Advise your patient to inform all their health care professionals that they should not be exposed to diathermy treatment.

Injury to the patient or damage to the device can occur during diathermy treatment when:

- the neurostimulation system is turned on or off.
- diathermy is used anywhere on the body—not just at the location of the neurostimulation system.
- diathermy delivers heat or no heat.
- any component of the neurostimulation system (lead, extension, neurostimulator) remains in the body.

Magnetic resonance imaging (MRI) using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area

Some specific types of MRI are contraindicated for patients with any implanted DBS System or system component. Tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death can occur if performing an MRI procedure that involves the use of:

- a full body transmit radio-frequency (RF) coil
- a receive-only head coil
- a head transmit coil that extends over the chest area

Refer to the MRI guidelines manual packaged with this product for comprehensive safety information and instructions.

Unable to operate patient devices - Patients who are unable, or do not have the necessary assistance, to properly operate the DBS Therapy patient programmer, magnet, or a charging system (applicable to rechargeable DBS Systems only).

Transcranial magnetic stimulation (TMS) - Contraindicated for use in patients with an implanted DBS System.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic DBS System for Epilepsy labeling.

V. DEVICE DESCRIPTION

The Medtronic DBS System for Epilepsy is a totally implanted device that delivers bilateral stimulation to the anterior nucleus of the thalamus (ANT) in the brain. The main components of the Medtronic DBS System for Epilepsy are shown in Figure 1 below:



Figure 1: (a) Implantable Neurostimulator (INS), (b) Leads, (c) Extension, (d) External Neurostimulator (ENS), (e) Clinician Programmer, and (f) Patient Programmer

A. Implanted Components

The implanted components of the Medtronic DBS System for Epilepsy include the following:

- Activa PC Neurostimulator (Model 37601)

The Activa PC neurostimulator is a dual channel, multi-programmable implantable neurostimulator (INS) which is implanted subcutaneously near the clavicle, and generates electrical signals that are delivered via the extensions and leads to the targeted brain structure. It is powered by a 6.3 amp hour, 3.2 V sealed primary cell HC silver vanadium oxide (HCSVO) battery. The electronic circuitry of the INS sends pulses of controlled electrical stimulation through the implanted lead-extensions to the brain. The connector assembly accommodates two extensions, forming a dual channel system. Setscrews and Bal Seals provide electrical contact between the INS and the leads/extensions. Approximate dimensions of the IPG are 65 mm (height), 49mm (width) and 15 mm (thickness). The stimulation parameters can be non-invasively adjusted via radio-frequency communication using the Model

8840 N' Vision programmer with the Model 8870 Software application card (see below). The stimulation output parameters are listed in Table 1 below:

Table 1: Stimulation Output Parameters^a

Waveform	Square Wave
Method of Charge Balancing	Capacitive Coupling
Current or Voltage Regulated	Either
Maximum Current Amplitude @ 500 Ω	0 – 25.5 mA (current mode)
Maximum Output Voltage @ 500 Ω	0 – 10.5 V (voltage mode)
Pulse Width	60 – 450 μ s
Frequency ^b	30 – 250 Hz (current mode) 2 to 250 Hz (voltage mode)
Maximum Charge Density ^{cb}	30 μ C/cm ² /phase
Current Path Options ^d	1 to 4 electrodes per lead as anode, cathode, or Off Case defined as anode or Off
Number of Channels	2
Number of Defined Groups ^e	1 to 4
Number of Programs per Group	1 to 4

^a Certain combinations of high amplitude, pulse width, and rate settings are not allowed by the clinician programmer. High-output interlocks can prevent certain values from being available for programming.

^b Rate limited to 125 Hz when two programs are active on a single lead

^c A survey of literature regarding electrical stimulation of neural tissue suggests that damage may occur above 30 μ C/cm²/phase. The Medtronic DBS System is capable of producing charge densities in excess of 30 μ C/cm²/phase on an electrode surface area of 0.06 cm² (for the DBS Model 3387 Lead and DBS Model 3389 Lead). If the maximum charge density threshold is reached, the Charge Density warning message appears and must be overridden to proceed.

^d In constant current mode a maximum of 2 electrodes (including the case) can be configured as anode or cathode

^e A program is a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination. Up to four programs can be combined into a group. When using more than one program, the pulses are delivered sequentially—first a pulse from one program, then a pulse from the next program.

- **DBS™ Lead Kits (Model 3387S and Model 3389S)**

The DBS leads connect to a lead extension and deliver electrical signals to the targeted brain structure. The DBS leads have with four 1.5 mm platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. Lead models include Model 3387S, in which the 4 electrodes are spaced 1.5 mm apart and Model 3389S, in which the electrodes are spaced 0.5 mm apart. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring. Accessories that come with the lead kit include the following: Straight and Short Stylets, Torque Wrench, Depth Stop Gauge (lead), Burr Hole Ring and Cap, Connector Boot, Tunneling Tools, and a Lead Cap. Lead specifications are provided in Table 2 below:

Table 2: Lead Specifications

Lead Length	10-50 cm
Lead Diameter	1.27 mm
Number of Electrodes	4
Electrode Material	Platinum-Iridium
Electrode Length	1.5 mm
Electrode Spacing (edge-to-edge)	1.5 mm & 0.5 mm
Electrode Span	10.5 mm & 7.5 mm
Electrode Surface Area	0.06 cm ²
Impedance (Ω) [†]	< 100 Ω
Conductor Wire Material	Platinum-Iridium
Lead Body Insulation	Polyurethane

[†] Electrical resistance is proportional to lead length.

- DBS Extension Kit (Model 37086)

The extension is a set of wires within silicone tubing and polyurethane insulation that provides an electrical path that allows stimulation to be delivered to the target site. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the INS. The extension comes in lengths of 10 to 110 cm. Accessories that come with the lead kit include the following: Connector Boots, In-line Neurostimulator Plug, Torque Wrench, and Extar Setscrews.

B. External Components

The external components of the Medtronic DBS System for Epilepsy include the following:

- Intercept Patient Programmer (Model 37441)

The Intercept Model 37441 Patient Programmer is a hand-held device for use with the Activa PC neurostimulator. It allows the patient to turn the neurostimulator on and off, check whether the neurostimulator is on or off, check the status of the neurostimulator battery, adjust programmed parameters within physician-prescribed limits, reset the stimulation cycle, and record a seizure event.

- N'Vision Programmer (Model 8840) and Software Application Card (Model 8870)

The Model 8840 N'Vision Programmer is used to noninvasively interrogate and program implantable medical devices developed by Medtronic's Neuromodulation Division. The programmer is a hand-held device containing hardware and software which provide the capabilities to program the implantable neurostimulators. The programmer is battery powered and uses a telemetry head for communication with the implanted devices. A graphical user interface allows the clinician access to the programming functions.

The N' Vision Application Card contains the application software necessary to program Medtronic Neuromodulation neurostimulators, while also having the capability to store data from programming sessions. The neurostimulator application software on the Model 8870 Application Card contains the software to program the Activa PC Model 37601 Neurostimulator. The software applications are accessed by interrogating a neurostimulator via the programmer's telemetry module. Following interrogation, the programmer will automatically select the application software required for programming the interrogated neurostimulator.

- External Neurostimulator (Model 37022)
The external neurostimulator is a temporary external power source used for perioperative testing. Parameters that can be adjusted include amplitude, pulse width, rate and electrode selection.
- Lead Frame Kits (Model 3353/3354)
The lead frame kits (which are designed to fit legally-marketed Elekta/Leksell and Radionics or Radionics-like stereotactic frames) are used to stabilize the lead in the insertion cannula during implantation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently three major treatment modalities for which there is evidence of effectiveness in the treatment of refractory epilepsy: Pharmacotherapy with antiepileptic drugs (AEDs), resective surgery, and device-based therapy including vagus nerve stimulation (VNS) and cortical stimulation of 1 or 2 seizure foci using the Responsive Neurostimulation (RNS[®]) System. Antiepileptic medications are the usual first line treatment for epilepsy. For those patients that do not respond to the initial AED, physicians generally will try other AEDs, either as monotherapy or in combination with other AEDs. In people with epilepsy for whom medications are not effective or who have unacceptable medication-related side effects, resective surgery and/or device-based therapies may be an option. Device-based therapies are often used as an adjunct to AED therapy. Resective surgery is most successful in patients with a clearly defined seizure onset location, where the location of the resection will not lead to postoperative deficits or morbidity. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Medtronic deep brain stimulation for the treatment of epilepsy is currently approved in Europe and other geographies. Medtronic markets devices for other deep brain stimulation therapies, as summarized below.

Indication	Description	PMA/HDE
Parkinson's disease and Essential Tremor	DBS™ Therapy	P960009
Dystonia	DBS™ Therapy	H020007
Obsessive-Compulsive Disorder	Reclaim® DBS™ Therapy	H050003

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.

- **Surgical complications.** Surgical complications may include, but are not limited to, the following:
 - Intracranial hemorrhage (which can lead to stroke, paralysis, or death)
 - Subcutaneous hemorrhage or seroma
 - Hematoma
 - Cerebrospinal fluid leakage and/or cerebrospinal fluid abnormality
 - Brain contusion
 - Infection and/or inflammation
 - Antibiotic anaphylaxis
 - Skin disorder
 - Edema
 - Persistent pain at surgery site and/or IPG site
 - Erosion
 - Brachial plexus injury (nerves to chest, shoulder and arm)
 - Postoperative pain, stress, or discomfort
 - Neuropathy (nerve degeneration)
 - Hemiparesis (muscular weakness or partial paralysis on one side of body)
 - Confusion – transient, nocturnal or ongoing
 - Cognitive impairment, including delirium, dementia, disorientation, psychosis and speech difficulties
 - Aphasia
 - Deep vein thrombosis
 - Complications from anesthesia
 - Phlebitis (vein inflammation)
 - Pulmonary embolism (sudden blood vessel obstruction)
 - Aborted procedures (air embolism, unable to find target, surgical complication, etc.)
 - Complications from unusual physiological variations in patients, including foreign body rejection phenomena
 - Pneumonia, seizure or convulsions
 - Paralysis (loss of motor function, inability to move)

- Stroke
- Death.
- **Deep brain stimulation complications.** Deep brain stimulation complications may include, but are not limited to, the following:
 - Device-related complications: Undesirable changes in stimulation possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture
 - Loss of therapeutic benefit as a result of change in electrode positions, loose electrical connections or lead/extension fracture
 - Depression, suicidal thoughts, suicide
 - Memory impairment or déjà vu
 - Status epilepticus
 - Changes in seizures: new seizure type or worsening seizures (increased seizure frequency, duration and/or severity)
 - Anxiety, panic attack
 - Paresthesia (tingling, shocking, vibration, or buzzing sensation)
 - Stimulation not effective, insufficient seizure control
 - Agitation, anger, psychosis
 - Confusion
 - Abnormal thoughts
 - Dizziness
 - Vomiting
 - Tension
 - Abnormal face or body movements, convulsions
 - Trouble sleeping
 - Pain at implant site
 - Abnormal feelings or sensations
 - Discomfort
 - Headaches
 - Infection, including meningitis
 - Lead fracture, migration, or dislodgement
 - Misplaced lead
 - Extension malfunction, fracture or disconnect
 - Deep brain stimulation system failure or battery failure within the device
 - Deep brain stimulation system malfunction or dislodgement
 - Spontaneous turning on or off of the pulse generator (IPG)
 - Allergic or rejection response to implanted materials
 - Persistent pain, tightness, or redness at the incision sites or general pain
 - General erosion or local skin erosion over the pulse generator (IPG) or other device component
 - Persistent pain, tightness or discomfort around the implanted parts (e.g., along the extension path in the neck)

- Impaired wound healing (e.g., incision site drainage), infection or abscess formation
- Additional neurosurgical procedure to manage one of the above complications or to replace a malfunctioning component
- Death, including SUDEP

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

IX. SUMMARY OF PRECLINICAL STUDIES

With the exception of the Intercept Model 37441 Patient Programmer, all components of the Medtronic DBS System for Epilepsy are commercially approved as part of the Medtronic Activa Tremor Control System (P960009, P960009/S3), the Medtronic Kinetra Neurostimulation System (P960009/S27) or the Medtronic Activa PC Neurostimulation System (P960009/S52 & P960009/S134). Therefore, the preclinical testing of these components provided in prior Medtronic Activa System PMA/PMA supplements is also applicable to the Medtronic DBS System for Epilepsy.

A. Laboratory Studies

1. Model 37601 Activa PC Neurostimulator

The Model 37601 Activa PC Neurostimulator underwent various testing for electrical safety and mechanical verification. Key testing on the neurostimulator is summarized in Table 3 below. Testing demonstrated the Model 37601 Activa PC Neurostimulator operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 3. Model 37601 Activa PC Neurostimulator Summary of Testing

Test	Test Purpose	Acceptance Criteria
Mechanical Verification	Verifies the mechanical and electrical testing of the Activa PC IPG. Testing included:	Testing demonstrated that all acceptance criteria was met at a minimum, to the standards noted where applicable.
	• Dimensions including weight	Device meets specified dimensional requirements.
	• Exposures to multiple ETO sterilization cycles	Device meets device functional test specifications after multiple ETO cycles per EN 45502-1:1997-08.
	• Radiopaque identification	Radiopaque is legible on x-ray.
	• Environmental temperature exposure and thermal shock	Device meets functional specifications after static and transient exposures per 45502-1: 2003-12.

Test	Test Purpose	Acceptance Criteria
	<ul style="list-style-type: none"> Mechanical vibration Mechanical shock Free fall drop 	Device meets functional test specifications after mechanical vibration and shock tests per 45502-2-1:2003, 45502-2-2: 2008 and multiple 30 cm drops on all axes.
	<ul style="list-style-type: none"> Shield deflection strength Shield deflection fatigue 	Device meets functional test specifications after low cycle testing at 18 lbs and high cycle testing at 3 lbs.
	<ul style="list-style-type: none"> Barometric pressure 	Device meets functional test specifications after testing per BS EN 45502-1:1998.
	<ul style="list-style-type: none"> Lead insertion & extraction force with set screw loose 	Lead/extension can be inserted into connector with less than 13.4 N and extracted with less than 1.75 lb.
	<ul style="list-style-type: none"> Lead retention force 	Lead/extension is retained within the connector at specified force.
	<ul style="list-style-type: none"> Contact resistance 	Contact impedance shall vary less than +/- 4.5 Ohms over life of device.
	<ul style="list-style-type: none"> Connector attach strength Connector attach fatigue 	Device meets leakage impedance requirements after low cycle static force testing for strength and 210,000 cycles for fatigue testing.
	<ul style="list-style-type: none"> Electrical leakage impedance 	Device meets requirements when tested per method described in ISO 5841-3:2000-2010.
Electrical Output Verification	Verify the electrical output of the Activa PC IPG. (amplitude, pulse width, frequency, etc.)	The IPG output parameters are within specified tolerances.
Electrical Leakage Current and DC Imbalance	Verify that leakage currents and DC imbalance of the outputs are within limits	IPG outputs meet section 16.2 of EN45502-1 / ISO 14708-1.
Temperature rise during single fault condition	Temperature should not rise more than the specified limit	Temperature rise is less than or equal to 2°C limit during single fault conditions per EN 45502-1: 1997 17.1.

2. Model 3387 and 3389 DBS Leads

The Model 3387 and 3389 DBS leads underwent various testing for electrical and mechanical verifications. Key testing on the lead is summarized in Table 4 below. Testing demonstrated the Model 3387 and 3389 DBS leads operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 4. Model 3387 and 3389 DBS Lead Summary of Testing

Test	Test Purpose	Acceptance Criteria
Mechanical	To verify the mechanical and electrical properties of the DBS leads.	All tests successfully met acceptance criteria per requirements based on intended use.
	<ul style="list-style-type: none"> • Lead Body 	Lead body meets intended design requirements.
	<ul style="list-style-type: none"> • Lead Length 	Lead meets specific length requirements.
	<ul style="list-style-type: none"> • Connector 	Lead connector allows connection to extensions, Lead cap, and OR cables.
	<ul style="list-style-type: none"> • Electrodes 	Lead meets electrode dimensions.
	<ul style="list-style-type: none"> • Flex Life 	Lead body shall be flexed for a minimum number of cycles with no damage based on intended use.
	<ul style="list-style-type: none"> • Bending Stiffness 	Lead able to withstand 3 point bending test.
	<ul style="list-style-type: none"> • Crush Strength 	Static crush strength shall be greater than 50 lbs/in.
	<ul style="list-style-type: none"> • Weld Neck Down Between Electrodes and Coil 	Lead weld neck down is within specifications.
	<ul style="list-style-type: none"> • Smoothness 	OD of lead shall fit through specified ID tube.
	<ul style="list-style-type: none"> • Straightness 	Lead shall have maximum warp of 0.150 inches.
	<ul style="list-style-type: none"> • Lead tip Straightness 	Lead tip meets minimum straightness specification.
	<ul style="list-style-type: none"> • Operating Temperature Range 	Lead maintains properties within specified temperature ranges.
	<ul style="list-style-type: none"> • Storage Temperature Range 	Lead maintains properties within specified storage temperature ranges.
	<ul style="list-style-type: none"> • Process Requirements 	Lead exposure to controlled environments, temperatures, and solvents.
	<ul style="list-style-type: none"> • Insertion /withdrawal Forces 	Lead connector meets maximum insertion and withdrawal forces.
	<ul style="list-style-type: none"> • Set Screw Exposure 	Lead contacts shall withstand a minimum torque of 5 in-oz.
	<ul style="list-style-type: none"> • No sharp corners or edges 	Lead meets acceptance criteria per requirements.
	<ul style="list-style-type: none"> • Sterilization 	Lead to be ETO sterilized.
<ul style="list-style-type: none"> • Vibration 	Reference ASTM D4169-86.	
<ul style="list-style-type: none"> • Mechanical Shock 	Reference ASTM D4169-86.	
Electrical	<ul style="list-style-type: none"> • DC resistance 	Less than 100 ohms.
	<ul style="list-style-type: none"> • Cross Circuit Resistance 	Lead meets minimum cross circuit resistance.

3. Model 37086 DBS Extension

The Model 3387 and 3389 DBS leads underwent various testing for electrical and mechanical verifications. Key testing on the lead is summarized in Table 5 below. Testing demonstrated the Model 3387 and 3389 DBS leads operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 5. Model 37086 DBS Extension Summary of Testing

Test	Test Purpose	Acceptance Criteria
Mechanical	To verify the mechanical and electrical properties of the DBS Extensions.	All tests successfully met acceptance criteria per requirements based on intended use.
	<ul style="list-style-type: none"> • Electrode/Contact Configuration 	Extension body meets intended design requirements.
	<ul style="list-style-type: none"> • Extension Lengths 	Extension meets specific length requirements.
	<ul style="list-style-type: none"> • Surface Features 	Extension meets specific surface feature requirements.
	<ul style="list-style-type: none"> • Force at Maximum Extension 	Extension lead body meets force requirements when extended 15%.
	<ul style="list-style-type: none"> • Contact Strength (Proximal End) 	Extension shall meet electrical and mechanical requirements when set screw contacts are tightened to 5 in-oz, with no permanent damage to contacts.
	<ul style="list-style-type: none"> • Connector Block (Distal End) 	Each extension set screw block shall be exposed to a maximum torque of 5 in-oz (minus specified tolerance).
	<ul style="list-style-type: none"> • Tunneling Tool (exposure) 	Extension shall be exposed to a force based on intended use conditions while inserted into carrier.
	<ul style="list-style-type: none"> • Torque Limiting Wrench (compatibility) 	Extension sets screws to be compatible with specific torque wrench.
	<ul style="list-style-type: none"> • Particulate Matter 	Per EN45502-1.
	<ul style="list-style-type: none"> • Proximal Extension Body Kink 	Extension proximal end meets specific kink requirements.
	<ul style="list-style-type: none"> • Dynamic Axial Load 	Extension shall meet cyclic requirements when stretched 15 percent.
	<ul style="list-style-type: none"> • Dynamic Flex 	Extension shall be flexed for a minimum number of cycles with no damage based on intended use.
Electrical	<ul style="list-style-type: none"> • DC resistance 	Maximum 38 ohms.
	<ul style="list-style-type: none"> • DC leakage Current 	Leakage between circuits shall not affect INS out put.

4. Model 37441 Intercept Patient Programmer

The Intercept Model 37441 Patient Programmer is a derivative of the patient programmer developed for use with the Activa PC Neurostimulation System for Parkinson’s Disease and Essential Tremor. Modifications were made to adapt the programmer for use by epilepsy patients. These included the incorporation of a seizure button, soft key control of neurostimulator on/off activations, and simplified navigation. To verify and validate these changes, software testing, system validation, and human factors validation were completed. Medtronic conducted design verification and validation testing pertaining to aspects of the patient programmers impacted by the design and software changes. The electrical, mechanical, and telemetry design verification testing was performed with a “verification by equivalence” approach. Key testing on the Intercept Patient Programmer is summarized in Table 6 below. In addition, the previous packaging validation is still applicable to the Intercept model.

Table 6. Model 37441 Intercept Patient Programmer Summary of Testing

Test	Test Purpose	Acceptance Criteria
Usability Validation	Validates the intended users can use the Intercept EP Patient Programmer, and that the Intercept EP Patient Programmer meets its intended use.	<ul style="list-style-type: none"> • All participants successfully complete selected patient programmer tasks using Simple Mode without errors of a hazardous nature. • All participants successfully complete the following patient programmer tasks using Simple Mode: record a seizure event, check neurostimulator battery, check patient programmer battery, and turn stimulation OFF.
Software Verification	Verifies functionality of the Patient Programmer software application and Patient Electronics Module (PEM, including: <ul style="list-style-type: none"> • 53 baseline (ie MvD) conditions confirmed • 13 Epilepsy conditions tested 	All tests successfully met acceptance criteria per requirements including: <ul style="list-style-type: none"> • Application download and versions • General display and key press • Lead connection check • Advanced and simple mode • Seizure button features (count, display etc.) • Telemetry failures
Mechanical Testing	Verifies by similarity that the Model 37441 Intercept Patient Programmer meets mechanical requirements to Model 37642 DBS Patient Programmer. Tests included:	All tests successfully met acceptance criteria per requirements including:
	<ul style="list-style-type: none"> • Operating/storage temperature 	Device operates after exposed to the temperature extremes of 9°C (48°F) and 43°C (110°F).

Test	Test Purpose	Acceptance Criteria
	<ul style="list-style-type: none"> Thermal shock 	Device operates per specification after being exposed to temperature cycles of -40°C (-40°F) and 65°C (150°F).
	<ul style="list-style-type: none"> Mechanical shock 	Device operates after multiple drops from 1 meter on all axes.
	<ul style="list-style-type: none"> Humidity 	Device operates after being exposed in a chamber at 95% relative humidity and 95°F for the listed number of days.
	<ul style="list-style-type: none"> Chemical resistance 	Device labels and exposed surfaces are not damaged by exposure to standard household chemicals.
	<ul style="list-style-type: none"> Seizure button color 	Seizure button is per color spec and has a different icon shape on the button surface.
	<ul style="list-style-type: none"> Front Lens/graphics 	The front lens is made of the same material and is the same shape and size.
System Verification	Verifies that the Intercept EP patient programmer application supports the Activa PC INS.	Using the Intercept EP patient programmer, a Lead Connection Check is successfully performed on the DBS for Epilepsy System.
	Verifies that the Intercept EP patient programmer is based off of the Activa RC/PC Patient Programmer platform.	Inspection of the mechanical assembly drawings and product specifications demonstrate that the Intercept EP patient programmer hardware design is based off of the Activa RC/PC Patient Programmer platform.
	<p>Verifies the Intercept EP patient programmer seizure key functionality, including:</p> <ul style="list-style-type: none"> Seizure key press to record a seizure Seizure key press to restart the stimulation cycle Maximum number of seizure key presses count Seizure key press counts are stored by the system. Seizure key press count data is reset after each programming session with the N'Vision 8840 Clinician Programmer. 	<ul style="list-style-type: none"> After pressing the seizure key once, the seizure confirmation screen appears and the seizure key count on the therapy screen increases by one. With Intercept EP patient programmer restart stim feature ON, the Activa PC INS restarts the stimulation cycle after a single press of the seizure button. The Intercept EP patient programmer increments the seizure count with each key press up to the maximum number The DBS for Epilepsy system stores the seizure key press count. The Intercept EP Patient Programmer displays a seizure key count of zero after each programming session with the N'Vision 8840 Clinician Programmer.

Test	Test Purpose	Acceptance Criteria
System Validation	<p>Validates that customer needs and intended uses are met by the DBS for Epilepsy System. Customer needs and intended uses include:</p> <ul style="list-style-type: none"> • Seizure tracking • Therapy monitoring and configuration using the clinician programmer • Therapy monitoring and adjustment using the patient programmer • Patient Programmer Therapy ON/OFF 	<p>All tests successfully met acceptance criteria per requirements. DBS for Epilepsy therapy Customer Needs and Intended uses were validated through bench testing.</p> <ul style="list-style-type: none"> • Seizure button presses are tracked between clinician programming sessions. • Amplitude, pulse width, rate can be adjusted using the patient programmer. Groups and programs can be selected using the patient programmer. • The stimulation cycle restarts with a seizure button press. • Therapy ON/OFF is programmable using the patient programmer.

5. Sterilization

The Activa PC INS, leads and extensions are sterilized in their packaging using 100% ethylene oxide (EtO) gas sterilant. The EtO sterilization process includes all the requirements necessary to ensure product sterility. These requirements include sterilization process validation, which ensures a sterility assurance level (SAL) of at least 10^{-6} , sterilization process monitoring requirements, sterile lot control requirements, and parametric release requirements. The method of sterilization cycle validation meets the requirements as stated in the applicable standards, including *EN/ISO 11135-1:2007, Medical Devices—Validation and Routine Control of Ethylene Oxide Sterilization*, to provide a 10^{-6} SAL. DBS leads are tested for product bacterial endotoxin not more than 2.15 EU/device. These limits were verified using Limulus Amebocyte Lysate (LAL) testing.

6. Packaging and Shelf-life

Packaging and shelf life verification testing was successfully completed for the DBS Leads, DBS Extensions, and Neurostimulator per BS EN ISO 11607-1:2006 - *Packaging for terminally sterilized devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems*. Packaging verification testing was also successfully completed for the Patient Programmer, N'Vison Programmer, External Neurostimulator, and accessories per ASTM D4169:2008. The testing confirmed that the device packaging adequately protects the product during conditions that may be encountered during storage, shipping, and handling.

The Activa PC Neurostimulator has a maximum shelf life of 18 months from the date of battery attachment. The DBS Leads and DBS Extensions have a maximum shelf life of 4 years from the date of sterilization.

7. Biocompatibility

Biocompatibility of materials of all patient-contacting components of the Medtronic DBS System for Epilepsy was tested according to the ISO 10993 Biological evaluation of medical devices (current at the time of testing) and/or other applicable standards, or in some cases a rationale for no additional testing was provided. The neurostimulator, DBS Leads and Extensions are considered permanent (> 30 days) implants with tissue/bone contact. Biocompatibility testing conducted on the tissue contacting materials is summarized in Table 7, Table 8, and Table 9 below. All pre-specified test acceptance criteria were met and all tests passed.

Table 7. Model 37601 Activa PC Biocompatibility Summary

Biological Effect	Test Reference	Acceptance Criteria	Results
Cytotoxicity	Cytotoxicity Test (MEM Elution)	Reactivity grade is not greater than mild reactivity (Grade 2).	Non-cytotoxic
Sensitization	Maximization Sensitization Test (Guinea Pig)	Grades of <1 in the test group provided grades of < 1 are observed on the control animals.	Non-sensitizing
Irritation or Intracutaneous Reactivity	Intracutaneous/Intradermal Test (Rabbit)	The difference between the test article and the control mean score is ≤ 1.0 .	No evidence of significant irritation.
Systemic Toxicity (acute)	Systemic Toxicity (Mice)	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	No mortality or systemic toxicity
	Material Mediated Pyrogenicity (Rabbit)	No rabbit shows an individual rise in temperature of 0.5 °C or more above the baseline temperature.	Non-pyrogenic
Genotoxicity	Reverse Mutation Test (Bacterial Cells)	No significant increase in the mutation frequency of the test article compared to the negative control article.	Non-mutagenic
	<i>In Vitro</i> Mammalian Chromosome Aberration Test (Chinese Hamster Ovary Cells)	No statistically significant increase in the number of structural chromosomal aberrations compared to the negative control.	Did not induce chromosomal aberrations
	Micronucleus Assay (Mice)	There is no statistically significant increase in micronucleated cells as compared to the negative control.	Non-mutagenic
Implantation	Intramuscular Implant in Rabbits (12 weeks)	Difference between mean test score and mean control score: Non-toxic < 1 Slightly toxic ≥ 1 and < 2 Mildly toxic ≥ 2 and < 3 Moderately toxic ≥ 3 and < 4 Severely toxic ≥ 4	Non-toxic

Table 8. Model 3387/3389 Leads Biocompatibility Summary

Biological Effect	Test Reference	Acceptance Criteria	Results
Cytotoxicity	Cytotoxicity Test (MEM Elution) (All materials except platinum/iridium)	Reactivity grade is not greater than mild reactivity (Grade 2).	Non-cytotoxic
Sensitization	Maximization Sensitization Test (Guinea Pig)	Grades of <1 in the test group provided grades of < 1 are observed on the control animals.	Non-sensitizing
Irritation or Intracutaneous Reactivity	Intracutaneous / Intradermal Test (Rabbit) (All materials except platinum/iridium)	The difference between the test article and the control mean score is ≤ 1.0 .	No evidence of significant irritation
Systemic Toxicity (acute)	Systemic Toxicity (Mice) (All materials except platinum/iridium)	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	No mortality or systemic toxicity
	Material Mediated Pyrogenicity (Rabbit) (All materials except platinum/iridium)	No rabbit shows an individual rise in temperature of 0.5 °C or more above the baseline temperature.	Non-pyrogenic
Genotoxicity	Reverse Mutation Test (Bacterial Cells) (All materials except platinum/iridium)	No significant increase in the mutation frequency of the test article compared to the negative control article.	Non-mutagenic
	<i>In Vitro</i> Mammalian Chromosome Aberration Test (Chinese Hamster Ovary Cells) (All materials except polyurethane 80A adhesive and platinum/iridium)	No statistically significant increase in the number of structural chromosomal aberrations compared to the negative control.	Did not induce chromosomal aberrations
	Micronucleus Assay (Mice) (All materials except polyurethane 80A adhesive and platinum/iridium)	There is no statistically significant increase in micronucleated cells as compared to the negative control.	Non-mutagenic
Implantation	Intramuscular Implant in Rabbits (12 weeks) (All materials except platinum/iridium and MP35N)	Difference between mean test score and mean control score: Non-toxic < 1 Slightly toxic ≥ 1 and < 2 Mildly toxic ≥ 2 and < 3 Moderately toxic ≥ 3 and < 4 Severely toxic ≥ 4	Non-toxic

Table 9. Model 37086 DBS Extension Biocompatibility Summary

Biological Effect	Test Reference	Acceptance Criteria	Results
Cytotoxicity	Cytotoxicity Test (MEM Elution) Cytotoxicity Test (Agar Diffusion) (epoxy)	Reactivity grade is not greater than mild reactivity (Grade 2).	Non-cytotoxic
Sensitization	Maximization Sensitization Test (Guinea Pig) (All materials except epoxy)	Grades of <1 in the test group provided grades of < 1 are observed on the control animals.	Non-sensitizing
Irritation or Intracutaneous Reactivity	Intracutaneous / Intradermal Test (Rabbit)	The difference between the test article and the control mean score is ≤ 1.0 .	No evidence of significant irritation
Systemic Toxicity (acute)	Systemic Toxicity (Mice)	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	No mortality or systemic toxicity
	Material Mediated Pyrogenicity (Rabbit)	No rabbit shows an individual rise in temperature of 0.5 °C or more above the baseline temperature.	Non-pyrogenic
Subacute and Subchronic Toxicity (ETR silicone rubber and ETR silicone rubber with barium sulfate) (N/A for MP35N, stainless steel 316L, and titanium 6Al-4V*)	Subchronic Toxicity (Mice)	No statistically significant difference in clinical observations, gross necropsy, histopathological findings, and hematological parameters between test and control articles.	Non-toxic
Genotoxicity (No testing for epoxy) (N/A for MP35N, stainless steel 316L, and titanium 6Al-4V*)	Reverse Mutation Test (Bacterial Cells)	No significant increase in the mutation frequency of the test article compared to the negative control article.	Non-mutagenic
	<i>In Vitro</i> Mammalian Chromosome Aberration Test (Chinese Hamster Ovary Cells)	No statistically significant increase in the number of structural chromosomal aberrations compared to the negative control.	Did not induce chromosomal aberrations
	Micronucleus Assay (Mice)	There is no statistically significant increase in micronucleated cells as compared to the negative control.	Non-mutagenic
Implantation (N/A for MP35N,	Intramuscular Implant in Rabbits	Difference between mean test score and mean control score:	Non-toxic

Biological Effect	Test Reference	Acceptance Criteria	Results
stainless steel 316L, and titanium 6Al-4V*)	(12 weeks)	Non-toxic < 1 Slightly toxic ≥ 1 and < 2 Mildly toxic ≥ 2 and < 3 Moderately toxic ≥ 3 and < 4 Severely toxic ≥ 4	

* The tissue contact of MP35N, stainless steel 316L, and titanium 6Al-4V is less than 24 hours. Therefore, the biological tests of Subacute and Subchronic Toxicity, Genotoxicity and Implantation are not applicable for these materials.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Pivotal Study

A Pivotal study, SANTÉ (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy), was performed to establish a *reasonable assurance of safety and effectiveness* of bilateral stimulation of the anterior nucleus of the thalamus (ANT) with the Medtronic DBS System for Epilepsy as an adjunctive therapy in individuals 18 years of age or older with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications. Subjects in the SANTÉ study had an average of 6 or more partial-onset seizures per month, were refractory to at least 3 antiepileptic drugs (AEDs), and were taking 1-4 AEDs at the time of enrollment. This study was performed in the United States under IDE # G030065. Data from this clinical study (from the blinded and long-term open-label phases) was the basis for the PMA approval decision that demonstrated sustained improvements in seizure reduction. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled in the study beginning on December 11, 2003 and the last implant was June 27, 2007 and includes 110 subjects in the Pivotal trial. The database for this PMA supplement reflects data collected through April 15, 2014 and includes data for all subjects who had not discontinued the study. There were 17 investigational sites in the US.

The SANTÉ study was a multicenter, prospective, randomized, double-blind, parallel groups clinical study. The study design included a 3-month Baseline Phase, a 1-month Operative Phase, a 3-month Blinded Phase, and a 9-month Unblinded Phase, followed by a Long-Term Follow-up Phase.

Enrolled subjects collected baseline seizure data for three months prior to implantation of the DBS system. Subjects received a DBS system as adjunctive therapy if they met all inclusion and no exclusion criteria during the Baseline Phase.

Devices were implanted in a single surgical procedure under local or general anesthesia. Post-implant MRI was performed to confirm lead location. DBS leads

were implanted bilaterally in the ANT and connected subcutaneously to a neurostimulator via lead extensions tunneled down the side of the neck. Four weeks after device implant, subjects were randomized to active (treatment) or control groups in a 1:1 ratio. The active group received stimulation at 5 V, 145 Hz, 90 μ s, a cycling on interval of 1 minute, and a cycling off interval of 5 minutes. The control group was programmed to 0 V, 145 Hz, 90 μ s, a cycling on interval of 1 minute, and a cycling off interval of 5 minutes. Study subjects, the investigator, and study center staff were blinded to the randomization assignments. One programmer at each site was unblinded for purposes of programming and treatment of adverse events. Subjects kept seizure diaries and were seen in the clinic at 2 months, 3 months, and 4 months post-implant for follow-up during the Blinded (randomized) Phase of the study.

At the end of the Month 4 visit, the control group subjects had the stimulation programmed on, and active group subjects continued stimulation. Subjects in both groups continued to be unaware of their prior stimulation status during the previous Blinded Phase. Programming changes were restricted through the Unblinded Phase of the study (Months 4-13) and AEDs (antiepileptic drugs) remained stable. During the Long-Term Follow-Up Phase (beyond Month 13), there were no restrictions on programming or AED changes. Visits occurred monthly through the Blinded and Unblinded Phases, and every 6 months during the Long-Term Follow-Up Phase. In addition to the semi-annual and annual visits, subjects were contacted by phone once a month in the Long-Term Follow-Up Phase to review the diary and record health care utilization and adverse events. See Figure 2 for an overview of the study phases.

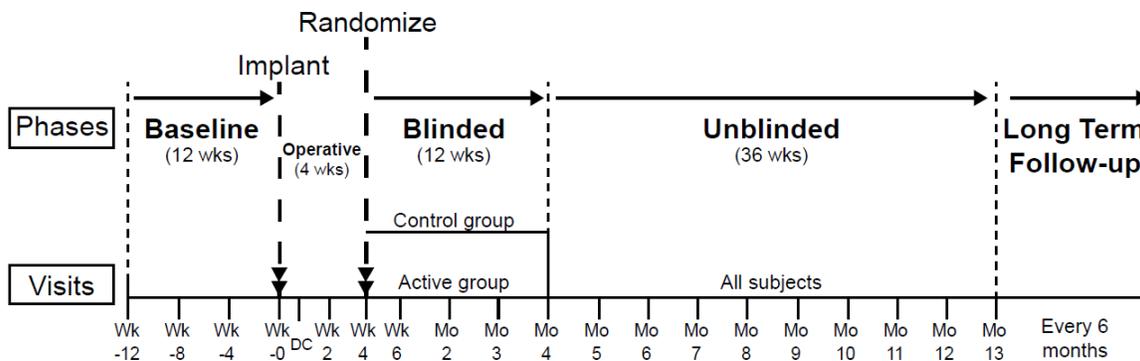


Figure 2. Study design schema.¹

¹ Abbreviations: wk(s), week(s); mo, month; DC, hospital discharge

The study was designed to have 80% power with an overall 1-sided Type 1 error rate of 0.025 (equivalent to two-sided Type 1 error of 0.05), assuming 25% difference between groups in seizure frequency reduction. To meet these criteria, 102 subjects were required at the end of the Blinded Phase. To ensure that patient enrollment was adequate to meet the minimum sample size requirement (taking into account an approximate 30% baseline dropout and losses to follow-up), the recommended enrollment sample size was 150 subjects. The sample size for the secondary outcome

measures and additional study measures was not pre-specified to show a statistically significant difference in those measures.

An independent Data Monitoring Committee (DMC) for the SANTÉ study was established. The DMC was responsible for independently monitoring the safety of interventions during the investigation by reviewing the data available by Medtronic acting in the capacity of the Coordinating Center. For the first year of the study, the DMC met every 6 months. After that time, the DMC met at least annually to review the safety data and study conduct. One preplanned interim analysis for futility was performed by DMC liaison statistician. The Clinical Events Committee (CEC), consisting of several Medtronic Clinical Study Team functions, periodically reviewed all adverse events reported during the study to assure appropriate and consistent classification. Central laboratory services for MRI (magnetic resonance imaging) analysis were provided by Hennepin County Medical Center, Department of Radiology.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the SANTÉ study was limited to patients who met the following inclusion criteria:

- Partial-onset seizures with or without secondary generalization.
- An average of 6 or more partial-onset seizures (with or without secondary generalized seizures) per month during the Baseline Phase, with no more than 30 days between seizures.
- Refractory to antiepileptic drugs (subjects were considered refractory if they failed at least 3 AEDs due to lack of efficacy).
- Receiving 1 to 4 currently marketed AEDs.
- Aged 18 to 65 years, inclusive.
- If female, not pregnant.

Patients were not permitted to enroll in the SANTÉ study if they met any of the following exclusion criteria:

- Multilobar (>3 different lobes) anatomic areas of seizure onset.
- Symptomatic generalized epilepsy.
- Averaged more than 10 complex partial seizures/day over the 3-month period prior to baseline.
- Experienced only simple partial seizures that had no outward clinical manifestations observable by either the subject or caregiver.

- Any episode of convulsive status epilepticus within the 12 months prior to baseline.
- Previous diagnosis of psychogenic/non epileptic seizures.
- Surgical candidate for, and willing to undergo, partial temporal lobectomy or lesionectomy.
- Diagnosis or evidence of a neurological disorder or condition affecting the brain likely to progress (e.g., brain tumor, active encephalitis, active meningitis or abscess, arteriovenous malformations or cavernous angiomas that were likely to progress).
- Intelligence quotient (IQ) less than 70 based on the baseline WASI (Wechsler Abbreviated Scale of Intelligence) test.
- Presence of any of the following: psychiatric illness hospitalization, suicide attempt or symptoms of psychosis (e.g., hallucinations, delusions) unrelated to an ictal state, a postictal state or a medication.
- Malignancy or history of malignancy (excluding resected basal cell carcinomas).
- Presence of an implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemakers, spinal cord stimulator) or any metallic implants in the head (e.g., aneurysm clip, cochlear implant). Vagus nerve stimulation (VNS) devices were allowed if the device had been turned off and the subject agreed to have the generator explanted.
- Risk factors that would put the subject at risk for intraoperative or postoperative bleeding
- Condition or disease that was known to require repeat MRIs.

2. Follow-up Schedule

A schematic of the study timeline is provided in Figure 2 above. The primary effectiveness analysis compared the change in the total seizure rates in active group and in the control group over the 3-month Blinded Phase. Primary safety analyses include adverse event data over the first 3 months post-implantation. Secondary safety and effectiveness analyses included data from all periods of the study.

Information regarding daily seizure counts, adverse events and subject well-being was collected at all visits by a physician investigator blinded to the subject's randomization status. All patients were scheduled to return for follow-up examinations monthly during the Blinded and Unblinded Phases and every 6 months during the Long-Term Follow-Up Phase.

Preoperatively, a 3-month baseline seizure diary was completed by all subjects to gather data on seizure classification and frequency. The Liverpool Seizure

Severity Scale, Quality of Life (QOLIE-31), neuropsychological testing and health care utilization data were collected in addition to adverse event data during the Baseline Phase. Postoperatively, and during the Blinded Phase, the objective parameters measured during the study included the data administered during the Baseline Phase, as well as neurostimulator monitoring, subject satisfaction and a blinding assessment. Adverse events and complications were recorded at all visits.

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

3. Clinical Endpoints

Safety:

The primary safety objective for the Pivotal study was to characterize the adverse events and incidence of sudden unexplained death in epilepsy (SUDEP) experienced with the deep brain stimulation (DBS) system stimulating the anterior nucleus in subjects with refractory epilepsy. For safety and unblinded Phase effectiveness analyses, all implanted subjects that were followed during the time interval of interest were included in the analyses.

Effectiveness:

The primary effectiveness objective was to demonstrate that the reduction in the total seizure rate in the active group was greater than in the control group over the entire Blinded Phase compared to the Baseline Phase. The pre-specified analysis utilized a generalized estimating equations (GEE) model to test for the difference in seizure rates between groups and required that subjects record a minimum of 70 days of diary in the entire Blinded Phase. One subject was excluded for having less than the required number of diary days and one subject in the active group was also excluded as this subject was determined to be an outlier.

This “outlier” subject, randomized to the active group, was identified to be an extreme and highly influential observation from a statistical and medical perspective. Inclusion of this subject’s data markedly changes the estimate of the treatment effect. This subject experienced a nearly immediate increase in the occurrence of frequent and brief seizures of a new complex partial type subsequent to the initiation of stimulation (210 seizures in 3 days compared to this subject’s baseline seizure rate of 19 seizures per month) which immediately ceased when voltage was reduced. The subject later had voltage increased beyond the level that was associated with the initial increase in seizures, with no recurrence of those seizures. The subject experienced two more seizures of this type, on the same day, during the Long-Term Follow-Up Phase.

Sensitivity analyses were performed to assess the potential impact of missing data on the long-term effectiveness results. Two analyses were performed that included all randomized subjects: LOCF (last observation carried forward) and Worst case. For both of these analyses, if the subject had at least 28 days of diary in the last 3 months

prior to the annual visit, the percent change from baseline was calculated from those data. If there were less than 28 days, the percent change from the last visit was used to calculate missing values for the LOCF method. The Worst case imputation used 100% worsening if there were less than 28 days of diary.

For other effectiveness objectives, chi-square tests were used for categorical responses, Wilcoxon rank-sum (for comparison between active and control) and Wilcoxon signed-rank (for change from baseline) tests for non-normally distributed continuous endpoints, and t-tests (for comparison between active and control) or paired t-tests (for change from baseline) for normally distributed continuous endpoints.

Secondary effectiveness objectives were as follows:

- To demonstrate that the proportion of responders in the active group is greater than in the control group. Responders were defined as subjects whose seizure frequency was reduced by $\geq 50\%$ as compared with baseline.
- To demonstrate that the mean percentage of seizure-free days and maximum length of seizure-free intervals in the active group is greater than in the control group.
- To demonstrate that the proportion of treatment failures in the active group is less than in the control group

Additional study measures:

- To characterize seizure type and severity experienced during the Baseline and Blinded Phases in the active and control groups.
- To characterize the number of patient programmer activations during the Blinded Phase in the active and control groups.
- To characterize the scores of the Quality of Life in Epilepsy (QOLIE-31), the subject satisfaction and subject outcome questions in the active and control groups.
- To characterize the results of the neuropsychological testing in the active and control groups.
- To characterize health care resource utilization in the active and control groups.
- To characterize the number of times subjects in the active and control groups used rescue medications.

B. Accountability of PMA Cohort

At the time of database lock, of 157 patients enrolled in the PMA study, 110 were implanted and 66.3% (73) of subjects were available for analysis at the completion of the study, i.e. the 7 years post-operative visit. The safety analysis populations for the study included all 110 subjects that were implanted and the primary effectiveness

analysis population included 108 subjects, excluding the following 2 implanted subjects: one subject who exited the study before randomization (due to an infection), and one subject who did not have 70 days of diary entries in both the Baseline and Blinded Phases. One subject who was deemed to be an “outlier” was excluded from the post-hoc analysis.

Figure 3 summarizes the distribution of subjects entering each study phase and the number of subjects active in each phase at the time of the database cutoff.

Withdrawals and discontinuations

Forty-seven subjects discontinued from the study prior to implant: eligibility or implant criteria not met (24), withdrawal of consent by subject (17), investigator decision due to safety reason (2), adverse event (1), death (1), lost to follow-up (1), and instability after VNS device turned off (1).

No subjects discontinued from the study during the Blinded Phase.

Five subjects discontinued from the study in the Unblinded Phase: death (1) and adverse event (implant site infection [2], implant site pain [1], and involuntary muscle contractions [1]).

Thirty-six subjects discontinued from the study in the Long-Term Follow-Up Phase: death (5), withdrawal of consent by subject (5), investigator decision (3), elective medical device removal (1), and adverse event (therapeutic product ineffective [13], implant site infection [3], anxiety [2], cognitive disorder [1], meningitis [1], psychotic disorder [1], and sensory disturbance [1]).

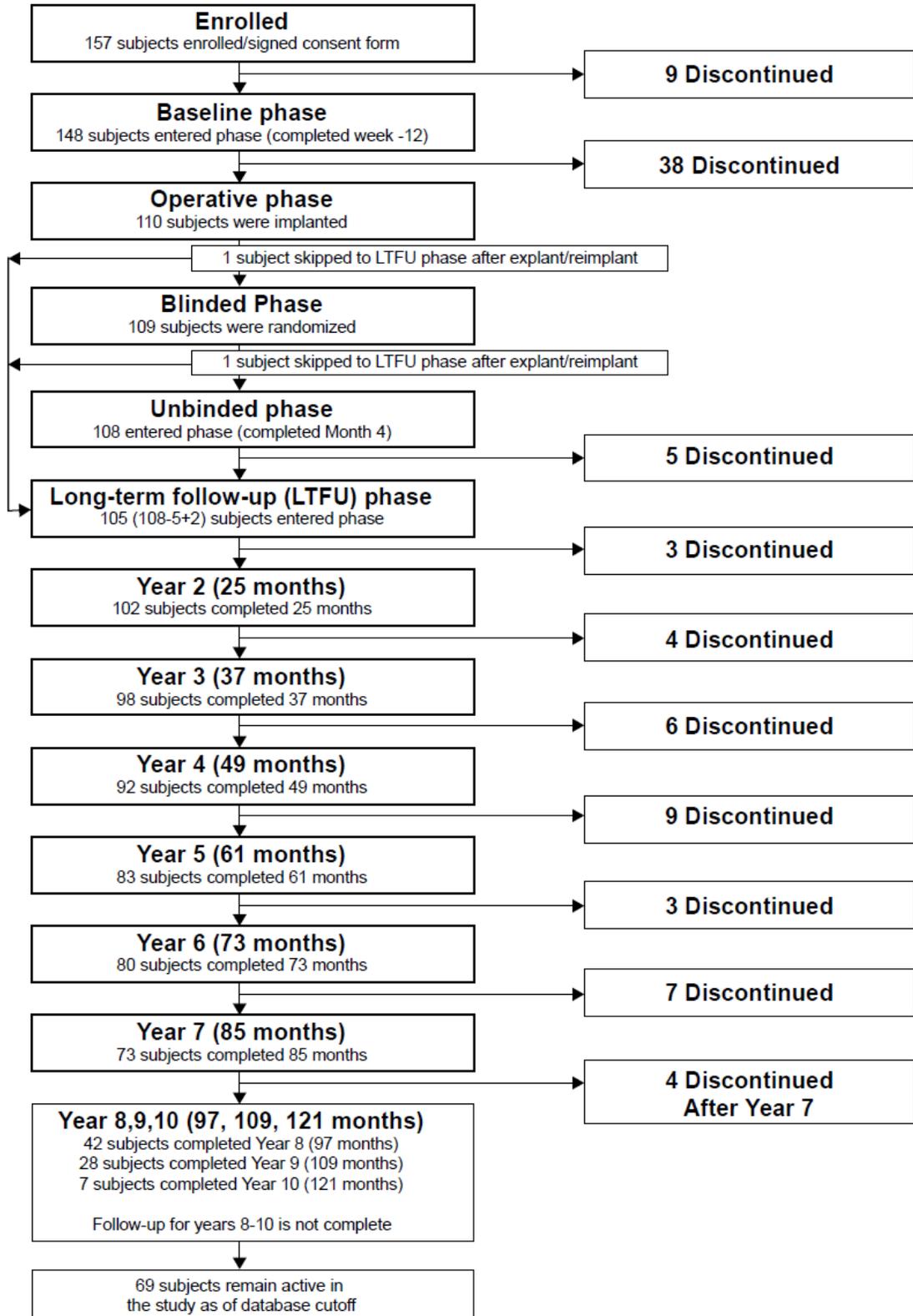


Figure 3. Subject disposition

C. Study Population Demographics and Baseline Parameters

Demographic information is provided in Tables 10 and 11 below.

Table 10. Demographic and baseline characteristics – age, years with epilepsy, baseline seizure counts

	All implanted (n=110)	By treatment group				p-value
		Active (n=54)		Control (n=55)		
	Mean ± std	Mean ± std	Range	Mean ± std	Range	
Age (years)	36.1 ± 11.2	35.3 ± 11.0	18.2 – 55.4	36.8 ± 11.5	19.6 – 60.9	0.484
Years with epilepsy	22.3 ± 13.3	21.6 ± 13.3	2 – 48	22.9 ± 13.5	2 – 60	0.608
Baseline Phase seizure counts (per month)	56.1 ± 101.0 median 19.5	57.9 ± 105.2 median 18.4	7 – 555	55.2 ± 98.4 median 20.4	6 – 604	0.985

Table 11. Demographic and baseline characteristics – gender, surgical procedure for epilepsy, number of epilepsy medications, seizure types, seizure onset locations

	All implanted (n=110)		By treatment group				p-value
	No. of subjects	%	Active (n=54)		Control (n=55)		
	No. of subjects	%	No. of subjects	%	No. of subjects	%	
Gender							
Male	55	50.0%	25	46.3%	30	54.5%	0.389
Female	55	50.0%	29	53.7%	25	45.5%	
Surgical procedure for epilepsy							
VNS system implant	49	44.5%	21	38.9%	28	50.9%	0.389
Previous epilepsy surgery	27	24.5%	11	20.4%	16	29.1%	0.292
Number of epilepsy medications							
1	12	10.9%	6	11.1%	6	10.9%	0.287
2	54	49.1%	25	46.3%	28	50.9%	
3	41	37.3%	23	42.6%	18	32.7%	
4	3	2.7%	0	0.0%	3	5.5%	
Seizure types ^a							
Complex partial	102	92.7%	51	94.4%	50	92.6%	0.716
Partial to generalized	85	77.3%	38	70.4%	46	85.2%	0.115
Simple partial	74	67.3%	37	68.5%	36	66.7%	0.839
Primary generalized	5	4.5%	3	5.6%	2	3.7%	0.679
Other	1	0.9%	0	0.0%	1	1.9%	1.000
Seizure onset locations ^b							
Temporal lobe	66	60.0%	35	64.8%	30	54.5%	0.331
Frontal lobe	30	27.3%	15	27.8%	15	27.3%	1.000
Diffuse or multifocal	10	9.1%	5	9.3%	5	9.1%	1.000
Other	10	9.1%	5	9.3%	5	9.1%	1.000
Parietal lobe	5	4.5%	2	3.7%	3	5.5%	1.000
Occipital lobe	4	3.6%	3	5.6%	1	1.8%	0.363

^a Subjects may experience more than 1 seizure type.

^b Subjects may have seizures originating from more than 1 onset location.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of primary safety endpoint was based on the cohort of 110 implanted subjects available for the 3-month evaluation. Data from the study, including the open label period, were used to assess overall safety in which all subjects active in the study were followed for a minimum of 7 years after device implantation. The key safety outcomes for this study are presented below in tables 12 to 14.

Adverse effects are reported in tables 15 to 32.

Adverse effects that occurred in the PMA clinical study:

The SANTÉ study evaluated the safety of bilateral stimulation of the ANT for the treatment of epilepsy in 110 implanted subjects with a combined 713 device-years of experience. The investigator classified each adverse event as serious or non-serious and as device-related or not device-related. Device-related adverse events include those related to the implanted device, programming/stimulation, surgery/anesthesia, or the implant procedure. Adverse events were considered serious if the event resulted in significant risks or consequences to the subject's acute or long-term health, serious injury or death, hospital admission, permanent impairment of a body function or permanent damage to a body structure or if invasive medical intervention was required to alleviate the adverse event. Adverse events are presented using MedDRA Coding according to the Preferred Term (PT).

Adverse events overview

Table 12 presents an overview of adverse events (AEs). As of the database cutoff, there were 2,845 adverse events reported in 110 subjects. Serious adverse events (SAEs) accounted for 5.9% of events and device-related SAEs were 1.7% of all events. A serious device-related adverse event was reported in 34.5% (38/110) of subjects. There were no unanticipated adverse device effects.

Table 12. Adverse event summary by cause – total post-implant

Event Type	No. of events (% of events)	Subjects (%) with an Event (n=110)^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110)^a
Device	394 (13.8%)	101 (91.8%)	47/2845 (1.7%)	38 (34.5%)
Non-Device	2451 (86.2%)	110 (100.0%)	121/2845 (4.3%)	55 (50.0%)
Total	2845	110 (100.0%)	168/2845 (5.9%)	73 (66.4%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Due to the long duration of this study, an overview of the adverse events that occurred from implant to Year 1 and from implant to Year 7 is also provided.

During the first year after device implant (Operative through the Unblinded Phases), 822 adverse events were reported in 109 subjects as shown in Table 13. The majority of events (70.8%) were not device-related. Serious adverse events accounted for 6.8% of all first year events and device-related SAEs accounted for 4.1% of all first year events. Overall, 25.5% (28/110) of subjects had a serious device-related adverse event in the first year after device implant.

Table 13. Adverse event summary by cause – implant to Year 1

Event Type	No. of events (% of events)	Subjects with an Event (n=110) ^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110) ^a
Device	240 (29.2%)	93 (84.5%)	34/822 (4.1%)	28 (25.5%)
Non-Device	582 (70.8%)	107 (97.3%)	22/822 (2.7%)	20 (18.2%)
Total	822	109 (99.1%)	56/822 (6.8%)	40 (36.4%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

During the first 7 years after device implant (Operative Phase through the Long-Term Follow-Up Phase Year 7 visit), 2,566 adverse events were reported in 110 subjects as shown in Table 14. The majority of events (85.5%) were not device-related. Serious adverse events accounted for 6.2% of events and device-related SAEs accounted for 1.7% of events. Overall, 32.7% (36/110) of subjects had a serious device-related adverse event in the first 7 years after device implant.

Table 14. Adverse event summary by cause – implant to Year 7

Event Type	No. of events (% of events)	Subjects with an Event (n=110) ^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110) ^a
Device	371 (14.5%)	100 (90.9%)	44/2566 (1.7%)	36 (32.7%)
Non-Device	2195 (85.5%)	110 (100.0%)	114/2566 (4.4%)	54 (49.1%)
Total	2566	110 (100.0%)	158/2566 (6.2%)	71 (64.5%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Significant adverse events

Deaths/SUDEP

There were 7 deaths in the study, with no death directly attributed by the investigator to the implant or therapy. One death occurred in the Baseline Phase prior to device implant, one in the Unblinded Phase, and 5 during the Long-Term Follow-Up Phase. Of the 7 deaths, four were attributed to definite (2 subjects), probable (1), or possible (1: drowning) SUDEP. Non-SUDEP deaths were attributed to completed suicide, cardiorespiratory arrest, and liver cancer.

Table 15 shows the SUDEP rates inclusive of definite or probable SUDEP determinations for the SANTÉ study and for the subjects who participated in the pilot studies. One probable SUDEP is not included in this table since it occurred during the Baseline Phase prior to device implant.

Table 15. Sudden unexplained death in epilepsy rate

Source of Data	# of SUDEP ^a	# of device years	SUDEP rate/1000 years	95% Poisson Confidence Interval
SANTÉ	2	713 years	2.8 /1000 years	[0.34, 10.13]
Pilot Follow-up ^b	0	76 years	0 /1000 years	[0, 48.54]
Total	2	789 years	2.5 /1000 years	[0.31, 9.16]

^a One probable SUDEP occurred during the Baseline Phase prior to device implant and is not included.

^b Combined data from 3 pilot centers participating in the Brain Stimulation for Epilepsy Long-Term Follow-up study and 2 pilot centers not participating in the follow-up study.

Intracranial hemorrhage

Intracranial hemorrhage events include those coded to MedDRA Preferred Terms of cerebral hemorrhage, hemorrhage intracranial, intraventricular hemorrhage, subdural hematoma, and post procedural hemorrhage. Eight intracranial hemorrhage events were reported in 8 of the 110 implanted subjects (7.3%). Six of the 8 events were categorized as device-related, corresponding to a device-related rate of 5.5%.

Of the 8 intracranial hemorrhage events, there was one SAE resulting in clinical manifestations reported in 1 subject (0.9%). This event was not device-related and was attributed to a head injury after 2 seizure-related falls. No surgical intervention was required and the event resolved without sequelae. The event occurred in the Long-Term Follow-Up Phase and was not related to a device implant or explant procedure.

Seven non-serious adverse events related to intracranial hemorrhage were reported in 7 subjects. None of these events resulted in clinical manifestations.

- Four of the events occurred during the Operative Phase and were radiologically detected after the initial implant procedure. Three of these 4 events were detected on the protocol-required postoperative MRI, and 1 was detected on a CT scan performed after a subject had worsening of seizures the day of implant. These 4 events resolved without sequelae.
- Three of the events occurred during the Long-Term Follow-Up Phase. One was noted on a postoperative MRI following device explant. This event resolved without sequelae. A second event was discovered on a CT scan that was performed after the subject experienced a seizure-related fall that occurred the same day following a complete system explant. The third event was discovered on postoperative CT scan following a complete system explant. The second and third events were both asymptomatic and subjects did not have imaging to confirm resolution at the time of discontinuation from the study.

Device-related infection

A total of 13 SAEs of implant site infection were reported in 12 subjects (10.9%). Serious adverse events of implant site infection occurred at the neurostimulator pocket (6), lead-extension tract (5), and burr hole site (2). None of the infections were in the brain parenchyma. One event was mild in severity, 4 were moderate, and 8 were severe.

All implant site infections were treated with oral or intravenous antibiotics with or without wound drainage or debridement.

Nine subjects (8.2%) required partial or complete system explant. The device components were subsequently replaced in 3 of the 9 explanted subjects.

Adverse events by study phase

Adverse events in the Operative Phase

Table 16 summarizes the 29 SAEs that occurred in 23 subjects (20.9%) during the Operative Phase. Of the 29 events, 25 were device-related in 22 subjects (20.0%). The most frequent serious adverse events during the Operative Phase were lead(s) not in target (8.2%) and implant site infection (3.6%). Fourteen leads were replaced in 9 subjects due to the lead not being placed within the targeted area as required by the protocol. The majority of subjects with a lead not within target were in the first half of implanted subjects (7/55). The incidence of lead not within target decreased in the last half of implanted subjects (2/55). Four subjects had a SAE of implant site infection, 3 requiring partial or complete system explant. No serious adverse events related to intracranial hemorrhage occurred in the Operative Phase.

Table 17 lists the device-related adverse events that occurred in $\geq 2.5\%$ of subjects during the Operative Phase.

Table 18 lists all the adverse events that occurred in $\geq 2.5\%$ of subjects during the Operative Phase.

Table 16. Serious adverse events during the Operative Phase

Preferred Term	No. of SAEs	Subjects (%) with SAE (n=110) ^a
Lead(s) not within target	12	9 (8.2%)
Implant site infection	4	4 (3.6%)
Post procedural pain	2	2 (1.8%)
Postoperative fever	2	2 (1.8%)
Vomiting	2	2 (1.8%)
Complex partial seizures	1	1 (0.9%)
Partial seizures with secondary generalization	1	1 (0.9%)

Preferred Term	No. of SAEs	Subjects (%) with SAE (n=110) ^a
Pyrexia	1	1 (0.9%)
Status epilepticus	1	1 (0.9%)
Set screws not adequately secured	1	1 (0.9%)
Urosepsis	1	1 (0.9%)
Wound drainage	1	1 (0.9%)
Total	29	23 (20.9%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Table 17. Device-related events occurring in $\geq 2.5\%$ of subjects during the Operative Phase

Preferred Term	Subjects (%) with an Event (n=110)
Lead(s) not within target	9 (8.2%)
Implant site pain	8 (7.3%)
Post procedural pain	7 (6.4%)
Implant site infection	5 (4.5%)
Postoperative fever	5 (4.5%)
Hypoaesthesia	3 (2.7%)
Procedural complication	3 (2.7%)
Vomiting	3 (2.7%)

Table 18. Adverse events occurring in $\geq 2.5\%$ of subjects during the Operative Phase

Preferred Term	Subjects (%) with an Event (n=110)
Lead(s) not within target	9 (8.2%)
Implant site pain	8 (7.3%)
Headache	7 (6.4%)
Post procedural pain	7 (6.4%)
Anticonvulsant toxicity	5 (4.5%)
Implant site infection	5 (4.5%)
Postoperative fever	5 (4.5%)
Head injury	4 (3.6%)
Contusion	3 (2.7%)
Drug toxicity	3 (2.7%)
Hypoaesthesia	3 (2.7%)
Procedural complication	3 (2.7%)
Simple partial seizures	3 (2.7%)
Vomiting	3 (2.7%)

The following events each occurred in 2 subjects: agitation, depression, dermatitis contact, documented hypersensitivity to administered drug, excoriation, implant site inflammation, incision site complication, injury, memory impairment, nasopharyngitis, pain in extremity, paraesthesia, pruritus, status epilepticus, tinnitus, and tremor.

The following events each occurred in 1 subject: anticonvulsant drug level decreased, anxiety, arthralgia, arthropod bite, asthenia, blister, blood magnesium

decreased, blood pressure increased, cerumen impaction, chest wall pain, chills, complex partial seizures, constipation, coordination abnormal, decreased appetite, deja vu, dizziness, dural tear, dyspnea, ecchymosis, extension fracture, face oedema, fatigue, gait disturbance, gastroenteritis viral, hemorrhage intracranial, hypoacusis, hyponatraemia, implant site effusion, implant site oedema, implant site scar, implant site swelling, incision site hemorrhage, influenza, insomnia, intraventricular hemorrhage, irritability, laceration, lead fracture, lead migration/dislodgment, musculoskeletal stiffness, nasal congestion, nausea, neck pain, onychomycosis, partial seizures with secondary generalization, peroneal muscular atrophy, pharyngolaryngeal pain, post procedural complication, post procedural drainage, post procedural hemorrhage, pyrexia, seasonal allergy, sensory disturbance, set screws not adequately secured, shoulder pain, sinusitis, skin infection, skin laceration, subdural hematoma, syncope vasovagal, tachycardia, thermal burn, urosepsis, visual disturbance, vocal cord disorder, wound dehiscence, and wound drainage.

Adverse events in the Blinded Phase

Table 19 lists the serious adverse events by treatment group that occurred during the Blinded Phase. A total of 8 SAEs were reported: 2 in the active group and 6 in the control group. There were no statistically significant differences between groups in the rates of any individual serious adverse event.

Table 20 lists the device-related adverse events that occurred in $\geq 2.5\%$ of subjects (in one or both treatment groups) during the Blinded Phase.

Table 21 presents adverse events occurring in $\geq 2.5\%$ of subjects (in one or both treatment groups) during the Blinded Phase. Statistically significant differences between active and control groups were noted for depression and memory impairment ($p < 0.05$). Depression and memory impairment are discussed in the Neuropsychological tests and adverse events section.

Table 19. Serious adverse events by treatment group during the Blinded Phase

Preferred Term	Active (n=54)	Control (n=55)
	Subjects (%) with SAE	Subjects (%) with SAE
Implant site infection	.	2 (3.6%)
Complex partial seizures	.	1 (1.8%)
Depression	1 (1.9%)	.
Partial seizures with secondary generalization	.	1 (1.8%)
Anxiety	.	1 (1.8%)
Muscle contractions involuntary	.	1 (1.8%)
Status epilepticus	1 (1.9%)	.
Total	2 (3.7%)	6 (10.9%)

Table 20. Device-related events occurring in $\geq 2.5\%$ of subjects in either the active or control group during the Blinded Phase

Preferred Term	Active (n=54)	Control (n=55)
	Subjects (%) with an Event	Subjects (%) with an Event
Paraesthesia	5 (9.3%)	1 (1.8%)
Implant site pain	3 (5.6%)	3 (5.5%)
Confusional state	3 (5.6%)	.
Memory impairment	3 (5.6%)	.
Anxiety	2 (3.7%)	.
Dizziness	2 (3.7%)	.
Implant site infection	1 (1.9%)	2 (3.6%)

Table 21. Adverse events occurring in $\geq 2.5\%$ of subjects in either the active or control group during the Blinded Phase

Preferred Term	Active		Control		Difference ^a	Fisher's Exact p-value
	No. of subjects with event	% of subjects (n=54)	No. of subjects with event	% of subjects (n=55)		
Depression	8	14.8%	1	1.8%	13.0%	0.016
Memory impairment	7	13.0%	1	1.8%	11.1%	0.032
Anxiety	5	9.3%	1	1.8%	7.4%	0.113
Confusional state	4	7.4%	.	.	7.4%	0.057
Paraesthesia	5	9.3%	2	3.6%	5.6%	0.271
Influenza	3	5.6%	.	.	5.6%	0.118
Partial seizures with secondary generalization	5	9.3%	3	5.5%	3.8%	0.489
Simple partial seizures	3	5.6%	1	1.8%	3.7%	0.363
Back pain	2	3.7%	.	.	3.7%	0.243
Tremor	2	3.7%	.	.	3.7%	0.243
Complex partial seizures	5	9.3%	4	7.3%	2.0%	0.742
Pharyngolaryngeal pain	2	3.7%	1	1.8%	1.9%	0.618
Implant site pain	3	5.6%	3	5.5%	0.1%	1.000
Anticonvulsant toxicity	3	5.6%	4	7.3%	-1.7%	1.000
Dizziness	3	5.6%	4	7.3%	-1.7%	1.000
Headache	2	3.7%	3	5.5%	-1.8%	1.000
Implant site infection	1	1.9%	2	3.6%	-1.8%	1.000
Excoriation	1	1.9%	3	5.5%	-3.6%	0.618
Dermatitis contact	.	.	2	3.6%	-3.6%	0.495
Hypoesthesia oral	.	.	2	3.6%	-3.6%	0.495
Sinusitis	.	.	2	3.6%	-3.6%	0.495
Somnolence	.	.	2	3.6%	-3.6%	0.495
Contusion	1	1.9%	4	7.3%	-5.4%	0.363
Nasopharyngitis	1	1.9%	5	9.1%	-7.2%	0.206
Upper respiratory tract infection	.	.	4	7.3%	-7.3%	0.118
Injury	1	1.9%	7	12.7%	-10.9%	0.060

^a Positive = more frequent in the active group; negative = more frequent in the control group. Table ordered by difference between groups.

Adverse events, total post implant

Table 22 summarizes the device-related adverse events reported in $\geq 2.5\%$ of subjects by time period. The most frequent device-related adverse events were implant site pain (31.8%), paraesthesia (23.6%), therapeutic product ineffective (14.5%), and implant site infection (13.6%).

Table 23 lists device-related serious adverse events by year. The most frequent device-related serious adverse events were implant site infection (10.9%) and lead(s) not within target (8.2%), with all others reported in 1.8% of subjects or fewer.

A full listing of adverse events by system organ class is provided in “Adverse events by system organ class, by time period” by time period.

Table 22. Device-related adverse events occurring in $\geq 2.5\%$ of subjects by time period

Preferred Term	Time Period ^a		Operative Phase (1 month) n=110 years=10		Implant to Year 1 (13 months) n=110 years=111		Implant to Year 7 (85 months) n=110 years=611		Total Post-implant ^b n=110 years=713	
	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event
Implant site pain	8	7.3%	21	19.1%	34	30.9%	35	31.8%		
Paraesthesia	1	0.9%	21	19.1%	26	23.6%	26	23.6%		
Therapeutic product ineffective	14	12.7%	16	14.5%		
Implant site infection	5	4.5%	10	9.1%	14	12.7%	15	13.6%		
Sensory disturbance	1	0.9%	8	7.3%	10	9.1%	10	9.1%		
Lead(s) not within target	9	8.2%	9	8.2%	9	8.2%	9	8.2%		
Implant site inflammation	2	1.8%	5	4.5%	8	7.3%	9	8.2%		
Memory impairment	.	.	6	5.5%	8	7.3%	8	7.3%		
Post procedural pain	7	6.4%	7	6.4%	7	6.4%	7	6.4%		
Dizziness	.	.	5	4.5%	7	6.4%	7	6.4%		
Neurostimulator migration	.	.	3	2.7%	6	5.5%	6	5.5%		
Postoperative fever	5	4.5%	5	4.5%	5	4.5%	6	5.5%		
Extension fracture	1	0.9%	5	4.5%	5	4.5%	6	5.5%		
Hypoaesthesia	3	2.7%	5	4.5%	5	4.5%	5	4.5%		
Headache	2	1.8%	4	3.6%	5	4.5%	5	4.5%		
Implant site effusion	1	0.9%	3	2.7%	5	4.5%	5	4.5%		
Anxiety	.	.	3	2.7%	5	4.5%	5	4.5%		
Confusional state	.	.	4	3.6%	4	3.6%	4	3.6%		
Complex partial seizures	.	.	2	1.8%	4	3.6%	4	3.6%		
Incision site complication	2	1.8%	3	2.7%	3	2.7%	4	3.6%		
Implant site erosion	2	1.8%	4	3.6%		
Procedural complication	3	2.7%	3	2.7%	3	2.7%	3	2.7%		
Vomiting	3	2.7%	3	2.7%	3	2.7%	3	2.7%		
Agitation	1	0.9%	3	2.7%	3	2.7%	3	2.7%		
Extension migration/dislodgment	.	.	3	2.7%	3	2.7%	3	2.7%		
Simple partial seizures	.	.	3	2.7%	3	2.7%	3	2.7%		
Thinking abnormal	.	.	3	2.7%	3	2.7%	3	2.7%		
Depression	.	.	2	1.8%	3	2.7%	3	2.7%		
High impedance	.	.	2	1.8%	3	2.7%	3	2.7%		

Time Period ^a	Operative Phase (1 month) n=110 years=10		Implant to Year 1 (13 months) n=110 years=111		Implant to Year 7 (85 months) n=110 years=611		Total Post-implant ^b n=110 years=713	
	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event
Preferred Term								
Panic attack	.	.	2	1.8%	3	2.7%	3	2.7%
Partial seizures with secondary generalization	.	.	2	1.8%	3	2.7%	3	2.7%
Lead fracture	1	0.9%	2	1.8%	2	1.8%	3	2.7%

^a 'months' is the number of scheduled months in the interval for each subject. 'n' is the number of subjects entering the interval. 'years' is the number of total device years in the interval.

^b Total post-implant includes the Operative Phase.

Table 23. Device-related serious adverse events by year

Time Interval ^a	Implant to Yr 1 (13 mo) n=110 yrs=111		Yr 1-2 (12 mo) n=105 yrs=95		Yr 2-3 (12 mo) n=102 yrs=92		Yr 3-4 (12 mo) n=97 yrs=88		Yr 4-5 (12 mo) n=92 yrs=77		Yr 5-6 (12 mo) n=82 yrs=76		Yr 6-7 (12 mo) n=80 yrs=71		Yr 7-8 (12 mo) n=73 yrs=51		Yr 8-9 (12 mo) n=42 yrs=31		Yr 9 and after n=28 yrs=20		Total Post-implant ^b n=110 yrs=713	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Implant site infection	8	7.3%	.	.	1	1.0%	.	.	2	2.2%	1	3.6%	12	10.9%
Lead(s) not within target	9	8.2%	9	8.2%
Post procedural pain	2	1.8%	2	1.8%
Postoperative fever	2	1.8%	2	1.8%
Vomiting	2	1.8%	2	1.8%
Therapeutic product ineffective	2	2.0%	2	1.8%
Muscle contractions involuntary	1	0.9%	1	0.9%
Partial seizures with secondary generalization	1	0.9%	1	0.9%
Pyrexia	1	0.9%	1	0.9%
Set screws not adequately secured	1	0.9%	1	0.9%
Status epilepticus	1	0.9%	1	0.9%
Tension	1	0.9%	1	0.9%
Unresponsive to verbal stimuli	1	0.9%	1	0.9%
Wound drainage	1	0.9%	1	0.9%
Implant site inflammation	.	.	1	1.0%	1	0.9%
Extension fracture	1	1.0%	1	0.9%
Implant site pain	1	1.1%	1	0.9%
Convulsion	1	1.3%	1	0.9%
Implant site erosion	1	2.4%	.	.	.	1	0.9%
Incision site complication	1	2.4%	.	.	.	1	0.9%
Total ^c	28	25.5%	1	1.0%	4	3.9%	0	0.0%	3	3.3%	0	0.0%	1	1.3%	0	0.0%	1	2.4%	1	3.6%	38	34.5%

^a 'mo' designates the number of scheduled months in the interval for each subject. 'yr' is the abbreviation for 'year'. 'yrs' designates the number of total device years in the interval. 'n' designates the number of subjects entering the interval. 'N' designates the number of subjects who experienced each event.

^b Row subtotals may not equal row sum, as subjects may have experienced an event in more than 1 year.

^c Column total may not equal column sum, as subjects may have experienced more than 1 event in the same time period.

Epilepsy-related adverse events

Status epilepticus

Status epilepticus was reported in 7 subjects (6.4%). The majority (4 of the 7 events) were nonconvulsive in nature. Six of the 7 subjects required hospitalization for the event and were considered serious adverse events. Three of the 7 events were reported in subjects who were not receiving stimulation at the time of the event. Two events occurred in the Operative Phase, 1 in the Blinded Phase (active subject), 1 in the Unblinded Phase, and 3 in the Long-Term Follow-Up Phase. One serious event occurred after stimulation was turned on in a control subject on the Month 4 visit. The stimulation amplitude was reduced to 0 volts and the event resolved within 6 days. The voltage was increased to 1 V approximately 2 weeks after onset of the event without incident. No subject experienced more than 1 episode of status epilepticus.

Seizures as adverse events

Seizures were recorded as adverse events if they were status epilepticus (included in the previous section), a new seizure type, required hospitalization, or at the discretion of the investigator (e.g., increased frequency or worsening of a seizure). The MedDRA Preferred Terms of epilepsy and convulsion were used when the seizure type was not reported. Table 24 presents seizure events by seizure type. A total of 180 seizure events were reported in 78 subjects (70.9%). There were 7 SAEs of complex partial seizures in 7 subjects (6.4%), 15 SAEs of partial seizures with secondary generalization in 11 subjects (10.0%), 3 SAEs of simple partial seizures in 3 subjects (2.7%), 3 SAEs of convulsion in 3 subjects (2.7%), 4 SAEs of epilepsy in 4 subjects (3.6%), and no SAEs of grand mal convulsion (0.0%).

Table 24. Seizures as adverse events

Preferred Term	Events (serious)	Subjects (%) with SAE^a	Subjects (%) with an Event^a
Complex partial seizures	62 (7)	7 (6.4%)	38 (34.5%)
Partial seizures with secondary generalization	54 (15)	11 (10.0%)	34 (30.9%)
Simple partial seizures	36 (3)	3 (2.7%)	31 (28.2%)
Convulsion	14 (3)	3 (2.7%)	11 (10.0%)
Epilepsy	8 (4)	4 (3.6%)	7 (6.4%)
Grand mal convulsion	6	0 (0%)	4 (3.6%)
Total	180 (32)	22 (20.0%)	78 (70.9%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Seizure events reported during the first week of stimulation

Five subjects reported adverse events of increased, worsening, or new seizures during the first week of stimulation. Three of these were subjects in the active group. One subject had a new type of complex partial seizure upon initiation of stimulation (outlier subject described in the “Clinical Endpoints: Effectiveness” section). Another subject experienced a new simple partial seizure starting 5 days after stimulation was turned on. There was no intervention and the subject continued to report seizures of this type (the subject experienced 5 other seizures of this type through Month 103 of the study). A third subject had a longer and more intense aura as part of their simple partial seizure starting the day that stimulation was turned on which resolved with

programming. Two control group subjects experienced adverse events related to seizures during the first week of stimulation was turned on. One subject experienced a serious adverse event of status epilepticus and is described in the “Status epilepticus” section. A second subject had a longer than normal simple partial seizure on the day that stimulation was turned on which resolved the same day with no intervention.

Epilepsy-related injury

Seventy-two (65.5%) subjects experienced 344 epilepsy-related injury events in the study, with 4 subjects (3.6%) experiencing serious adverse events related to epilepsy-related injury.

Table 25 summarizes the Blinded Phase injury events that occurred as a direct result of a seizure for all randomized subjects. None of the events were serious. Epilepsy-related injury occurred more frequently in the control group (25.5%) than in the active group (7.4%).

Table 25. Epilepsy-related injury in the Blinded Phase

Preferred Term	Active (n=54)	Control (n=55)	Total Fisher's Exact p-value
	Subjects (%) with an Event	Subjects (%) with an Event	
Injury	1 (1.9%)	6 (10.9%)	0.019
Contusion	1 (1.9%)	4 (7.3%)	
Excoriation	0.0%	2 (3.6%)	
Laceration	1 (1.9%)	0.0%	
Mouth injury	1 (1.9%)	0.0%	
Coccydynia	0.0%	1 (1.8%)	
Face injury	0.0%	1 (1.8%)	
Head injury	0.0%	1 (1.8%)	
Joint sprain	0.0%	1 (1.8%)	
Oedema	0.0%	1 (1.8%)	
Periorbital hematoma	0.0%	1 (1.8%)	
Total	4 (7.4%)	14 (25.5%)	

Neuropsychological tests and adverse events

Neuropsychological tests

Table 26 summarizes changes between baseline and Month 4 by treatment group for neuropsychological testing, for randomized subjects with assessments at baseline and Month 4. There was no statistically significant difference between groups at the end of the Blinded Phase, including test scores for visual memory, verbal memory, and depression. The baseline scores for both groups indicate mild impairment especially in verbal and visual memory, verbal fluency, and aspects of executive functioning such as cognitive flexibility. At baseline, subjects self-reported levels of executive dysfunction and apathy approached clinically significant impairment. On a group basis, the impairment observed at baseline was not aggravated by treatment.

Table 27 summarizes the changes between baseline and Years 1 and 7 for those subjects with assessments at baseline and the respective follow-up time point. Improvements over baseline were seen at these follow-up periods, with the most improvement observed in visual attention,

executive function, and subjective cognitive function. None of the domains showed a consistent worsening during follow-up.

Table 26. Neuropsychological results – Blinded Phase

Test	Active Group				Control group				Wilcoxon p-value
	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	
Visual motor speed									
D-KEFS Trailmaking Motor Speed (ss)	54	9.5 ± 3.4	9.3 ± 2.9	-0.2 ± 2.0	46	8.7 ± 3.6	9.1 ± 3.1	0.4 ± 2.5	0.182
General verbal ability									
WASI Vocabulary (T)	54	42.5 ± 10.1	41.4 ± 11.7	-1.1 ± 7.0	43	41.3 ± 10.5	40.1 ± 9.8	-1.1 ± 6.4	0.786
General visuospatial ability									
WASI Matrix Reasoning (T)	53	50.9 ± 9.9	49.7 ± 10.8	-1.2 ± 7.7	43	49.5 ± 9.4	49.8 ± 10.8	0.3 ± 8.9	0.566
Verbal memory									
CVLT Trials 1-5 Total (T)	54	40.6 ± 12.1	40.4 ± 11.6	-0.2 ± 8.6	46	41.1 ± 13.0	39.8 ± 12.4	-1.3 ± 9.2	0.537
CVLT Long Delay Free Recall (z)	54	-1.4 ± 1.5	-1.4 ± 1.4	-0.1 ± 0.9	46	-1.6 ± 1.5	-1.5 ± 1.5	0.1 ± 1.2	0.232
CVLT Recognition Hits (z)	54	-1.1 ± 1.6	-1.1 ± 1.4	0.0 ± 1.4	46	-1.4 ± 1.6	-1.5 ± 1.6	-0.1 ± 1.5	0.845
CVLT Discriminability (z)	54	-1.0 ± 1.5	-0.9 ± 1.4	0.1 ± 1.1	46	-0.9 ± 1.2	-1.1 ± 1.4	-0.2 ± 1.2	0.154
Visual memory									
BVMT-R Total Recall (T)	54	37.4 ± 12.8	37.2 ± 12.9	-0.2 ± 11.0	46	33.8 ± 12.3	35.7 ± 13.2	1.9 ± 11.4	0.317
BVMT-R Delayed Recall (T)	54	39.8 ± 14.8	38.4 ± 14.5	-1.3 ± 14.1	46	34.7 ± 14.4	37.1 ± 12.6	2.4 ± 13.7	0.156
BVMT-R Recognition Hits (z)	54	5.4 ± 0.9	5.4 ± 0.9	0.0 ± 0.9	46	5.4 ± 0.9	5.5 ± 0.6	0.1 ± 0.9	0.378
BVMT-R False Alarms (z)	54	0.4 ± 1.1	0.2 ± 0.5	-0.2 ± 1.1	46	0.3 ± 1.0	0.2 ± 0.5	-0.1 ± 1.1	0.797
Language									
D-KEFS Verbal Fluency: Category Fluency (ss)	54	5.8 ± 4.7	5.2 ± 4.0	-0.7 ± 2.8	46	5.4 ± 3.4	4.8 ± 3.4	-0.6 ± 2.8	0.922
D-KEFS Verbal Fluency: Letter Fluency (ss)	54	6.8 ± 3.8	6.4 ± 3.4	-0.3 ± 2.2	46	6.2 ± 3.3	6.0 ± 3.2	-0.2 ± 1.8	0.780
Design fluency									
D-KEFS Design Fluency – Total Correct (ss)	54	8.5 ± 2.9	9.0 ± 3.6	0.5 ± 2.5	46	8.6 ± 3.5	9.6 ± 4.0	1.0 ± 2.7	0.379
Executive function									
D-KEFS Trailmaking Number-letter switching (ss)	53	7.0 ± 4.3	7.7 ± 4.3	0.7 ± 2.4	46	7.5 ± 4.2	8.0 ± 4.0	0.6 ± 2.4	0.595
D-KEFS Inhibition/Switching (ss)	52	6.2 ± 4.4	6.8 ± 4.7	0.6 ± 2.3	46	6.6 ± 4.5	6.5 ± 4.2	-0.1 ± 2.4	0.109
D-KEFS Tower Test Total (ss)	54	8.4 ± 3.4	10.1 ± 3.3	1.7 ± 2.8	46	8.6 ± 3.3	10.5 ± 3.3	1.9 ± 2.5	0.813
D-KEFS Verbal Fluency: Category Switching (ss)	53	6.4 ± 3.8	5.8 ± 3.7	-0.6 ± 2.7	46	6.7 ± 3.5	6.2 ± 3.2	-0.5 ± 3.0	0.573
Subjective cognitive function									
POMS Confusion/Bewilderment (T) ^a	54	60.8 ± 11.1	60.2 ± 10.2	-0.7 ± 9.1	45	58.9 ± 12.2	56.8 ± 9.6	-2.1 ± 9.9	0.841
FrSBe Executive	53	66.0 ± 17.1	64.1 ± 13.7	-1.9 ± 12.8	46	68.0 ± 18.8	64.8 ± 17.4	-3.2 ± 13.8	0.571

Test	Active Group				Control group				Wilcoxon p-value
	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	
Dysfunction (T) ^a									
FrSBe Total (T) ^a	53	66.5 ± 18.3	62.7 ± 13.9	-3.8 ± 12.8	46	67.3 ± 18.5	63.5 ± 18.8	-3.8 ± 10.5	0.785
Depression and apathy									
POMS Depression (T) ^a	54	57.2 ± 12.4	57.9 ± 12.3	0.7 ± 9.3	45	54.6 ± 10.6	54.2 ± 10.0	-0.5 ± 7.4	0.396
FrSBe Apathy (T) ^a	53	67.4 ± 16.9	63.5 ± 14.4	-3.9 ± 13.7	46	67.8 ± 15.8	63.6 ± 17.7	-4.2 ± 10.1	0.641
Subjective behavioral disturbance									
FrSBe Disinhibition (T) ^a	53	57.4 ± 15.4	53.5 ± 14.1	-3.9 ± 11.2	46	56.6 ± 17.7	53.8 ± 15.5	-2.8 ± 12.2	0.978
Subjective fatigue and energy									
POMS Fatigue (T) ^a	54	54.6 ± 10.7	53.6 ± 9.3	-1.0 ± 10.6	45	53.9 ± 11.0	51.7 ± 8.5	-2.2 ± 8.6	0.472
POMS Vigor (T) ^a	54	43.4 ± 7.8	43.8 ± 8.2	0.3 ± 7.6	45	43.8 ± 8.3	43.3 ± 7.9	-0.6 ± 7.6	0.850
Anxiety									
POMS Tension (T) ^a	54	60.0 ± 11.1	58.3 ± 10.7	-1.7 ± 12.1	45	57.3 ± 11.4	54.4 ± 10.2	-2.8 ± 9.3	0.795
Visual attention									
D-KEFS Trailmaking Visual Scanning (ss)	54	8.4 ± 3.3	8.8 ± 3.0	0.4 ± 2.5	46	7.8 ± 4.0	7.8 ± 4.2	0.0 ± 2.3	0.689
D-KEFS Trailmaking Letter Sequencing (ss)	54	7.4 ± 3.9	8.2 ± 4.2	0.8 ± 2.9	46	7.6 ± 4.3	8.3 ± 4.2	0.7 ± 1.8	0.980
D-KEFS Trailmaking Number Sequencing (ss)	54	7.3 ± 3.3	8.4 ± 4.0	1.1 ± 2.9	46	7.9 ± 4.2	8.5 ± 3.8	0.5 ± 2.4	0.509
Processing speed									
D-KEFS Color-Word interference Color Naming (ss)	54	6.0 ± 4.1	6.2 ± 4.4	0.3 ± 2.2	46	7.6 ± 3.6	7.7 ± 3.6	0.1 ± 2.0	0.737
D-KEFS Color-Word interference Word Reading (ss)	54	6.0 ± 3.9	6.3 ± 4.2	0.3 ± 2.3	46	6.9 ± 3.5	6.8 ± 3.7	-0.1 ± 2.1	0.432

^a Higher values (positive change) indicate improvement with the exception of the footnoted tests where lower values (negative change) indicate improvement.

Abbreviations: Brief Visual Memory Test-revised (BVMT-R), California Verbal Learning Test (CVLT), Delis-Kaplan Executive Function System (D-KEFS), Frontal Systems Behavior Scale (FrSBe), Profile of Mood States (POMS), Wechsler Abbreviated Scale of Intelligence (WASI).

Scoring:

- Scaled scores (ss) have mean = 10 and standard deviation = 3.
- T-scores have mean = 50 and standard deviation = 10.
- z-scores have mean = 0 and standard deviation = 1.

Table 27. Neuropsychological results – Year 1 and Year 7

Test	Change at year 1			Change at year 7		
	N	mean ± std	Wilcoxon p-value	N	mean ± std	Wilcoxon p-value
Visual motor speed						
D-KEFS Trailmaking Motor Speed (ss)	105	0.5 ± 2.5	0.040	67	0.6 ± 2.9	0.104
Verbal memory						
CVLT Trials 1-5 Total (T)	105	0.8 ± 10.4	0.267	66	0.2 ± 10.9	0.758
CVLT Long Delay Free Recall (z)	105	0.2 ± 1.1	0.360	66	0.2 ± 1.2	0.347
CVLT Recognition Hits (z)	105	0.1 ± 1.7	0.501	66	0.1 ± 1.8	0.707
CVLT Discriminability (z)	105	0.1 ± 1.2	0.247	66	-0.1 ± 1.3	0.423
Visuospatial memory						
BVMT-R Total Recall (T)	105	1.7 ± 10.4	0.135	66	2.9 ± 10.1	0.012
BVMT-R Delayed Recall (T)	105	0.7 ± 11.5	0.462	66	0.4 ± 12.3	0.624
BVMT-R Recognition Hits (z)	104	0.1 ± 0.9	0.255	65	-0.1 ± 0.9	0.272

Test	Change at year 1			Change at year 7		
	N	mean ± std	Wilcoxon p-value	N	mean ± std	Wilcoxon p-value
BVMT-R False Alarms (z)	104	0.0 ± 1.0	0.713	65	0.0 ± 1.1	0.603
Language						
D-KEFS Verbal Fluency: Category Fluency (ss)	105	-0.4 ± 2.9	0.174	66	-0.3 ± 3.4	0.408
D-KEFS Verbal Fluency: Letter Fluency (ss)	105	0.0 ± 2.2	0.747	66	0.6 ± 2.3	0.053
Design fluency						
D-KEFS Design Fluency – Total Correct (ss)	105	1.0 ± 2.5	<0.001	66	1.8 ± 2.8	<0.001
Executive function						
D-KEFS Trailmaking Number-letter switching (ss)	104	1.3 ± 2.4	<0.001	67	1.1 ± 3.7	0.019
D-KEFS Inhibition/Switching (ss)	101	0.6 ± 2.6	0.004	64	1.1 ± 3.6	0.015
D-KEFS Tower Test Total (ss)	105	2.6 ± 3.2	<0.001	65	4.1 ± 3.3	<0.001
D-KEFS Verbal Fluency: Category Switching (ss)	103	-0.3 ± 3.3	0.343	65	-0.5 ± 3.6	0.325
Subjective cognitive function						
POMS Confusion/Bewilderment (T) ^a	105	0.1 ± 10.0	0.895	66	0.0 ± 11.0	0.876
FrSBe Executive Dysfunction (T) ^a	105	-5.0 ± 12.1	<0.001	66	-2.4 ± 16.7	0.299
FrSBe Total (T) ^a	105	-4.4 ± 11.1	<0.001	66	-2.9 ± 16.6	0.178
Depression and apathy						
POMS Depression (T) ^a	105	0.5 ± 10.9	0.864	66	0.1 ± 11.6	0.964
FrSBe Apathy (T) ^a	105	-3.9 ± 12.1	0.001	66	-2.7 ± 15.2	0.130
Subjective behavioral disturbance						
FrSBe Disinhibition (T) ^a	105	-1.9 ± 11.5	0.029	66	-1.7 ± 15.8	0.336
Subjective fatigue and energy						
POMS Fatigue (T) ^a	105	-2.4 ± 10.6	0.059	66	-1.6 ± 10.7	0.245
POMS Vigor (T) ^a	105	-0.9 ± 7.8	0.140	66	0.6 ± 8.7	0.521
Anxiety						
POMS Tension (T) ^a	105	-2.5 ± 11.0	0.002	66	-2.3 ± 11.8	0.226
Visual attention						
D-KEFS Trailmaking Visual Scanning (ss)	105	0.6 ± 2.4	0.007	67	0.1 ± 3.4	0.663
D-KEFS Trailmaking Letter Sequencing (ss)	105	1.4 ± 3.1	<0.001	67	1.5 ± 3.3	<0.001
D-KEFS Trailmaking Number Sequencing (ss)	105	1.7 ± 2.7	<0.001	67	1.7 ± 3.1	<0.001
Processing speed						
D-KEFS Color-Word interference Color Naming (ss)	105	-0.1 ± 2.5	0.619	66	0.3 ± 2.9	0.395
D-KEFS Color-Word interference Word Reading (ss)	105	0.1 ± 2.3	0.551	66	0.1 ± 3.1	0.453

^a Higher values (positive change) indicate improvement with the exception of the footnoted tests where lower values (negative change) indicate improvement.

Depression

A total of 46.4% of the implanted subjects had a prior medical history of depression. Over half (54.9%, 28/51) of subjects with a prior history of depression reported a post-implant depression event, compared to 25.4% (15/59) of subjects without a prior history of depression.

Forty-six depression events were reported in 43 subjects (39.1%). Of these 43 subjects, 65.1% (28/43) had a prior history of depression. One subject (0.9%) in the study experienced a serious adverse event of depression that occurred in the Blinded Phase. This subject had a prior history of depression. Three events in 3 subjects were device-related events. None of these events were considered serious. All 3 of the device-related events resolved, in an average of 61 days.

During the Blinded Phase, spontaneously self-reported worsening or new onset depression occurred in 14.8% (8/54) of the active subjects and 1.8% (1/55) of the control subjects (p=0.016). Of the 8 events in the active group subjects, one event was serious and required inpatient hospitalization on 2 separate occasions. All of the events were mild or moderate in severity; none were severe. Six of the 8 subjects had a prior medical history of depression that

was reported as worsened during the Blinded Phase. There were 2 de novo depression events. One of the two de novo depression events was determined by the investigator to be related to stimulation and resolved after programming. Depression resolved in 4 subjects and was ongoing in 4 subjects as of the database cutoff. Three of the 4 ongoing events were in subjects with pre-existing depression. Five of the 8 subjects had >35% reduction in seizure frequency by the end of the Blinded Phase; 4 of the 8 were responders (>50% reduction in seizure frequency). No subject discontinued from the study due to depression.

Suicidality

Suicidality events include those coded to MedDRA Preferred Terms of completed suicide, suicide attempt, depression suicidal, suicidal ideation, and intentional self-injury. Twelve subjects (10.9%) reported 15 suicidality events. Nine of the 15 events were serious in 7 subjects (6.4%). The serious adverse events were completed suicide (1), suicide attempt (4), depression suicidal (1), and suicidal ideation (3). The completed suicide occurred in 1 subject who was not receiving stimulation at the time of the event; the neurostimulator battery was depleted and the subject was being scheduled for a replacement procedure. The subject's seizure frequency had not increased following battery depletion. This subject had previously been a responder (at least 50% seizure reduction) at the last 2 annual visits prior to the battery depletion event. Of the 7 subjects reporting suicidality SAEs, 6 had a medical history of depression or suicide attempt.

Memory impairment

A total of 33.6% of the implanted subjects had a prior medical history of memory impairment. Approximately one-third (35.1%, 13/37) of subjects with a prior history of memory impairment reported a memory impairment event, compared to 28.8% (21/73) of subjects without a prior history of memory impairment.

Thirty-seven memory impairment events were reported in 34 subjects (30.9%). Of these 34 subjects, 38.2% (13/34) had a prior history of memory impairment. Eight events in 8 subjects (7.3%) were device-related. Seven of the 8 events resolved, in an average of 43 days. None of the memory impairment events were considered serious.

During the Blinded Phase, spontaneously self-reported worsening or new onset memory impairment occurred in 13.0% (7/54) of the active subjects and 1.8% (1/55) of the control subjects ($p=0.032$). Of the 7 events in the active group subjects, none were serious. Four of the events were mild and 3 were moderate in severity; none were severe. Two of the 7 subjects had a prior medical history of memory impairment that was reported as worsened during the Blinded Phase. Although 6 of the 7 events started the day of randomization, only 3 of the 7 events were determined by the investigator to be stimulation-related. Memory impairment resolved in all subjects, 5 without intervention. Of the 3 events related to programming/stimulation, 1 of the events resolved with reprogramming, and the other 2 events resolved with no intervention. No subject discontinued from the study due to memory impairment.

Device modifications

Device modifications were categorized as replacements, revisions, or explants. Table 28 presents an overview of device modifications by system component (or complete system).

Table 28. Device replacements, revisions, or explants

Component(s) modified	Number of components (Number of subjects)		
	Replacement	Revision	Explant
Complete system ^a	5 (5)	1 (1)	29 (29)
Neurostimulator	233 (84)	6 (6)	2 (2)
Leads	17 (12)	3 (2)	0 (0)
Extensions	26 (10)	3 (3)	2 (1)

^a Neurostimulator, leads, and extensions. Complete system revisions are not included in the counts for each individual component.

Complete system

The complete system was replaced in 5 subjects due to implant site infection (2), tension (1), implant site erosion (1), and extension fracture and therapy ineffectiveness (1). The tension event is described as intermittent tense feelings related to stimulation.

The complete system was revised in 1 subject who had an infection and erosion at the implant site.

The most common causes of the complete system being explanted and not replaced in 29 subjects were therapy ineffectiveness (12), implant site infection (6), anxiety (2), and SUDEP (2, explanted posthumously). Other causes were 1 each of the following: involuntary muscle contractions, elective medical device removal, discomfort, cognitive disorder, psychotic disorder, meningitis, and undesirable change in stimulation.

Table 29 summarizes the reasons for complete system replacement, revision, or explant.

Table 29. Reason for complete system modification

Reason	Number of complete systems		
	Replacement	Revision	Explant
Therapy ineffectiveness	0	0	12
Implant site infection	2	0	6
Anxiety	0	0	2
SUDEP	0	0	2
Cognitive disorder	0	0	1
Discomfort	0	0	1
Elective medical device removal	0	0	1
Extension fracture/ therapy ineffectiveness ^a	1	0	0
Implant site erosion	1	0	0
Implant site infection/erosion ^b	0	1	0
Involuntary muscle contractions	0	0	1
Meningitis	0	0	1
Psychotic disorder	0	0	1
Tension	1	0	0
Undesirable change in stimulation	0	0	1
Total	5	1	29

^a One subject underwent replacement of the extensions due to extension fracture and replacement of the leads secondary to therapy ineffectiveness; the neurostimulator was replaced at the time of extension replacement so as to prolong time to another procedure; thus, the entire system was replaced in one procedure.

^b One subject underwent revision of the leads and extensions due to implant site infection and revision of the neurostimulator due to implant site erosion in one procedure.

Neurostimulator

The neurostimulator was replaced 233 times in 84 subjects with 219 of the replacements due to normal battery depletion. Two subjects had undergone a neurostimulator replacement secondary to paresthesia and two subjects due to a Medtronic device recall. One subject had the neurostimulator replaced as a result of implant site pain and 1 replacement was due to implant site infection. There were 8 subjects with instances where the neurostimulator was replaced because of 2 separate events. These include normal battery depletion and neurostimulator migration (2), normal battery depletion and high impedance (2), and 1 each of the following: normal battery depletion and implant site pain, normal battery depletion and discomfort, normal battery depletion and sensory disturbance, and implant site scar with elective neurostimulator replacement.

The neurostimulator was revised in 6 subjects. The most common events resulting in a revision were neurostimulator migration (2) and set screws not adequately secured (2). One subject underwent revision due to accidental injury and 1 subject had the neurostimulator revised as a result of insufficient coupling of the device secondary to excessive depth of the neurostimulator pocket.

The neurostimulator was explanted and not replaced in 2 subjects. One was explanted posthumously and the other was explanted due to therapy ineffectiveness.

Table 30 summarizes the reasons for neurostimulator replacement, revision, or explant.

Table 30. Reason for neurostimulator modification

Reason	Number of neurostimulators		
	Replacement	Revision	Explant
Normal battery depletion	219	0	0
Medtronic device recall	2	0	0
Normal battery depletion/ high impedance ^a	2	0	0
Normal battery depletion/ neurostimulator migration ^a	2	0	0
Neurostimulator migration	0	2	0
Paresthesia	2	0	0
Set screws not adequately secured	0	2	0
Accidental injury	0	1	0
Death	0	0	1
Implant site infection	1	0	0
Implant site pain	1	0	0
Implant site scar/ elective neurostimulator replacement ^a	1	0	0
Normal battery depletion/ discomfort ^a	1	0	0
Normal battery depletion/ implant site pain ^a	1	0	0
Normal battery depletion/ sensory disturbance ^a	1	0	0
Insufficient coupling of the device	0	1	0
Therapy ineffectiveness	0	0	1
Total	233	6	2

^a There were 8 instances in which the neurostimulator was replaced because of 2 separate events.

A Kaplan-Meier survival analysis was conducted to the first battery replacement. Subjects who did not have a neurostimulator replacement were censored at their last follow-up visit to date. The results of this analysis showed that half of the subjects in the study (i.e., median survival from battery replacement) needed a neurostimulator replacement after 35.4 months (3.0 years). A second Kaplan-Meier survival analysis was conducted for all battery replacements, and half of the total neurostimulators were replaced after 25.8 months (2.2 years). Of the remaining 69 subjects active in the study (as of the database cutoff), 2 subjects have not yet undergone a battery replacement.

Lead

There were a total of 20 lead modifications that were reported in 14 subjects. Fourteen leads were replaced in 9 subjects due to the lead not being placed within the targeted area; the 14 leads were replaced in 11 surgical procedures. Other events that led to lead replacement included unilateral lead fracture (2 subjects) and unilateral lead migration/dislodgement (1). One subject had undergone a bilateral lead revision secondary to high impedances and one subject had a unilateral lead revised due to a post-implant procedural complication.

Table 31 summarizes the reasons for lead replacement, revision, or explant.

Table 31. Reason for lead modification

Reason	Number of leads		
	Replacement	Revision	Explant
Lead not in target area	14	0	0
High impedance	0	2	0
Unilateral lead fracture	2	0	0
Post-implant procedural complications	0	1	0
Unilateral lead migration/dislodgement	1	0	0
Total	17	3	0

Extension

There were 31 extension modifications that were reported in 14 subjects. Sixteen extensions were replaced in 5 subjects as a result of extension fracture. Five of these were due to fractures that occurred in two subjects during an initial implant or replacement procedure. Two subjects underwent bilateral extension replacement due to implant site pain. Other events that resulted in bilateral extension replacements include involuntary muscle contractions, implant site infection, and extension migration/dislodgment. Three unilateral extension revisions were reported in 3 subjects. Two revisions were secondary to extension migration/dislodgment and one was the result of an implant site infection. Two extensions were explanted posthumously in one subject.

Table 32 summarizes the reasons for extension replacement, revision, or explant.

Table 32. Reason for extension modification

Reason	Number of extensions		
	Replacement	Revision	Explant
Extension fracture	16	0	0
Extension migration/ dislodgment	2	2	0
Implant site pain	4	0	0
Implant site infection	2	1	0
Death	0	0	2
Involuntary muscle contraction	2	0	0
Total	26	3	2

Programming parameters

The stimulation parameters used in the active group during the Blinded Phase of the SANTÉ study were the following:

Amplitude: 5.0 V

Pulse width: 90 μ s

Rate: 145 Hz

Cycling on interval: 1 minute

Cycling off interval: 5 minutes

During the Unblinded Phase, either voltage increases to 7.5 V or rate increases to 185 Hz were allowed, but not both. In the Long-Term Follow-Up Phase, there were no programming restrictions and parameters were changed at the discretion of the investigator. Table 33 summarizes the programming parameters at the Year 2 through Year 7 visits. Subjects were excluded from the amplitude parameters if therapy was delivered to only one hemisphere. Subjects were excluded from the cycling interval parameters (cycling on interval and cycling off interval) if cycling was disabled (i.e., continuous stimulation was used). Caution should be exercised when interpreting this data. The study design was intended to limit variability in programming during the Blinded and Unblinded Phases and a prospective evaluation of the impact of unlimited programming changes was not included. In some subjects, multiple programming parameters were adjusted concurrently, making it difficult to assess the impact of any one parameter. Lastly, while some subjects had improved seizure reduction temporally related to stimulation changes, others seemed to respond to a cumulative effect of stimulation.

Table 33. Programming parameters – Year 2 through Year 7

Parameter	Year	n	Mean	Standard Deviation	Minimum	25th percentile	Median	75th percentile	Maximum
Amplitude (V)	2	97	6.5	1.6	2.75	5.0	7.2	7.5	10.0
	3	93	6.3	2.0	0	5.0	7.5	7.5	10.0
	4	87	6.6	1.6	0	5.5	7.5	7.5	9.5
	5	79	6.6	1.9	0	5.0	7.5	7.5	10.0
	6	74	6.6	1.6	1.00	5.6	7.5	7.5	9.5
Pulse width (µs)	2	99	94.2	12.9	60	90	90	90	150
	3	93	98.1	23.9	60	90	90	90	210
	4	87	97.2	17.1	60	90	90	90	150
	5	79	99.1	17.6	60	90	90	120	150
	6	74	99.3	17.9	90	90	90	90	150
Rate (Hz)	2	99	156.5	25.8	70	145	145	185	185
	3	93	152.6	35.7	3	145	145	185	240
	4	87	160.0	21.0	100	145	145	185	200
	5	79	162.8	20.1	140	145	145	185	200
	6	74	163.8	20.4	130	145	147.5	185	200
Cycling on interval (min)	2	98	1.0	0.4	0.250	1	1	1	4
	3	88	1.0	0.4	0.002	1	1	1	4
	4	83	1.1	1.1	0.500	1	1	1	10
	5	79	1.2	1.0	0.017	1	1	1	6
	6	71	1.2	0.8	0.333	1	1	1	5
Cycling off interval (min)	2	98	3.4	1.7	0.083	2	3	5	5
	3	87	3.3	1.7	0.170	2	3	5	5
	4	83	3.2	1.6	0.500	2	3	5	5
	5	79	3.1	1.6	0.033	2	3	5	5
	6	71	4.0	6.9	0.333	2	3	5	60
	7	56	3.6	2.2	0.330	2	3	5	15

2. Effectiveness Results

Observed Data

A total of 54 subjects entered the active group and 55 subjects entered the control group during the Blinded Phase of the study. The analyses are presented as both as primary analysis population (excluding one subject who did not have 70 days of diary entries in the control group) and the post-hoc analysis, which excluded the outlier subject in the active group and the subject without complete diary entries in the control group. The analyses were a comparison between both the active group and the control group compared to baseline at the end of the entire Blinded Phase time point. Key effectiveness outcomes are presented in Tables 34 to 36.

Primary effectiveness analysis – total seizure frequency

The protocol pre-specified a GEE analysis for the evaluation of the treatment effect on seizure frequency, and allowed for subject exclusion in the case of diary non-compliance. With this primary analysis dataset, the GEE analysis showed that the active group experienced on average 8% fewer seizures (2 seizures per month)

compared with the control group over the Blinded phase (95% confidence interval (CI): -29.2%, 20.0%). This was not statistically significant.

With post-hoc removal of the outlier subject, the primary objective was met over the entire Blinded Phase using the original GEE analysis, demonstrating a statistically significant improvement in the total seizure rate in the active group as compared with the control group (p=0.045, two-sided). The active group experienced 17% fewer seizures compared with the control group over the entire Blinded Phase (95% confidence interval (CI): -30.8%, -0.4%).

As shown in Table 34, for a subject with 26 seizures per month at baseline and 34 years of age (i.e., the average of the model covariates), the number of seizures per month over the Blinded Phase as calculated from the GEE model would be 17.5 if that subject was in the active group and 21.1 if that subject was in the control group.

Table 34. Primary objective analysis – GEE model with outlier removed

Treatment group	Treatment effect parameter estimate (log scale) ^a	Estimated number of seizures per day (original scale) ^b	Mean seizure counts per month from GEE model (original scale) [95% confidence interval] ^c
Active (n=53)	-0.4698	0.6251	17.5 [15.2, 20.1]
Control (n=54)	-0.2838	0.7529	21.1 [18.6, 23.8]

^a The estimated treatment effect from the GEE model. The model includes the natural log of age and baseline seizure count as covariates.

^b Exponentiating transforms the estimates from the natural log scale to the original scale

^c The daily mean seizure count is converted to a monthly count by multiplying by 28

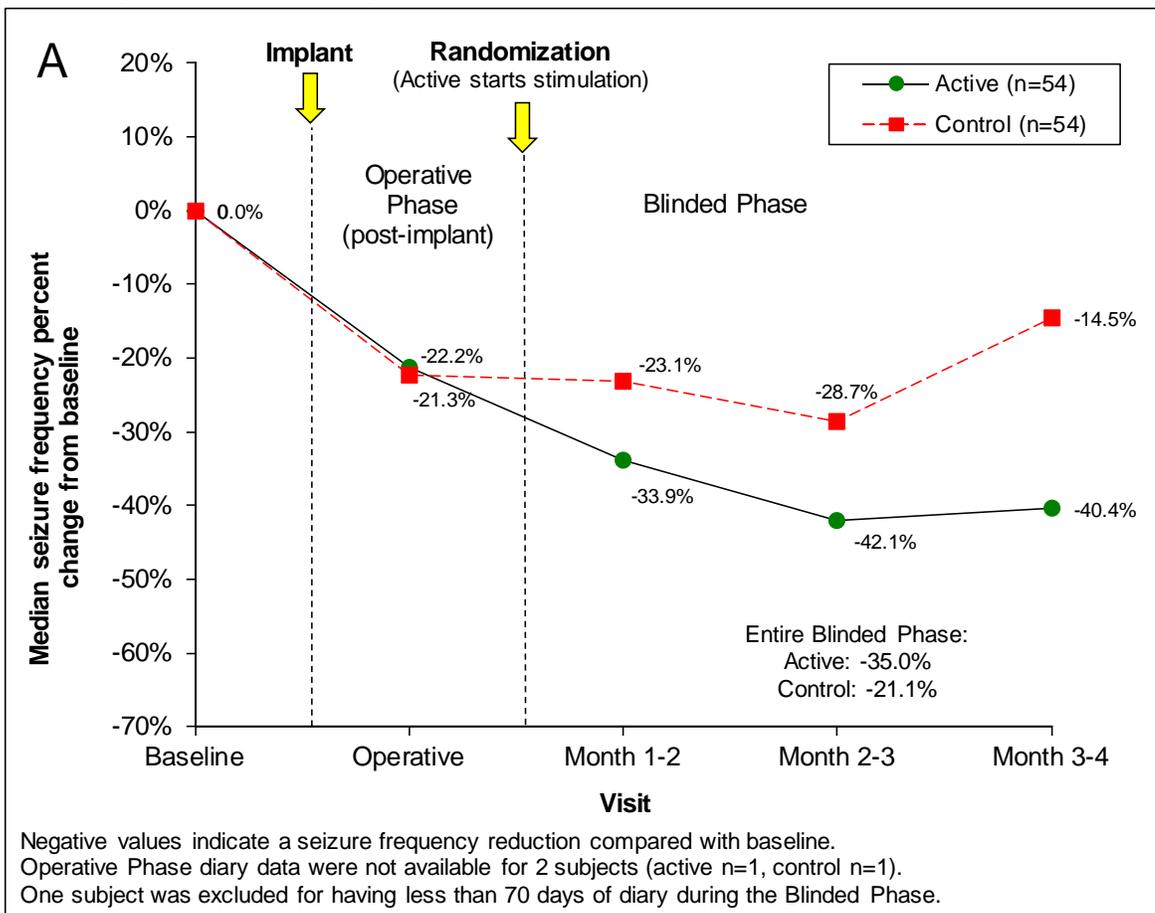
Observed data – median total seizure frequency

Figure 4 displays the median total seizure frequency percent change from baseline in the Operative and Blinded Phases using the primary analysis dataset (Figure 4A and with the outlier removed (Figure 4B)). The differences between the two figures are small, which is the result of the robustness of medians to extreme values such as for the outlier subject. Interaction between the number of seizures and the post randomization month should be considered when interpreting the results. There was a similar reduction in seizure frequency in both groups post-implant, prior to randomization and initiation of stimulation in the active group. Thereafter, when active stimulation was initiated, the median seizure frequency change from baseline in the active group continued to decrease, whereas the median seizure frequency change from baseline for the control group initially decreased but then increased at Month 3-4. The net effect was an increasing difference between the active and control groups at each visit in the Blinded Phase.

Using the primary analysis dataset, the median percent change from baseline in total seizure frequency over the entire Blinded Phase was -35.0% for the active

group and -21.1% for the control group (p=0.119, post-hoc Wilcoxon rank sum test). Table 35 summarizes the median along with the 25th and 75th percentiles (i.e., interquartile range).

When removing the outlier subject from the analysis, the median percent change from baseline in total seizure frequency over the entire Blinded phase was -35.0% for the active group and -21.1% for the control group. The active group achieved a median percent change from baseline of -38.0% during the final month of the Blinded phase.



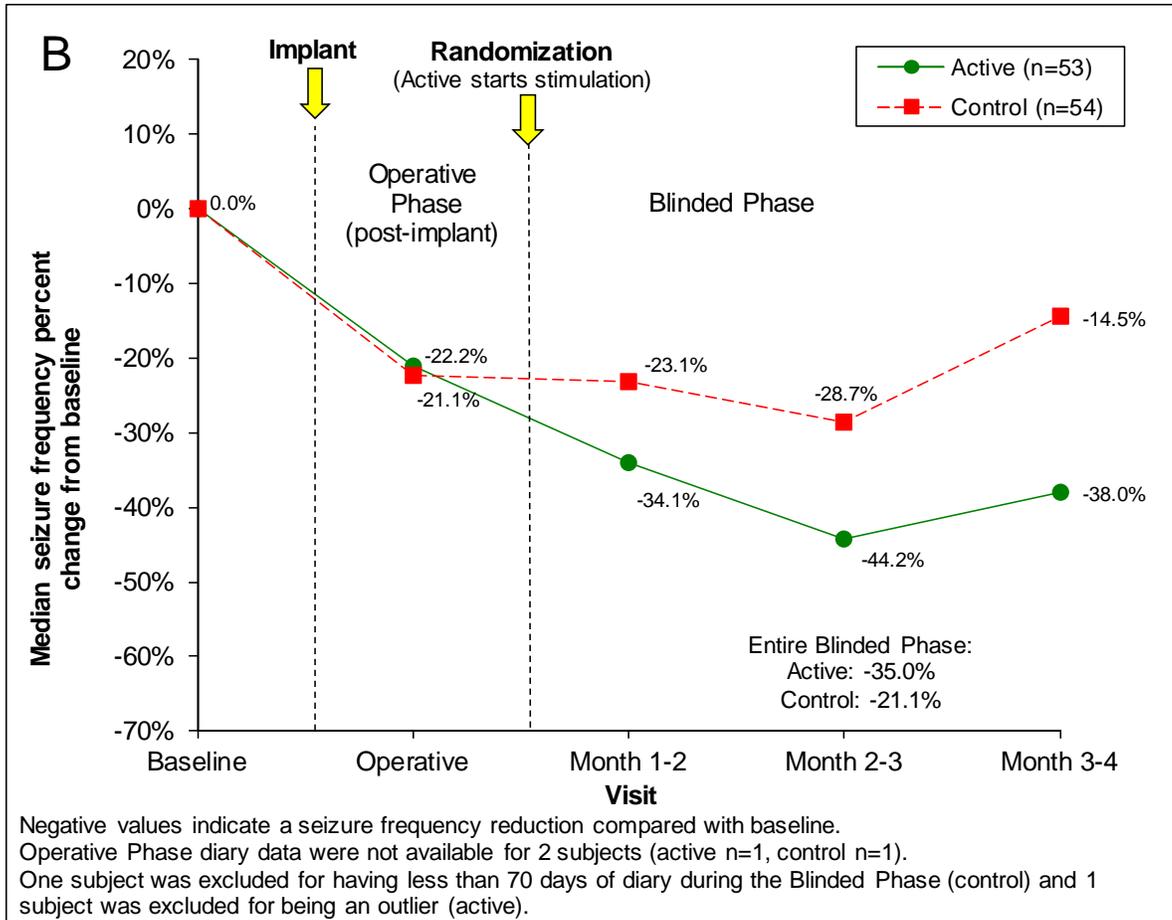


Figure 4. Unadjusted median total seizure frequency percent change from baseline with primary analysis dataset (A) and outlier removed (B).

Table 35. Unadjusted median total seizure frequency percent change from baseline

Visit	Active				Control			
	N	Median	25th percentile	75th percentile	n	Median	25th percentile	75th percentile
Baseline	54	0.0%	0.0%	0.0%	54	0.0%	0.0%	0.0%
Operative ^a	53	-21.3%	-42.5%	5.3%	53	-22.2%	-62.7%	9.3%
Month 1-2	54	-33.9%	-59.7%	17.3%	54	-23.1%	-51.7%	13.8%
Month 2-3	54	-42.1%	-61.0%	-19.3%	54	-28.7%	-66.4%	-5.0%
Month 3-4	54	-40.4%	-60.9%	-21.6%	54	-14.5%	-51.6%	20.0%
Entire Blinded Phase	54	-35.0%	-53.9%	-13.0%	54	-21.1%	-51.5%	7.5%

^a Operative Phase diary data were not available for 2 subjects (active n=1, control n=1)

Individual subject results

As shown in Figure 5, 81.5% (44/54) of subjects in the active group and 70.9% (39/55) of subjects in the control group reported any decrease in seizures (i.e., any improvement from baseline) during the Blinded Phase. This analysis includes all randomized subjects.

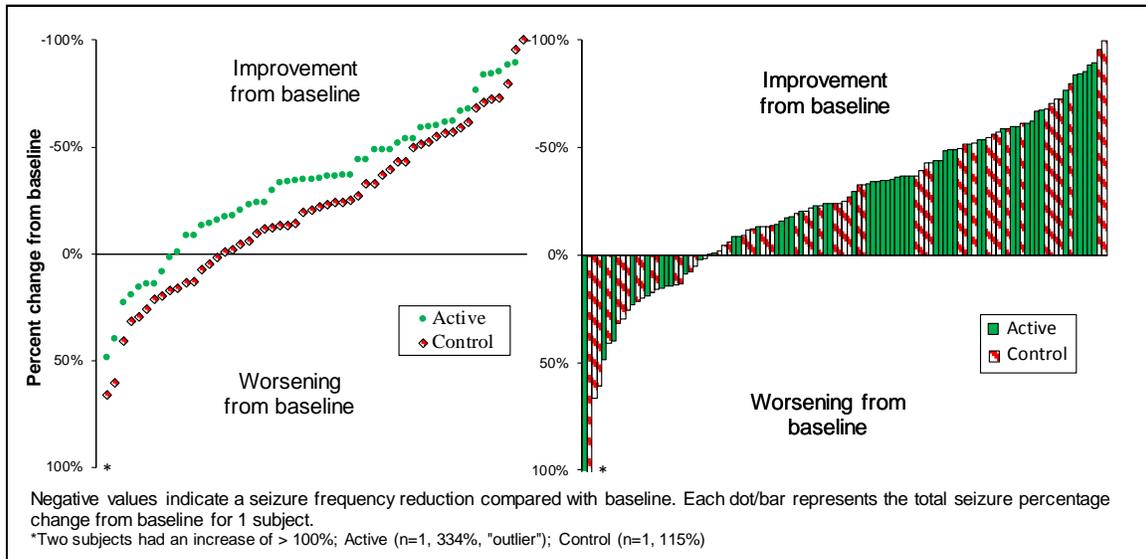


Figure 5. By-subject plot of total seizure frequency percent change from baseline.

Unblinded and Long-Term Follow-Up Phases

Since this is open label data, its interpretation is limited by several factors, including:

- All subjects were aware that they were receiving stimulation (expectation bias).
- Those who may not do well could exit the study; 108 out of 110 implanted subjects entered the Unblinded Phase, 105 subjects entered the Long-Term Follow-Up Phase, and 73 subjects completed the year 7 visit (selection bias).
- Limited programming parameters were allowed during the Unblinded Phase. After Month 13, programming parameters and antiepileptic drug changes were allowed (confounding factors).

The control group had stimulation turned on at the Month 4 visit at the same settings as the active group in the Blinded Phase. The control group had a median total seizure frequency percent change from baseline of -13.9% during the final month of the Blinded Phase (Month 3-4) which improved to -40.7% after 1 month of stimulation (Month 4-5 in Figure 6). Figure 6 includes subjects with at least 70 days of diary in each 3-month time interval (n=86).

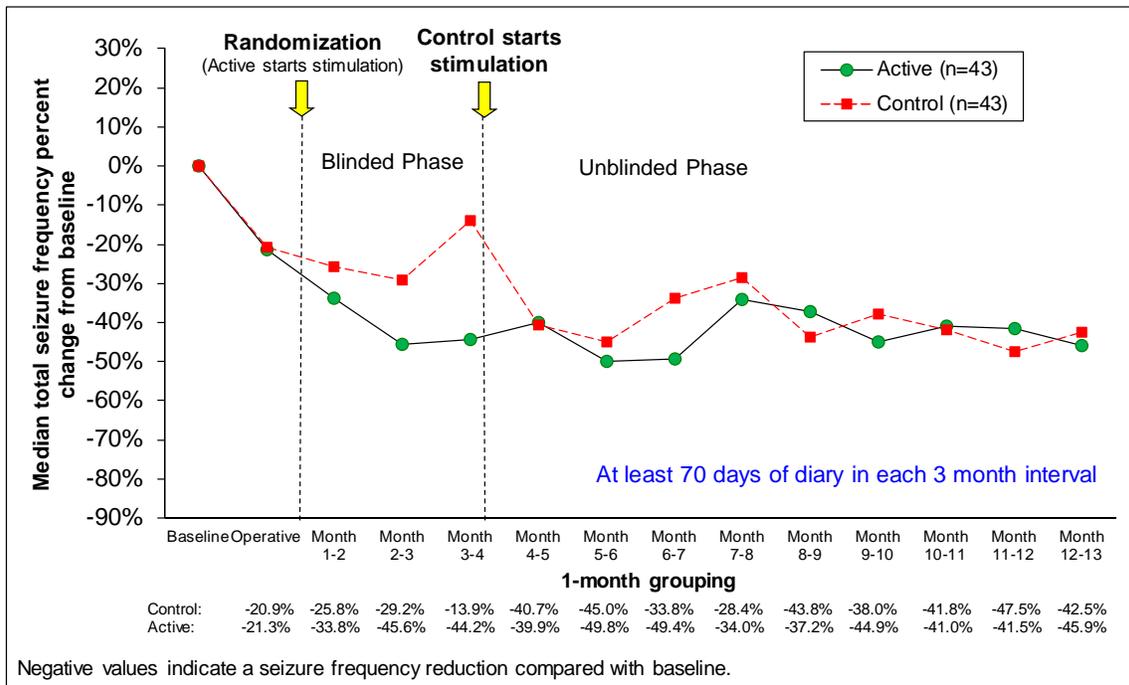


Figure 6. Median total seizure frequency percent change from baseline by treatment group – Operative Phase through year 1.

Seizure reduction continued to improve in the Long-Term Follow-Up Phase. Table 36 shows that the median total seizure frequency percent change from baseline ranged from -41% at 1 year to -75% at 7 years after device implant for those subjects with at least 70 days of diary in the 3 months prior to each annual visit. Sensitivity analyses including LOCF and Worst case are also included in Table 36.

Figure 7 shows the distribution of median total seizure frequency percent change from baseline to the most recent 3-month follow-up (as of database cutoff) with at least 70 days during the interval for all implanted subjects. For this interval, 11% (12/110) of subjects were seizure-free and 69% (76/110) were responders.

Table 36. Median total seizure frequency percent change from baseline – Blinded Phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value
Analysis using all subjects with at least 70 days of diary during the time period ^{a,b}					
Blinded Phase - Active	54	-35.0%	-53.9%	-13.0%	0.119
Blinded Phase - Control	54	-21.1%	-51.5%	7.5%	
Year 1	99	-41.4%	-76.0%	-12.3%	<0.001
Year 2	82	-55.6%	-78.6%	-25.6%	<0.001
Year 3	75	-52.9%	-79.8%	-31.8%	<0.001
Year 4	76	-65.9%	-85.0%	-25.9%	<0.001
Year 5	59	-69.4%	-96.4%	-41.7%	<0.001
Year 6	64	-74.9%	-90.9%	-46.6%	<0.001

Year 7	50	-74.8%	-92.2%	-39.3%	<0.001
Analysis of long term data using LOCF^a					
Year 1	109	-44.0%	-74.5%	-12.9%	<0.001
Year 2	109	-56.8%	-76.4%	-17.6%	<0.001
Year 3	109	-56.6%	-79.8%	-27.9%	<0.001
Year 4	109	-61.5%	-84.8%	-22.8%	<0.001
Year 5	109	-65.4%	-86.0%	-26.5%	<0.001
Year 6	109	-70.4%	-86.5%	-29.8%	<0.001
Year 7	109	-70.4%	-89.0%	-27.1%	<0.001
Analysis of long term data using Worst case^a					
Year 1	109	-40.3%	-74.5%	-11.6%	<0.001
Year 2	109	-54.3%	-76.1%	-8.0%	<0.001
Year 3	109	-51.4%	-77.6%	-12.1%	<0.001
Year 4	109	-43.0%	-80.5%	16.1%	0.060
Year 5	109	-49.7%	-82.1%	100%	0.534
Year 6	109	-52.9%	-85.0%	100%	0.961
Year 7	109	-39.3%	-86.4%	100%	0.046

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses.

^b No imputation was applied for missing data.

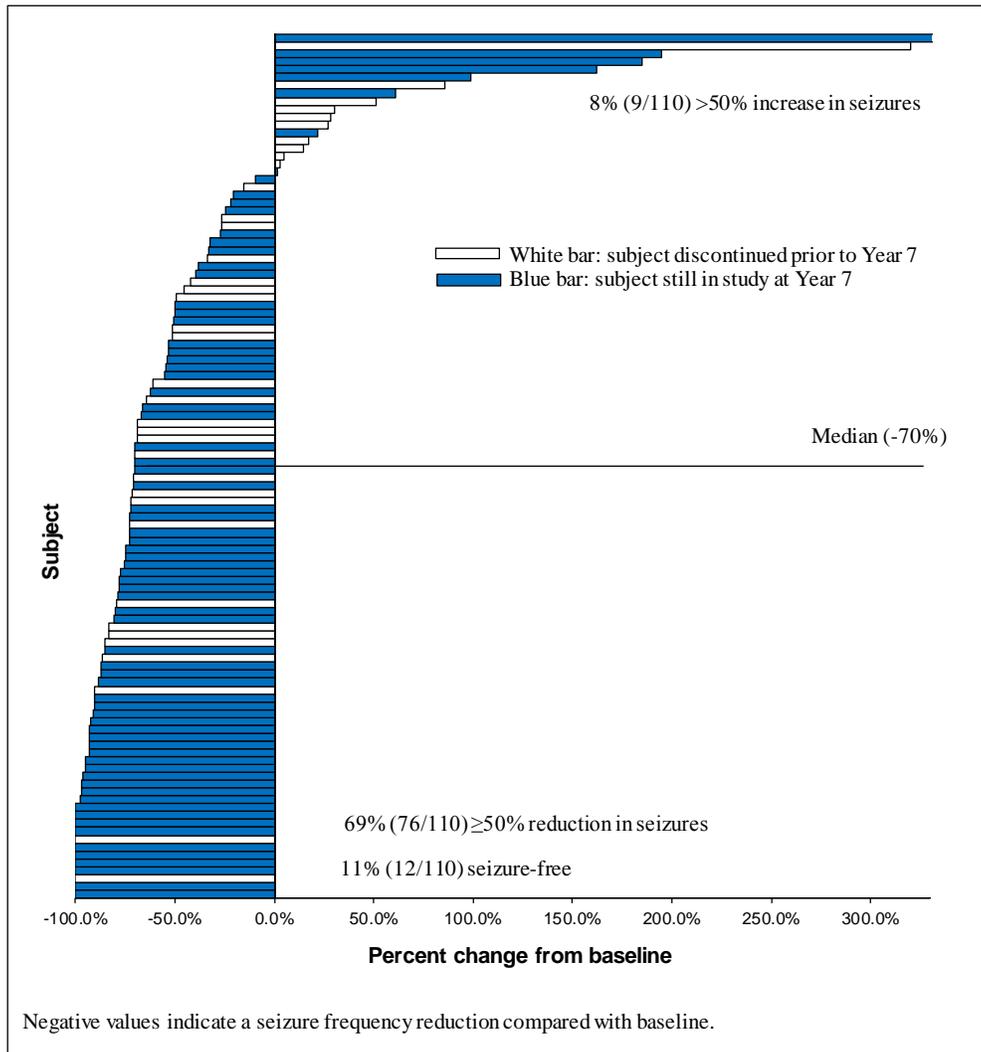


Figure 7. Subject total seizure frequency percent change from baseline to most recent 3 months of follow-up.

Secondary outcome measures

Responder rate

A responder is a subject whose seizure frequency is reduced by $\geq 50\%$ as compared with baseline. The difference in the responder rate between the active and control groups was not statistically significant ($p=0.830$, Fisher's exact test). Table 37 shows the responder rates in the Blinded Phase and through Long-Term Follow-Up Phases for those subjects with at least 70 days of diary in the 3 months prior to each annual visit. By the end of Year 1 the responder rate was 43% and by Year 7 it had increased to 74%.

Table 37. Responder rate – Blinded Phase through Year 7^a

Time period	n	Responder rate
Blinded Phase - Active	54	29.6%
Blinded Phase - Control	54	25.9%
Year 1	99	43.4%
Year 2	82	53.7%
Year 3	75	56.0%
Year 4	76	56.6%
Year 5	59	67.8%
Year 6	64	71.9%
Year 7	50	74.0%

^a The p-value for active vs control group in the Blinded Phase is not statistically significant.

Seizure-free days and seizure-free intervals

As shown in Table 38, there was no statistically significant difference in percent change in seizure-free days or percent change in maximum length of seizure-free intervals between the active and control groups over the Blinded Phase.

Table 38. Seizure-free days and seizure-free intervals – Blinded Phase

	Active	Control	Wilcoxon p-value
Median % change in seizure-free days ^a	15.3%	8.8%	0.112
Median % change in maximum length of seizure-free intervals	35.0%	25.0%	0.768

^a % change in seizure-free days was not calculated for subjects with no seizure-free days during baseline (active: n=4, control: n=4)

Figure 8 shows that at any time between implant and Year 7, 18% (20/110) of implanted subjects were seizure-free for at least 6 months, this included 9 subjects who were seizure-free for over 2 years. In addition, there were 10 subjects with 2 or more seizure-free intervals of at least 6 months. Ten had an ongoing 6-month or longer seizure-free interval at the time of the Year 7 visit or discontinuation, including one subject who had been seizure-free for over 6 of the 7 total years, and another subject who had been seizure-free for over 5 years. Because the seizure-free interval could be of variable length, only subjects with reliable and complete diary collection were included and the interval was required to have a diary compliance of at least 83.3%.

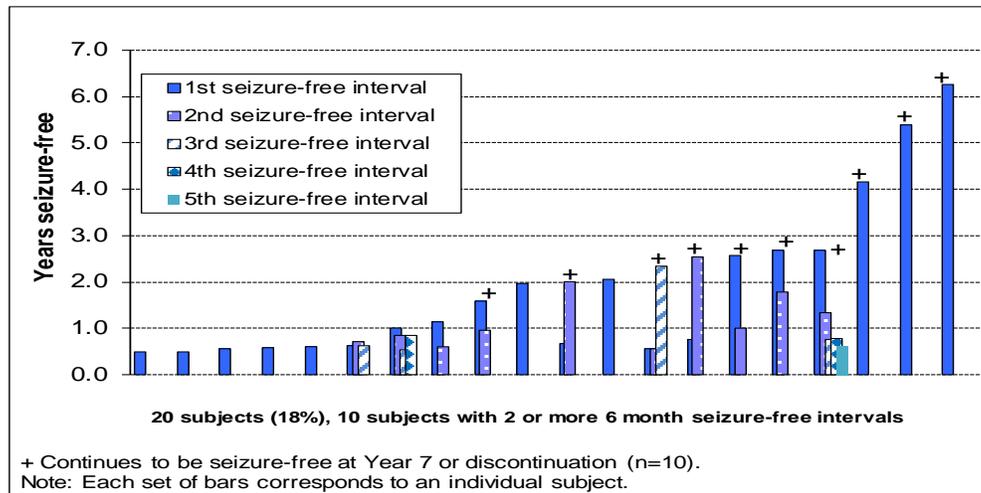


Figure 8. Subjects seizure-free for at least 6 months, by subject.

Treatment failure

A treatment failure was a subject who 1) required 3 or more doses of rescue medication within 48 hours, 3 times during the Blinded Phase; or 2) had 3 episodes of convulsive status epilepticus during the Blinded Phase. There were no treatment failures in the active or control groups in the Blinded Phase and the difference in treatment failures between groups was not statistically significant (p=1.0, Fisher’s exact test).

Additional study measures

Seizure types and severity

Subjects recorded descriptions of their seizures and dates of occurrence. The seizure descriptions were categorized into the following types: simple partial, complex partial, partial to generalized, generalized, and other. In addition, subjects were asked at baseline to identify which of their seizure types they considered to be the most severe. They were counted in each seizure type category if they experienced that particular seizure type during the Baseline Phase. Table 39 summarizes the most severe seizure types at baseline.

Table 39. Most severe seizure type at baseline

Seizure Type	Active		Control	
	n	%	n	%
Complex partial	22	51.2%	17	44.7%
Simple partial	5	11.6%	1	2.6%
Partial to generalized	15	34.9%	20	52.6%
Primary generalized	1	2.3%	0	0.0%
Total	43	100%	38	100%

Table 40 shows median seizure reductions from baseline during the Blinded Phase and through Year 7 of long-term follow-up by seizure type (simple partial

seizures, complex partial seizures, partial to generalized seizures, and most severe seizures). The most severe seizure type showed a statistically significant difference between active and control groups during the Blinded Phase (p=0.048). As shown in Table 41, when the outlier subject was removed from the analysis, the complex partial seizure types also showed a statistically significant difference between groups during the Blinded Phase (p=0.041). Only results for simple partial and complex partial seizure types are shown in Table 41 as this subject did not experience other seizure types.

Table 40. Median total seizure frequency percent change from baseline by seizure type – Blinded Phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Simple partial seizures					
Blinded Phase - Active	37	-39.9%	-65.8%	-4.3%	0.701
Blinded Phase - Control	32	-38.5%	-74.0%	11.5%	
Year 1	61	-47.3%	-100.0%	-12.2%	<0.001
Year 2	50	-73.0%	-100.0%	-41.3%	<0.001
Year 3	45	-68.5%	-100.0%	-25.3%	<0.001
Year 4	47	-76.7%	-100.0%	-8.1%	<0.001
Year 5	40	-86.0%	-100.0%	-53.6%	<0.001
Year 6	37	-97.9%	-100.0%	-60.2%	<0.001
Year 7	32	-92.2%	-100.0%	-66.4%	<0.001
Complex partial seizures					
Blinded Phase - Active	48	-36.3%	-65.5%	10.2%	0.065
Blinded Phase - Control	49	-12.1%	-41.2%	16.1%	
Year 1	90	-47.5%	-84.8%	-11.1%	<0.001
Year 2	73	-55.9%	-84.3%	-7.7%	<0.001
Year 3	69	-58.0%	-90.5%	-23.0%	<0.001
Year 4	71	-70.4%	-95.1%	-25.4%	<0.001
Year 5	54	-80.8%	-100.0%	-36.5%	<0.001
Year 6	58	-75.4%	-98.2%	-44.7%	<0.001
Year 7	44	-77.8%	-91.6%	-25.9%	<0.001
Partial to generalized seizures					
Blinded Phase - Active	19	-48.2%	-100.0%	-0.5%	0.647
Blinded Phase - Control	21	-24.7%	-66.7%	15.7%	
Year 1	37	-29.8%	-93.8%	24.7%	0.069
Year 2	28	-46.8%	-100.0%	1.8%	0.001
Year 3	25	-61.9%	-100.0%	-9.7%	0.002
Year 4	22	-43.2%	-81.4%	33.7%	0.439
Year 5	19	-82.4%	-100.0%	-30.9%	0.100
Year 6	22	-62.0%	-91.8%	11.7%	0.439
Year 7	20	-71.1%	-100.0%	-29.4%	0.006
Self-reported most severe seizures					
Blinded Phase - Active	43	-39.6%	-82.7%	-7.1%	0.048
Blinded Phase - Control	38	-20.4%	-50.0%	29.3%	
Year 1	74	-39.2%	-90.3%	-8.3%	<0.001
Year 2	62	-58.4%	-87.6%	-10.8%	<0.001
Year 3	55	-61.9%	-92.1%	-18.5%	<0.001
Year 4	55	-47.5%	-86.1%	-13.5%	<0.001
Year 5	42	-75.4%	-100.0%	-42.4%	<0.001

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Year 6	44	-63.7%	-91.5%	-14.7%	0.005
Year 7	30	-71.1%	-100.0%	-25.5%	<0.001

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Table 41. Median total seizure frequency percent change from baseline by seizure type – Blinded Phase, outlier subject removed ^a

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value
Simple partial seizures					
Blinded Phase - Active	36	-39.3%	-65.9%	-2.2%	0.713
Blinded Phase - Control	32	-38.5%	-74.0%	11.5%	
Complex partial seizures					
Blinded Phase - Active	47	-36.3%	-65.8%	9.5%	0.041
Blinded Phase - Control	49	-12.1%	-41.2%	16.1%	

^a Only results for simple partial and complex partial seizures types are shown as this subject did not experience other seizure types.

Liverpool seizure severity scale

Table 42 summarizes the Liverpool seizure severity scale scores at baseline and the change from baseline in the Blinded Phase by treatment group and at visits Year 1 through Year 7. Only subjects that had a test at baseline and at the respective follow-up period were included. No statistically significant difference was noted between the active and control groups during the Blinded Phase. A significant improvement over baseline is observed at the Year 1 through Year 7 visits.

Table 42. Liverpool Seizure Severity – Blinded Phase through year 7

Time period	n	Baseline mean ± std	Change mean ± std	t-test p-value ^a
Blinded Phase - Active	53	48.7 ± 17.9	-8.2 ± 17.8	0.699
Blinded Phase - Control	53	50.5 ± 18.1	-6.8 ± 19.6	
Year 1	103	48.9 ± 18.0	-13.4 ± 21.4	<0.001
Year 2	99	49.0 ± 18.2	-12.4 ± 20.7	<0.001
Year 3	93	48.1 ± 17.9	-14.6 ± 20.2	<0.001
Year 4	89	48.3 ± 18.0	-17.3 ± 23.0	<0.001
Year 5	81	49.3 ± 17.9	-18.3 ± 24.4	<0.001
Year 6	75	49.6 ± 17.9	-15.2 ± 20.3	<0.001
Year 7	67	49.0 ± 18.6	-18.1 ± 23.5	<0.001

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Patient programmer use

Subjects were provided a patient programmer at the week 4 randomization visit. Subjects were instructed to start a new stimulation cycle at the time they were experiencing a seizure. Both the control and active groups used the patient

programmer. Subjects were not included in this analysis if they were missing programming interrogation data where counters were reset, or if they did not receive the patient programmer at the week 4 visit due to center error. The active group had a slightly lower median number of activations (13) over the entire Blinded Phase compared to the control group (16) (active n=49, control n=48). However, the results were not statistically significantly different (p=0.837, Wilcoxon test).

Quality of life measures

Quality of life was measured with the QOLIE-31. The QOLIE-31 scores are summarized in Table 43 for the Blinded and Long-Term Follow-Up Phases. Only subjects who had results both at baseline and follow-up were included in the analysis. Changes from baseline to Month 4 between active and control groups were not statistically significantly different. However, a significant improvement over baseline is observed at the Year 1 through Year 7 visits.

A change in 5 points in the QOLIE-31 score is considered clinically meaningful. The percentage of subjects experiencing at least a 5-point change from baseline in QOLIE-31 score is shown in Table 44. At the end of the Blinded Phase, 48% of subjects in the active group had at least a 5-point improvement compared to 32% of subjects in the control group. Seven years after device implant, 43% of subjects had at least a 5-point improvement in their QOLIE-31 score.

The percentage of subjects reported to be satisfied or greatly satisfied with the results of their therapy was 74% (74/100) at Year 1 and 84% (54/64) at Year 7.

Table 43. QOLIE-31 score – Blinded Phase through year 7

Time period	n	Baseline mean ± std	Change mean ± std	Median change	Wilcoxon p-value ^a
Blinded Phase - Active	52	41.8 ± 8.6	2.5 ± 8.7	4.4	0.555
Blinded Phase - Control	53	43.4 ± 9.4	2.8 ± 8.0	2.4	
Year 1	102	42.5 ± 9.1	5.0 ± 9.2	4.1	<0.001
Year 2	98	42.4 ± 9.0	4.8 ± 9.3	3.2	<0.001
Year 3	92	42.6 ± 9.2	5.7 ± 9.1	3.5	<0.001
Year 4	88	42.9 ± 9.2	6.2 ± 10.2	3.8	<0.001
Year 5	80	42.2 ± 9.1	6.1 ± 10.1	4.5	<0.001
Year 6	74	42.3 ± 8.9	3.9 ± 8.6	2.5	<0.001
Year 7	67	42.6 ± 9.1	4.9 ± 11.1	3.3	<0.001

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Table 44. QOLIE-31 score responder rate – blinded Phase through year 7

Time period	n	Percent of subjects with 5-point change from baseline in the QOLIE-31 score
Blinded Phase - Active	52	48.1%
Blinded Phase - Control	53	32.1%
Year 1	102	46.1%
Year 2	98	38.8%
Year 3	92	43.5%
Year 4	88	45.5%
Year 5	80	47.5%
Year 6	74	37.8%
Year 7	67	43.3%

Neuropsychological results

Neuropsychological testing results are presented in the “Safety results” section.

Healthcare resource utilization

Table 45 summarizes the hospitalizations that occurred during the Blinded Phase by treatment group and over time with both groups combined. The hospitalizations included epilepsy-related and device-related visits. The Blinded Phase analysis included all randomized subjects. Although the active group had fewer visits, the difference between groups was not statistically significant ($p=0.105$, Wilcoxon test).

Table 45. Healthcare resource utilization^a

Group or Visit	n	Normalized annual hospitalizations (mean \pm std) ^b
Blinded Phase - Active	54	4.2 (0.08 \pm 0.56)
Blinded Phase - Control	55	20.2 (0.37 \pm 1.17)
Implant through Year 1 ^c	110	46.4 (0.42 \pm 0.90)
Year 1-2	105	6.5 (0.06 \pm 0.33)
Year 2-3	102	14.0 (0.14 \pm 0.55)
Year 3-4	98	9.6 (0.10 \pm 0.34)
Year 4-5	92	15.2 (0.17 \pm 0.51)
Year 5-6	83	4.6 (0.06 \pm 0.25)
Year 6-7	80	6.4 (0.08 \pm 0.28)

^a The p-value for the active vs. control group in the Blinded Phase is not statistically significant.

^b Results were normalized to a 365.25-day year, thus utilizations are not whole integer numbers. Annual hospitalizations are the total number of hospitalizations per year for the entire group of subjects during the interval. Mean is the mean annual number of hospitalizations per subject.

^c Implant through year 1 includes Operative and Blinded Phases.

Rescue medication use

Rescue medication use was allowed during the course of the study. For the Baseline and Blinded Phases, 22% of subjects in each group used a rescue medication at least one time. The annual rate of rescue medication use (mean \pm standard deviation) during the Blinded Phase was 3.5 ± 8.1 in the active group

and 8.3 ± 23.8 in the control group, although over 75% of all subjects did not have a use (75th percentile was 0). Differences between the groups in Blinded Phase rescue medication use were not statistically different ($p=0.866$, Wilcoxon test).

3. Subgroup Analyses

A comparison of seizure frequency for several subgroups was performed, including analyses by seizure onset location, by previous VNS device implant, by previous epilepsy surgery, and by medication status. None of these subgroup analyses were powered for statistical significance. Caution should be used when interpreting these results as the sample sizes are small and the variability is large.

- **Seizure onset location**

A post-hoc analysis was conducted to compare seizure frequency reduction by seizure onset location. Table 46 shows the median seizure frequency percent change from baseline for the Blinded and Long-Term Follow-Up Phases, by seizure onset location (temporal lobe seizures, frontal lobe seizures, and other seizure onset locations). A subject could be included in more than one subgroup category if the subject experienced seizures originating from more than one onset location. The differences observed between the active and control groups were statistically significant for temporal lobe seizures ($p=0.025$), but did not achieve statistical significance for frontal lobe seizures ($p=0.873$) nor for seizures originating outside the temporal and frontal lobes ($p=0.683$). However, improvements over baseline were observed for all subgroups, with statistically significant improvements after the Blinded Phase.

Table 46. Median total seizure frequency percent change from baseline by seizure onset location – Blinded Phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Temporal lobe					
Blinded Phase - Active	33	-43.9%	-67.7%	-24.1%	0.025
Blinded Phase - Control	29	-21.8%	-42.8%	13.6%	
Year 1	59	-44.2%	-78.8%	-16.1%	<0.001
Year 2	47	-61.2%	-78.9%	-29.1%	<0.001
Year 3	45	-58.0%	-76.4%	-33.2%	<0.001
Year 4	44	-69.7%	-83.1%	-23.7%	<0.001
Year 5	33	-75.6%	-100.0%	-54.1%	<0.001
Year 6	38	-81.0%	-91.8%	-61.9%	<0.001
Year 7	35	-77.5%	-92.9%	-54.6%	<0.001
Frontal lobe					
Blinded Phase - Active	14	-15.0%	-35.3%	14.1%	0.873
Blinded Phase - Control	14	-19.1%	-52.4%	-4.5%	
Year 1	25	-52.6%	-78.8%	-17.0%	0.001
Year 2	20	-47.2%	-80.9%	-8.5%	0.005
Year 3	14	-52.1%	-67.3%	-18.5%	0.002
Year 4	19	-73.7%	-95.4%	-33.9%	<0.001
Year 5	17	-58.8%	-96.4%	-41.7%	0.005

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Year 6	15	-69.1%	-86.5%	-42.5%	<0.001
Year 7	9	-85.6%	-92.2%	-54.8%	0.129
"Other" lobe					
Blinded Phase - Active	13	-35.0%	-36.7%	-0.8%	0.683
Blinded Phase - Control	14	-10.5%	-42.9%	5.1%	
Year 1	22	-33.9%	-60.4%	2.8%	0.012
Year 2	21	-54.3%	-75.0%	-13.2%	0.002
Year 3	21	-57.4%	-84.6%	-27.5%	<0.001
Year 4	18	-39.3%	-84.4%	-12.8%	0.081
Year 5	13	-68.0%	-78.3%	-36.5%	0.124
Year 6	15	-63.4%	-91.9%	31.3%	0.247
Year 7	11	-39.3%	-100.0%	21.8%	0.320

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

- Previous vagus nerve stimulation device implant**

A post-hoc analysis was conducted to compare seizure frequency reduction for subjects with a previously implanted VNS device. Table 47 shows the median total seizure frequency percent change from baseline during the Blinded and Long-Term Follow-Up Phases for subjects grouped by history of VNS. The differences observed between the active and control groups did not achieve statistical significance for either those with previous VNS (p=0.158) or without previous VNS (p=0.516). However, improvements over baseline were observed for both subgroups, with statistically significant improvements after the Blinded Phase.

Table 47. Median total seizure frequency percent change from baseline by VNS subgroup – Blinded Phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Previous VNS					
Blinded Phase - Active	21	-35.1%	-53.9%	2.0%	0.158
Blinded Phase - Control	27	-14.1%	-42.9%	7.5%	
Year 1	45	-39.6%	-73.8%	-6.2%	<0.001
Year 2	33	-48.8%	-75.0%	-26.3%	<0.001
Year 3	32	-58.5%	-84.2%	-37.3%	<0.001
Year 4	36	-50.3%	-82.8%	-26.6%	<0.001
Year 5	25	-69.4%	-86.0%	-41.7%	<0.001
Year 6	26	-74.7%	-86.5%	-51.1%	0.001
Year 7	21	-74.7%	-88.4%	-53.7%	0.047
No previous VNS					
Blinded Phase - Active	33	-35.0%	-53.9%	-14.5%	0.516
Blinded Phase - Control	27	-22.9%	-58.8%	13.6%	
Year 1	54	-44.9%	-78.8%	-13.4%	<0.001
Year 2	49	-60.8%	-82.3%	-25.6%	<0.001
Year 3	43	-51.6%	-74.8%	-27.5%	<0.001
Year 4	40	-72.6%	-85.1%	-24.1%	<0.001
Year 5	34	-69.4%	-98.9%	-41.8%	<0.001

Year 6	38	-74.9%	-91.8%	-44.2%	<0.001
Year 7	29	-77.5%	-95.1%	-39.3%	<0.001

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

- **Previous epilepsy surgery**

Table 48 shows the median total seizure frequency percent change from baseline results during the Blinded and Long-Term Follow-Up Phases, with subjects grouped by history of previous epilepsy surgery (e.g., resection). The differences observed between the active and control groups did not achieve statistical significance for either those with previous epilepsy surgery (p=0.481) or without previous epilepsy surgery (p=0.295). However, improvements over baseline were observed for both subgroups, with statistically significant improvements after the Blinded Phase. For the subgroup with previous epilepsy surgery, improvements were not statistically significant at Year 7.

Table 48. Median total seizure frequency percent change from baseline by epilepsy surgery subgroup– Blinded Phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value a
Previous epilepsy surgery					
Blinded Phase - Active	11	-22.9%	-36.6%	2.0%	0.481
Blinded Phase - Control	16	-12.8%	-29.9%	9.1%	
Year 1	24	-53.4%	-75.4%	-17.9%	<0.001
Year 2	15	-55.9%	-75.8%	-17.0%	0.008
Year 3	18	-47.4%	-82.7%	-27.5%	0.001
Year 4	19	-48.6%	-73.7%	-3.9%	0.002
Year 5	14	-67.1%	-86.0%	-41.7%	<0.001
Year 6	15	-77.1%	-86.5%	-52.9%	<0.001
Year 7	10	-69.0%	-80.3%	-27.1%	0.084
No previous epilepsy surgery					
Blinded Phase - Active	43	-36.2%	-59.6%	-14.5%	0.295
Blinded Phase - Control	38	-22.3%	-56.4%	7.5%	
Year 1	75	-39.7%	-77.4%	-8.3%	<0.001
Year 2	67	-55.4%	-79.5%	-25.6%	<0.001
Year 3	57	-57.4%	-78.9%	-32.1%	<0.001
Year 4	57	-72.7%	-85.4%	-26.7%	<0.001
Year 5	45	-70.4%	-96.4%	-41.8%	<0.001
Year 6	49	-72.8%	-91.4%	-44.2%	<0.001
Year 7	40	-76.4%	-94.0%	-44.8%	<0.001

^a Blinded Phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

- **Medication status**

A post-hoc analysis was conducted to compare seizure frequency reduction by medication status using the following categories for AED usage:

- **No change in AED burden** – subject is on the same medications at the same doses

- **Increase in AED burden** – subject is on an increased number or increased dosage of AEDs
- **Decrease in AED burden** – subject is on a decreased number or decreased dosage of AEDs
- **Combination** – one or more AEDs were increased or added while one or more were decreased or discontinued

AED usage was determined based on changes from the previous annual visit. For Year 1, AED usage was assessed relative to baseline. Figure 9 shows seizure reduction by AED usage category.

Figure 10 shows the effects of adding a new medication (as compared to baseline) on total seizure reduction. Subjects in the “AED added” category had at least one new medication added after implant, while those in the “no AED added” category had no medications added through Year 7. Overall, subjects with increases in AED burden and additions of new AEDs had results consistent with those subjects without such changes, indicating that the long term results were not driven by increases in AED burden or additions of new AEDs.

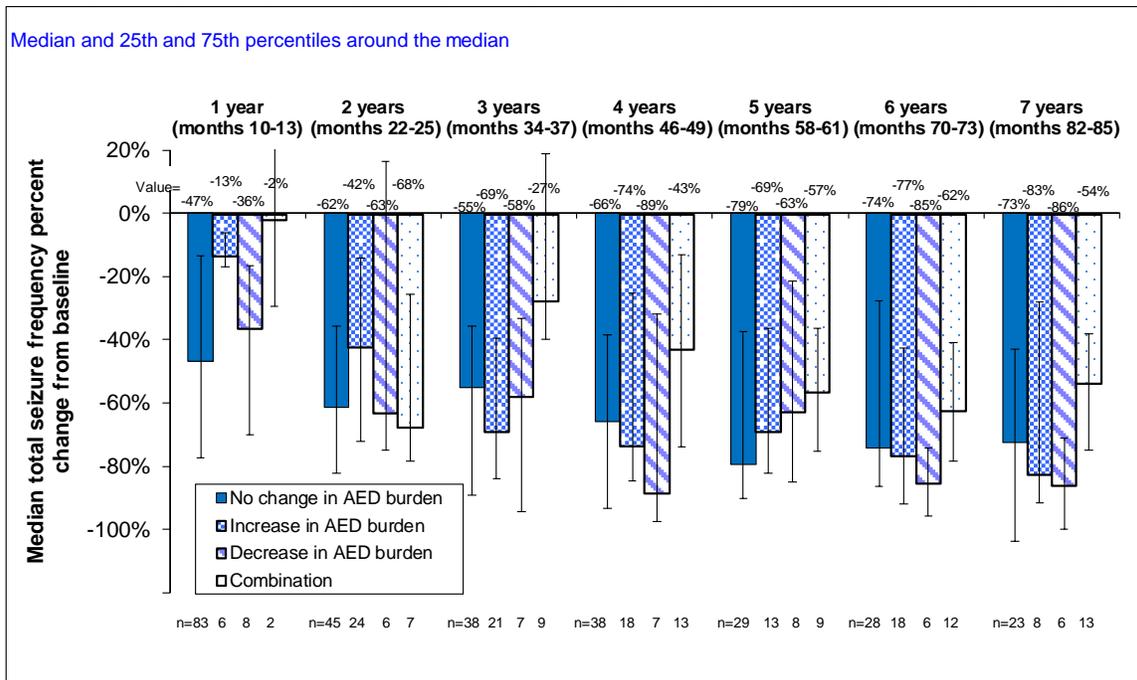


Figure 9. AED usage and median total seizure frequency percent change from baseline – year 1 through year 7.

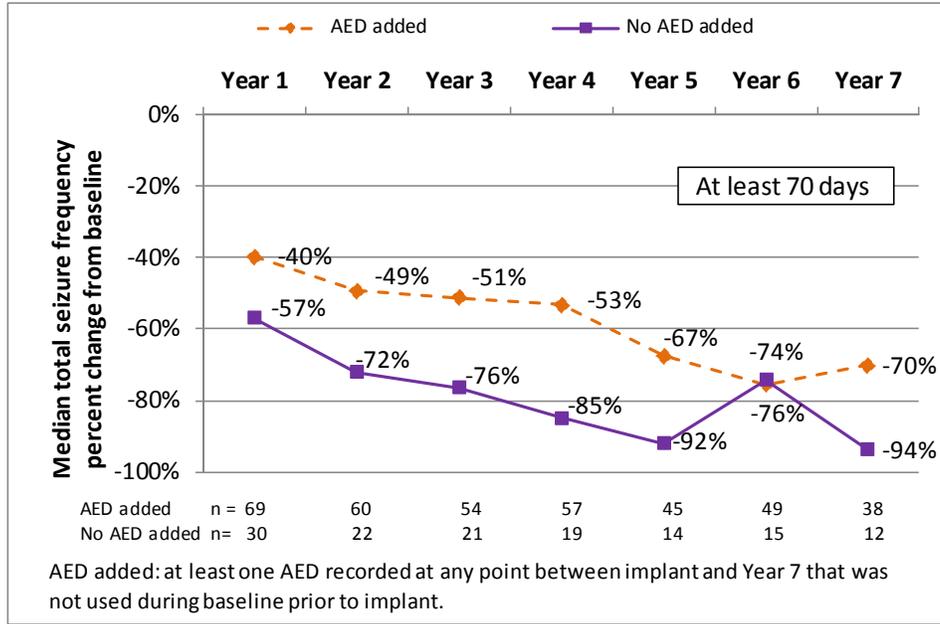


Figure 10. New AED use and median total seizure frequency percent change from baseline – year 1 through year 7.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 included 51 investigators of which none were full-time or part-time employees of the sponsor and 2 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 1 investigator
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 1 investigator

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study

outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION

Data from the study collected through 2009 were discussed at a meeting of the Neurological Devices Advisory Panel meeting on March 12, 2010. The overall recommendation from the Panel was to approve the indication with conditions related to labeling and a post-approval study.

Documentation from this Panel meeting can be found online at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm202072.htm>

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The SANTÉ study demonstrated that anterior thalamic deep brain stimulation is more effective than sham stimulation at reducing the frequency of seizures in subjects with epilepsy characterized by partial onset seizures that are refractory to at least 3 antiepileptic medications.

The primary objective of the study was met with post-hoc removal of an outlier demonstrating a reduction in total seizure frequency that was greater in the active group compared with the control group during the Blinded Phase of the study. The GEE model showed a least-squares means difference in seizure frequency reduction between groups of 17% ($p=0.045$, two-sided). With the same dataset, the median total seizure frequency percent change from baseline over the entire Blinded phase was -35.0% for the active group compared with -21.1% for the control group.

None of the secondary endpoints demonstrated statistically significant differences between groups during the Blinded Phase. However, the results showed a significant difference between groups in subjects' prospectively-defined most severe seizures, and in an analysis with the outlier removed, a significant difference in complex partial seizures.

The effectiveness of the treatment is further supported with long-term data demonstrating sustained improvements in seizure reduction over time with a median total seizure reduction of 75% and a responder rate of 74% at 7 years after device implant. A total of 20 (18%) subjects were seizure-free for at least 6 consecutive months during the study. While differences in quality of life between treatment groups were not found during the Blinded Phase, there were statistically significant improvements over baseline in quality of life at the end of the first year that were sustained through 7 years after device implant. Long-term, almost half of the subjects experienced clinically meaningful changes in their quality of life.

B. Safety Conclusions

This study evaluated the safety of bilateral stimulation of the ANT for epilepsy in 110 implanted subjects with a combined 713 device-years of experience. Data from the study, including the open-label period, were used to assess overall safety in which all active subjects were followed for a minimum of 7 years after device implantation. There were no unanticipated adverse device effects. Seven deaths occurred in the study; none of them were determined to be related to the device.

The SUDEP rate was determined based on the SANTÉ study experience and on previous pilot studies of ANT DBS for epilepsy. Based on this experience, the rate of SUDEP was 2.5 per 1000 person-years and is lower than the rate reported for surgical candidates for epilepsy of 9.3 per 1000 person-years.¹

Serious device-related adverse events were reported in 38 subjects (34.5%). The most frequent device-related serious adverse events were implant site infection (10.9%; 8.2% requiring explant) and lead(s) not in target (8.2%), with all others reported in 1.8% or fewer subjects. The majority of the device-related SAEs occurred during the Operative Phase. One subject experienced a serious adverse event related to intracranial hemorrhage which resolved without surgical intervention.

During the Blinded Phase, depression and memory impairment were reported in a significantly higher percentage of subjects in the active group as compared to the control group. None of the memory impairment events were serious; one of the depression events was serious in a subject reporting pre-existing depression. For the entire study follow-up period, no subjects discontinued due to depression or memory impairment events. Neuropsychological test results remained stable at the end of the Blinded Phase and long term through 7 years, including tests for cognition and mood.

When considering the total post-implant experience (713 device-years), 8 subjects experienced 8 intracranial hemorrhage events, 3 which occurred following a device explant procedure. One of the intracranial hemorrhage events was symptomatic. Nine subjects required at least one additional surgery to replace a lead implanted outside of the targeted area as required by the protocol. There were 7 subjects who experienced status epilepticus and 5 subjects who reported increased, worsening, or new seizures during the first week of stimulation. Suicidality events were reported by 12 subjects (7 subjects with SAEs), depression events were reported by 43 subjects (1 subject with SAE), and memory impairment events were reported by 34 subjects (none were serious).

Subject discontinuations after device implant through at least 7 years of follow-up included 12% due to an adverse event of therapeutic product ineffective, 5% due to implant site infection, 5% due to withdrawn consent, 5% due to death, and 5% due to other adverse events related to the device or therapy.

The safety profile for the Medtronic DBS System for Epilepsy is stable long term and has been well characterized with risks identified and quantified through a minimum of 7 years of post-implant follow-up.

1 Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 1991;8:216-222.

C. **Benefit-Risk Conclusions**

The benefits of ANT DBS therapy outweigh the risks. The SANTÉ study demonstrated that anterior thalamic deep brain stimulation is more effective than sham stimulation at reducing the frequency of seizures in a medically refractory patient population. The safety profile of ANT DBS has been well characterized and is stable long term in a study with an extensive follow-up period. A review of the published literature indicates that risks associated with DBS for epilepsy are consistent with those associated with refractory epilepsy, other approved implanted brain device therapies for epilepsy, and approved DBS devices.

The data support the safety and effectiveness of bilateral stimulation of the ANT as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years and older diagnosed with epilepsy, characterized by partial-onset seizures, who are refractory to at least 3 antiepileptic medications and who average six or more seizures per month in the 3 months prior to implant of the DBS system (with no more than 30 days between seizures).

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

Limitations

Additional factors to be considered in determining probable risks and benefits for the Medtronic DBS system for Epilepsy in the primary analysis is an effect with the surgical procedure, an effect of lead implantation, regression to the mean, or a placebo effect.

In addition, though the open-label, long-term data demonstrated sustained improvements in seizure reduction, the interpretation of open-label data is limited by selection bias, expectation bias and confounders such as anti-epileptic drug and stimulation changes. Sensitivity analyses for long-term effectiveness were conducted to assess the potential impact of missing data including LOCF and Worst case analyses; in addition, an analysis of long-term effectiveness by medication status was performed to evaluate the impact of changes in antiepileptic medications. However, the open-label portion could not assess the magnitude of the placebo response, regression to the mean, or the effect of changes in medications, stimulation settings or other treatments on decreasing seizure frequency.

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 probable benefit to health from the use of the device outweighs the probable risk of injury or illness from such use.

XIV. CDRH DECISION

CDRH issued an approval order on April 27, 2018.

The final conditions of approval cited in the approval order are described below.

The following post-approval study will be performed. The protocol for the Medtronic DBS Therapy for Epilepsy New Enrollment Post-Approval Study was agreed to via email on 8/19/2015.

Protocol Outline for “Medtronic DBS Therapy for Epilepsy New Enrollment Post-Approval Study”	
Study Element	Description
Postmarket Question	To further evaluate the long-term effectiveness of this device on seizure reduction in a newly enrolled population
Basic Study Design	This is an observational prospective, multicenter study of newly enrolled subject’s response to DBS + Current Medical Management (CMM) following CMM only. All subjects will receive CMM for 3 months. Those meeting per-protocol criteria will undergo DBS implant. The primary analysis will occur at 36 months of DBS+CMM.
Sample Size	A total of 216 subjects may be enrolled in order that 140 subjects be implanted and at least 112 provide 3 years of post-implant follow-up data.
Study Endpoints	<p>The primary effectiveness objective is to demonstrate a median percentage reduction in seizures of at least 40% from pre-implant to post-implant in subjects treated with the DBS system at 36 months.</p> <p>The primary safety objective is to demonstrate that there is not a 20% worsening in seizures over time in subjects treated with the DBS system beginning at 6 to 12 months post-implant and extending to 36 months.</p> <p>The secondary effectiveness objectives are to demonstrate that:</p>

Protocol Outline for “Medtronic DBS Therapy for Epilepsy New Enrollment Post-Approval Study”	
Study Element	Description
	<ul style="list-style-type: none"> • The total seizure rate during CMM is reduced after 12 subsequent months of DBS+CMM. • The disabling seizure rate during CMM is reduced after 12 subsequent months of DBS & CMM. • The rate of seizures originating in the temporal lobe during CMM is reduced after 12 subsequent months of DBS+CMM. <p>The secondary safety objective is the Sudden Unanticipated Death from Epilepsy (SUDEP) rate at 36 months.</p> <p>Additional study endpoints include characterizing:</p> <ul style="list-style-type: none"> • Any serious adverse events • Adverse events related to device implant and stimulation • Device deficiencies • Post-implant effects through the 6-month post-implant follow-up visit • Lead explants and revisions • Characterizing adverse events of depression, suicidality, memory impairment, and seizures in the CMM and DBS+CMM phases • SUDEP rate in the CMM and DBS+CMM phases • Neuropsychological outcomes related to memory impairment, depression, and suicidality • 3 year long-term DBS+CMM effectiveness (seizure frequency, responder rate, disabling seizures, frequency by seizure type, most severe seizure, seizure-related injuries, seizure freedom) • The effect of DBS+CMM in subject subgroups including various seizure onset zones (temporal lobe, frontal lobe, diffuse or multifocal, parietal, occipital and other), previous VNS, previous resection, number of previous AEDs, subjects aged 18-21. • DBS stimulation parameters used over time • Antiepileptic medication changes • Quality of life over time • Subject programmer use

Protocol Outline for “Medtronic DBS Therapy for Epilepsy New Enrollment Post-Approval Study”	
Study Element	Description
	<ul style="list-style-type: none"> Effectiveness of physician training programs (duration/number of acute events following stimulation initiation, lead re-operation rate)
Length of Follow-up	Follow-up will occur for 3 years, with descriptive evaluation of endpoints to be provided annually, and testing of the hypotheses associated with the primary effectiveness and primary safety endpoints to be performed at 36 months.

PAS reporting will occur every six-months for the first two years of the PAS and then yearly thereafter.

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

Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*. 2015 Feb 24;84(8):810-817.

Bjerknes S, Skogseid IM, Sæhle T, Dietrichs E, Toft M. Surgical site infections after deep brain stimulation surgery: frequency, characteristics and management in a 10-year period. *PLoS One*. 2014 Aug 14;9(8):e105288.

Fenoy AJ, Simpson RK Jr. Management of device-related wound complications in deep brain stimulation surgery. *J Neurosurg*. 2012 Jun;116(6):1324-32.

Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010 May;51(5):899-908.

Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011 Sep 27;77(13):1295-1304.

Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 2015;84:1017–1025.

Sprengers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy. *Cochrane Database Syst Rev* 2014 June 17; 6.

Tolleson C, Stroh J, Ehrenfeld J, Neimat J, Konrad P, Phibbs F. The factors involved in deep brain stimulation infection: a large case series. *Stereotact Funct Neurosurg*. 2014;92(4):227-33. doi: 10.1159/000362934. Epub 2014 Aug 5.