St. Jude Medical Infinity™ Implantable Pulse Generator

Models 6660, 6661, 6662, 6663

Clinician's Manual

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

⚠ WARNING: This product can expose you to chemicals including ethylene oxide, which is known to the State of California to cause cancer and birth defects or other reproductive harm. For more information, go to www.P65Warnings.ca.gov.

Contents

Prescription and Safety Information

Read this section to gather important prescription and safety information.

Intended Use

This neurostimulation system is designed to deliver low-intensity electrical impulses to nerve structures. The system is intended to be used with leads and associated extensions that are compatible with the system.

Indications for Use

The St. Jude Medical™ deep brain stimulation system is indicated for the following conditions:

- Bilateral stimulation of the subthalamic nucleus (STN) or the internal globus pallidus (GPi) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease that are not adequately controlled by medications.
- Unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Contraindications

This system is contraindicated for patients who meet the following criteria:

- Are unable to operate the system
- Have unsuccessful test stimulation

The following procedures are contraindicated for patients with a deep brain stimulation system. Advise patients to inform their healthcare professional that they cannot undergo the following procedures:

- Diathermy (short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy)
- Electroshock therapy and transcranial magnetic stimulation (TMS)

Warnings

The following warnings apply to this neurostimulation system.

Pregnancy and nursing. Safety and effectiveness of neurostimulation for use during pregnancy and nursing have not been established. Patients should not use this neurostimulation system if they are pregnant or nursing.

Magnetic resonance imaging (MRI). Do not perform MRI on a patient with any implanted neurostimulator or lead (or any portion of a lead) from this system. Even if the neurostimulator has been removed, the patient should not have an MRI if any part of a lead or the cranial prosthesis is still implanted. The neurostimulation system is MR Unsafe. Testing has not been performed to define conditions of use to ensure safety of the neurostimulation system in an MR environment.

High stimulation outputs and charge density limits. Avoid excessive stimulation. A risk of brain tissue damage exists with parameter settings using high amplitudes and wide pulse widths. **High amplitudes and wide pulse widths should only be programmed with due consideration of the warnings concerning charge densities.** The system can be programmed to use parameter settings outside the range of those used in the clinical studies. If the programming of stimulation parameters exceeds the charge density limit of 30 $\mu C/cm^2$, a screen will appear warning you that the charge density is too high. Charge density can be reduced by lowering the stimulation

amplitude or pulse width. For more information, see the clinician programmer manual.

Higher amplitudes and wider pulse widths may indicate a system problem or a suboptimal lead placement. Stimulation at high outputs may cause unpleasant sensations or motor disturbances or may render the patient incapable of controlling the patient controller. If unpleasant sensations occur, the device should be turned off immediately using the patient magnet.

Risk of depression, suicide ideations, and suicide. New onset or worsening depression, which may be temporary or permanent, is a risk that has been reported with DBS therapy. Suicidal ideation, suicide attempts, and suicide are events that have also been reported. Therefore, physicians should consider the following:

- Preoperatively, assess patients for the risks of depression and suicide. This assessment should consider both the risk of depression and suicide as well as the potential clinical benefits of DBS therapy for the condition being treated.
- Postoperatively, actively monitor patients for new or worsening symptoms of depression, suicidal thoughts or behaviors, or changes in mood or impulse control.
- If a patient experiences new or worsening depression or suicidal ideation, manage these symptoms appropriately.
- Educate patients and caregivers about these potential risks prior to implantation, and be sure that they know about the importance of ongoing support and follow-up, including when to contact their health care provider.

Poor surgical risks. Neurostimulation should not be used on patients who are poor surgical risks or patients with multiple illnesses or active general infections.

Explosive or flammable gases. Do not use the clinician programmer or patient controller in an environment where explosive or flammable gas fumes or vapors are present. The operation of the clinician programmer or patient controller could cause them to ignite, causing severe burns, injury, or death.

Operation of machinery and equipment. Patients should not operate potentially dangerous machinery, power tools, or vehicles or engage in any activity that could be unsafe if their symptoms were to unexpectedly return.

Device components. The use of components not approved for use by St. Jude Medical with this system may result in damage to the system and increased risk to the patient.

Electrosurgery. To avoid harming the patient or damaging the neurostimulation system, do not use monopolar electrosurgery devices on patients with implanted neurostimulation systems. Before using an electrosurgery device, place the device in Surgery Mode using the patient controller app or clinician programmer app. Confirm the neurostimulation system is functioning correctly after the procedure.

During implant procedures, if electrosurgery devices must be used, take the following actions:

- Use bipolar electrosurgery only.
- Complete any electrosurgery procedures before connecting the leads or extensions to the neurostimulator.
- Keep the current paths from the electrosurgery device as far from the neurostimulation system as possible.
- Set the electrosurgery device to the lowest possible energy setting.
- Confirm that the neurostimulation system is functioning correctly during the implant procedure and before closing the neurostimulator pocket.

Radiofrequency or microwave ablation. Careful consideration should be used before using radiofrequency (RF) or microwave ablation in patients who have an implanted neurostimulation

system since safety has not been established. Induced electrical currents may cause heating, especially at the lead electrode site, resulting in tissue damage.

Implanted cardiac systems. Physicians need to be aware of the risk and possible interaction between a neurostimulation system and an implanted cardiac system, such as a pacemaker or defibrillator. Electrical pulses from a neurostimulation system may interact with the sensing operation of an implanted cardiac system, causing the cardiac system to respond inappropriately. To minimize or prevent the implanted cardiac system from sensing the output of the neurostimulation system, (1) maximize the distance between the implanted systems; (2) verify that the neurostimulation system is not interfering with the functions of the implanted cardiac system; and (3) avoid programming either device in a unipolar mode (using the device's can as an anode) or using neurostimulation system settings that interfere with the function of the implantable cardiac system.

Other active implanted devices. The neurostimulation system may interfere with the normal operation of another active implanted device, such as a pacemaker, defibrillator, or another type of neurostimulator. Conversely, the other active implanted device may interfere with the operation of the neurostimulation system.

Case damage. If the case of the implantable pulse generator (IPG) is pierced or ruptured, severe burns could result from exposure to battery chemicals.

Cremation. The IPG should be explanted before cremation because the IPG could explode. Return the explanted IPG to St. Jude Medical.

Component disposal. Return all explanted components to St. Jude Medical for safe disposal. IPGs contain batteries as well as other potentially hazardous materials. Do not crush, puncture, or burn the IPG because explosion or fire may result.

Coagulopathies. Physicians should use extreme care with lead implantation in patients with a heightened risk of intracranial hemorrhage. Physicians should also consider underlying factors, such as previous neurological injury or prescribed medications (anticoagulants), that may predispose a patient to the risk of bleeding.

Low frequencies. Stimulation frequencies at less than 30 Hz may cause tremor to be driven (meaning that tremor occurs at the same frequency as the programmed frequency). For this reason, programming at frequencies less than 30 Hz is not recommended.

IPG placement. The IPG should be placed into the pocket, at a depth not to exceed 4 cm (1.57 in), with the logo side facing toward the skin surface. Placing the IPG deeper than 4 cm (1.57 in) can impede or prohibit IPG communications with the clinician programmer or patient controller.

Return of symptoms and rebound effect. The abrupt cessation of stimulation for any reason will probably cause disease symptoms to return. In some cases, symptoms may return with a greater intensity than what a patient experienced before system implantation (rebound effect). In rare cases, this can create a medical emergency.

Precautions

The following precautions apply to this neurostimulation system.

General Precautions

Surgeon training. Implanting physicians should be experienced in stereotactic and functional neurosurgery.

Clinician training. Clinicians should be familiar with deep brain stimulation therapy and be experienced in the diagnosis and treatment of the indication for which the deep brain stimulation components are being used.

Patient selection. Select patients appropriately for deep brain stimulation. The patient should be able and willing to use the patient controller and correctly interpret the icons and messages that appear on the screen.

Especially consider the following additional factors when selecting patients:

- Level of available support from a caregiver.
- Expected effect from cessation of therapy, should disease symptoms return unexpectedly.
- Patient's age, as very young or very old patients may have difficulty performing required monitoring of the device.
- Patient's mental capacity, as patients with cognitive impairment or those prone to developing dementia would likely have difficulty performing device-related tasks without assistance.
- Patient's physical ability, as patients with higher degrees of motor impairment might have difficulty with the physical requirements of monitoring the device.
- Patient's visual ability to read the patient controller screen.

Infection. Follow proper infection control procedures. Infections may require that the device be explanted.

Electromagnetic interference (EMI). Some equipment in home, work, medical, and public environments can generate EMI that is strong enough to interfere with the operation of a neurostimulation system or damage system components. Patients should avoid getting too close to these types of EMI sources, which include the following examples: commercial electrical equipment (such as arc welders and induction furnaces), communication equipment (such as microwave transmitters and high-power amateur transmitters), high-voltage power lines, radiofrequency identification (RFID) devices, and some medical procedures (such as therapeutic radiation and electromagnetic lithotripsy).

Security, antitheft, and radiofrequency identification (RFID) devices. Some antitheft devices, such as those used at entrances or exits of department stores, libraries, and other public places, and airport security screening devices may affect stimulation. Additionally, RFID devices, which are often used to read identification badges, as well as some tag deactivation devices, such as those used at payment counters at stores and loan desks at libraries, may also affect stimulation. Patients should cautiously approach such devices and should request help to bypass them. If they must go through or near a gate or doorway containing this type of device, patients should move quickly and then check their IPG to determine if it is turned on or off.

Unauthorized changes to stimulation parameters. Caution patients to not make unauthorized changes to physician-established stimulation parameters.

Damage to shallow implants. Falling and other traumatic accidents can damage shallowly implanted components such as the leads and extensions.

Keep programmers and controllers dry. The clinician programmer and patient controller are not waterproof. Keep them dry to avoid damage. Advise patients to not use the patient controller when engaging in activities that might cause it to get wet, such as swimming or bathing.

Handle the programmers and controllers with care. The clinician programmer and patient controllers are sensitive electronic devices that can be damaged by rough handling, such as dropping them on the ground.

Battery care. Batteries can explode, leak, or melt if disassembled, shorted (when battery connections contact metal), or exposed to high temperature or fire.

Long-term safety and effectiveness. The long-term safety and effectiveness of this neurostimulation system has not been established beyond 5 years. Safety and effectiveness has not been established for patients with a neurological disease other than Parkinson’s disease or

essential tremor, previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression; patients under 22 years; implantation in targets other than the STN or GPi for Parkinson's disease and the VIM for essential tremor; patients with an active implantable device; patients requiring MRI.

Sterilization and Storage

Single-use, sterile device. The implanted components of this neurostimulation system are intended for a single use only. Sterile components in this kit have been sterilized using ethylene oxide (EtO) gas before shipment and are supplied in sterile packaging to permit direct introduction into the sterile field. Do not resterilize or reimplant an explanted system for any reason.

Storage environment. Store components and their packaging where they will not come in contact with liquids of any kind. Detailed information on storage environment is provided in the appendix of this manual.

Handling and Implantation

Expiration date. An expiration date (or “use-before” date) is printed on the packaging. Do not use the system if the use-before date has expired.

Care and handling of components. Use extreme care when handling system components. Excessive heat, excessive traction, excessive bending, excessive twisting, or the use of sharp instruments may damage and cause failure of the components.

Package or component damage. Do not implant a device if the sterile package or components show signs of damage, if the sterile seal is ruptured, or if contamination is suspected for any reason. Return any suspect components to St. Jude Medical for evaluation.

Exposure to body fluids or saline. Prior to connection, exposure of the metal contacts, such as those on the connection end of a lead or extension, to body fluids or saline can lead to corrosion. If such exposure occurs, clean the affected parts with sterile, deionized water or sterile water for irrigation, and dry them completely prior to lead connection and implantation.

Skin erosion. To avoid the risk of skin erosion, implant components at the appropriate depth and inform patients to avoid touching their skin where components are implanted. The IPG should be placed into the pocket, at a depth not to exceed 4.0 cm (1.57 in), with the logo side facing toward the skin surface.

System testing. To ensure correct operation, always test the system during the implant procedure, before closing the neurostimulator pocket, and before the patient leaves the surgery suite.

Device modification. The equipment is not serviceable by the customer. To prevent injury or damage to the system, do not modify the equipment. If needed, return the equipment to St. Jude Medical for service.

Multiple leads. When multiple leads are implanted, route the lead extensions so the area between them is minimized. If the lead extensions are routed in a loop, the loop will increase the potential for electromagnetic interference (EMI).

Abandoned leads and replacement leads. The long-term safety associated with multiple implants, leads left in place without use, replacement of leads, multiple implants into the target structure, and lead explant is unknown.

Placement of lead connection in neck. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture.

Hospital and Medical Environments

Electrical medical treatment. In the case that a medical treatment is administered where an

electrical current is passed through the body from an external source, first deactivate the IPG by setting all electrodes to off, turning stimulation off, and setting amplitude to zero. Regardless if the device is deactivated, take care to monitor the device for proper function during and after treatment.

High-output ultrasonics and lithotripsy. The use of high-output devices, such as an electrohydraulic lithotriptor, may cause damage to the electronic circuitry of an implanted IPG. If lithotripsy must be used, do not focus the energy near the IPG.

Ultrasonic scanning equipment. The use of ultrasonic scanning equipment may cause mechanical damage to an implanted neurostimulation system if used directly over the implanted system.

External defibrillators. The safety of discharge of an external defibrillator on patients with implanted neurostimulation systems has not been established.

Therapeutic radiation. Therapeutic radiation may damage the electronic circuitry of an implanted neurostimulation system, although no testing has been done and no definite information on radiation effects is available. Sources of therapeutic radiation include therapeutic X rays, cobalt machines, and linear accelerators. If radiation therapy is required, the area over the implanted IPG should be shielded with lead. Damage to the system may not be immediately detectable.

Electrocardiograms. Ensure the neurostimulator is off before initiating an electrocardiogram (ECG). If the neurostimulator is on during an ECG, the ECG recording may be adversely affected, resulting in inaccurate ECG results. Inaccurate ECG results may lead to inappropriate treatment of the patient.

Home and Occupational Environments

Patient activities and environmental precautions. Patients should take reasonable care to avoid devices that generate strong EMI, which may cause the neurostimulation system to unintentionally turn on or off. Patients should also avoid any activities that would be potentially unsafe if their symptoms were to return unexpectedly. These activities include but are not limited to climbing ladders and operating potentially dangerous machinery, power tools, and vehicles. Sudden loss of stimulation may cause patients to fall or lose control of equipment or vehicles, injure others, or bring injury upon themselves.

Control of the patient controller. Advise patients to keep the patient controller away from children and pets in order to avoid potential damage or other hazards.

Activities requiring excessive twisting or stretching. Patients should avoid activities that may put undue stress on the implanted components of the neurostimulation system. Activities that include sudden, excessive or repetitive bending, twisting, or stretching can cause component fracture or dislodgement. Component fracture or dislodgement may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component.

Component manipulation by patient. Advise your patient to avoid manipulating the implanted system components (e.g., the neurostimulator, the burr hole site). This can result in component damage, lead dislodgement, skin erosion, or stimulation at the implant site. Manipulation may cause device inversion, inhibiting the ability to use the magnet to start or stop stimulation.

Scuba diving or hyperbaric chambers. Patients should not dive below 10 m (33 ft) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA). Pressures below 10 m (33 ft) of water (or above 2.0 ATA) could damage the neurostimulation system. Before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their physician.

Skydiving, skiing, or hiking in the mountains. High altitudes should not affect the neurostimulator; however, the patient should consider the movements involved in any planned activity and take precautions to avoid putting undue stress on the implanted system. Patients should be aware that during skydiving, the sudden jerking that occurs when the parachute opens may cause lead dislodgement or fractures, which may require surgery to repair or replace the lead.

Wireless use restrictions. In some environments, the use of wireless functions (e.g., Bluetooth® wireless technology) may be restricted. Such restrictions may apply aboard airplanes, in hospitals, near explosives, or in hazardous locations. If you are unsure of the policy that applies to the use of this device, please ask for authorization to use it before turning it on. (Bluetooth® is a registered trademark of Bluetooth SIG, Inc.)

Mobile phones. The effect of mobile phones on deep brain stimulation is unknown. Patients should be advised to avoid carrying mobile phones in their shirt pocket or otherwise placing them directly over the deep brain stimulation system components. If interference occurs, try holding the phone to the other ear or turning off the phone.

Household appliances. Household appliances that contain magnets (e.g., refrigerators, freezers, inductive cooktops, stereo speakers, mobile telephones, cordless telephones, standard wired telephones, AM/FM radios, and some power tools) may unintentionally cause the neurostimulation system to turn on or turn off.

Therapeutic magnets. Patients should be advised to not use therapeutic magnets. Therapeutic magnets (e.g., magnets used in pillows, mattress pads, back belts, knee braces, wrist bands, and insoles) may unintentionally cause the neurostimulation system to turn on or off.

Adverse Effects

Deep brain stimulation potentially has the following adverse effects:

Possible surgical complications. Surgical complications 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 or cerebrospinal fluid abnormality; brain contusion; infection or inflammation; antibiotic anaphylaxis; skin disorder; edema; persistent pain at surgery site 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); ballism or hemiballism (uncontrollable movements on both or only one side of the 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 and death.

Possible deep brain stimulation complications. Deep brain stimulation complications include, but are not limited to, the following:

- Device-related complications
  - Undesirable changes in stimulation related to cellular changes in tissue around the electrodes, changes in the electrode position, loose electrical connections, or lead fracture
  - Loss of therapeutic benefit as a result of change in electrode positions, loose electrical connections, or lead or extension fracture
  - Initial jolt or tingling during stimulation; jolting or shocking sensations

- Infection
- Paresthesia
- 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 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 IPG
- 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) or abscess formation
- Additional neurosurgical procedure to manage one of the above complications or to replace a malfunctioning component

▪ Stimulation-related complications or other complications
- Worsening of motor impairment and Parkinson's disease symptoms including dyskinesia, rigidity, akinesia or bradykinesia, myoclonus, motor fluctuations, abnormal gait or incoordination, ataxia, tremor, and dysphasia
- Paresis, asthenia, hemiplegia, or hemiparesis
- Dystonia
- Sensory disturbance or impairment including neuropathy, neuralgia, sensory deficit, headache, and hearing and visual disturbance
- Speech or language impairment including, aphasia, dysphagia, dysarthria, and hypophonia
- Cognitive impairment including attention deficit, confusion, disorientation, abnormal thinking, hallucinations, amnesia, delusions, dementia, inability to act or make decisions, psychic akinesia, long term memory impairment, psychiatric disturbances, depression, irritability or fatigue, mania or hypomania, psychosis, aggression, emotional lability, sleep disturbance, anxiety, apathy, drowsiness, alteration of mentation, postural instability and disequilibrium
- New onset or worsening depression, which may be temporary or permanent, and suicidal ideations, suicide attempts, and suicide.
- Restless leg syndrome
- Supranuclear gaze palsy
- Hypersexuality or increased libido
- Decreased therapeutic response
- Urinary incontinence or retention
- Diarrhea or constipation
- Cardiac dysfunction (e.g., hypotension, heart rate changes, or syncope)
- Difficulty breathing

- Increased salivation
- Weight gain or loss
- Eye disorder including eye apraxia or blepharospasm
- Nausea or vomiting
- Sweating
- Fever
- Hiccups
- Cough
- Cramps
- Worsening existing medical conditions

Instructions to Patients

The patient should be given simple and practical instructions regarding the operation and care of the neurostimulation system. Also, the patient should be given guidelines about how posture and activity can affect stimulation as well as under what circumstances the physician should be contacted regarding device problems.

Safety and Effectiveness Studies

For clinical data supporting the safety and effectiveness of St. Jude Medical™ neurostimulation systems, refer to the appropriate appendix in this manual.

System Overview

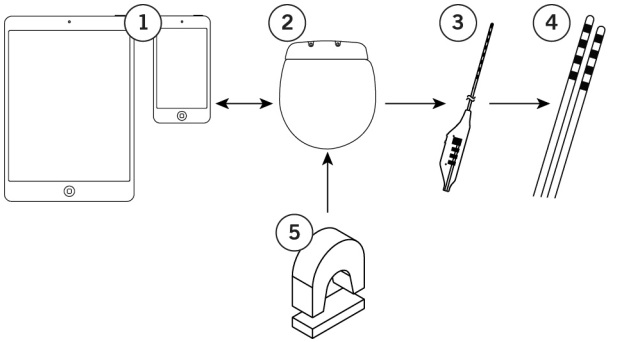
This neurostimulation system is designed to deliver electrical stimulation to targets in the brain. The neurostimulation system includes the following primary components:

- Implantable pulse generator (IPG)
- Extensions
- Leads
- Clinician programmer
- Patient controller
- Patient magnet

The IPG connects to the implanted extensions, which connect to the leads implanted in the brain. The IPG delivers electrical pulses through the extensions and leads to electrodes at a selected target in the brain in order to provide therapeutic stimulation. The patient magnet can turn the IPG on and off if the physician enabled this functionality. Physicians use the clinician programmer to create and modify a program for a patient. Patients use the patient controller to control their prescribed programs.

The following image shows how the major system components are intended to interact.

Figure 1. Interaction between major system components



1. Clinician programmer or patient controller
2. IPG
3. Extensions
4. Leads
5. Patient magnet

NOTE: This manual provides instructions for implanting the IPG. For instructions for using other components, see the applicable manuals for those components.

Product Description

This implantable pulse generator (IPG) is an electronic device designed to be connected to one or two extensions. It is powered by a hermetically sealed battery within a titanium case and uses microelectronic circuitry to generate constant-current electrical stimulation. The IPG is conductive on all sides, which allows the IPG case (also called a “can”) to be used as an anode for monopolar stimulation. The IPG communicates wirelessly with system programmers and controllers, and IPGs are available in small and large sizes to accommodate different power needs. The IPG can receive software upgrades after implantation to provide patients with additional features as approved by the respective regulatory agencies. To upgrade features on the IPG, a system programmer is needed. Some models contain a header that is designed to allow the IPG to connect to extensions from another manufacturer that meet the compatibility guidelines (referred to as "IPGs with compatible headers").

For more information about IPG features and specifications, see the appropriate appendix in this manual.

NOTE: In this document, the term "clinician programmer" refers to the St. Jude Medical™ Clinician Programmer device, "patient controller" refers to the St. Jude Medical™ Patient Controller device, "clinician programmer app" refers to the St. Jude Medical™ Clinician Programmer software application (app), and "patient controller app" refers to the St. Jude Medical™ Patient Controller app.

Package Contents

In addition to the product documentation, the IPG kit contains the following items:

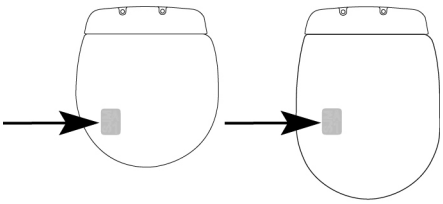
- 1 IPG (see the appendix in this manual for model numbers)
- 1 pocket sizer
- 1 torque wrench (Model 1101)
- 2 port plugs (Model 1111)

Identifying the IPG

Before implanting the IPG, you can view the model number engraved on the IPG. After implantation, you can identify the IPG using a radiopaque identification tag that you can view with standard X-ray procedures. The tag, which is located in the lower left corner of the IPG when the logo side of the IPG is facing toward you, contains a code in the following format: SJM*LN*. SJM designates St. Jude Medical as the manufacturer; *LN* is a letter and a number combination that identifies the model family (see the following figure).

For the St. Jude Medical Infinity™ IPG, the code is SJM A1. To determine the exact model IPG that is implanted, use the clinician programmer app to communicate with the IPG and view IPG information. See the clinician's manual for the clinician programmer for instructions.

Figure 2. Location of the IPG code on a small IPG (left) and large IPG (right)



Directions for Use

Read this section carefully for suggested directions for use related to the IPG. For directions for use for other system components not covered in this document, see the clinician's manual for the appropriate device.

> NOTE: Before the surgical procedure, set up communication between the clinician programmer and the IPG while the IPG is in its sterile packaging to ensure that it is functional. If the IPG has never established communication with a programmer, you must first activate the IPG for communication ("wake up" the IPG) by holding a magnet over the IPG for 10 seconds.

Connecting Extensions or Adapters to the IPG

To connect extensions to the IPG, follow these steps:

> NOTE: Follow the same steps when connecting either extensions or adapters to the IPG.

WARNING: To avoid harming the patient or damaging the neurostimulation system, ensure that any electrosurgery procedures are completed before connecting the extensions to the IPG.

1. Before connecting extensions to the IPG, verify that the IPG is functional. This step is recommended to be performed while the IPG is still in the manufacturer's packaging. Use the clinician programmer app to communicate with the IPG. See the clinician's manual for the clinician programmer app for instructions.

2. If needed, clean the proximal end of the extension with sterile, deionized or distilled water and dry it completely. Use clean gloves and ensure that all body fluids and saline residue are cleaned from the proximal end of the extension. This is important to reduce future corrosion and potential failure of the system.

   CAUTION: Exposure of the internal IPG contacts to body fluid or saline can affect stimulation. If this occurs, clean the contacts with sterile, deionized or distilled water (not saline) and dry completely prior to extension connection and subsequent implantation.

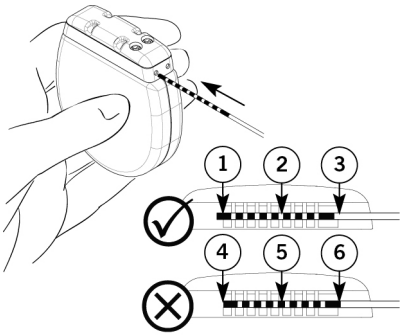
3. To help ensure that the extension can be fully inserted into the IPG header, insert the torque wrench through the septum on the IPG header, turn the torque wrench clockwise to tighten the setscrew until the torque wrench clicks, and then loosen the setscrew again by turning the wrench counterclockwise about 2.5 times.

   CAUTION: Use only the torque wrench included in the extension, IPG, or torque wrench kit. If you need to loosen the setscrew, turn the setscrew (in quarter turns counterclockwise) just enough to insert or remove the extension from the IPG header. Loosening the setscrew too far may cause it to fail to secure the extension.

   CAUTION: To avoid sharply bending and damaging the extension when performing the following step, insert the extension parallel with the header port. Additionally, try grasping the extension about 5 mm at a time from the opening of the header port while inserting.

4. Slide the proximal end of the extension into the IPG header until it stops. Confirm that the extension is correctly inserted by following these visual indicators and referring to the corresponding figures that follow:
   - For IPGs that connect to St. Jude Medical™ extensions, the first contact band (at the tip) of the extension extends slightly past the first header contact and is visible, the windows between each of the header contacts are clear, and the ninth contact band of the extension is not visible.
   - For IPGs with compatible headers, the windows between each of the header contacts are clear and none of the contact bands are visible.

Figure 3. Correct versus incorrect extension insertion (IPGs with St. Jude Medical extensions)



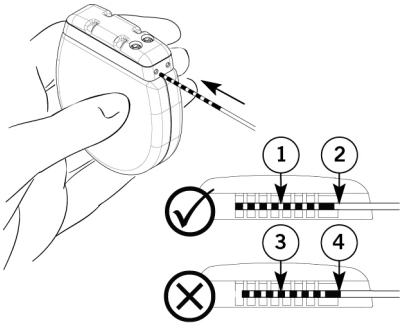
Fully inserted

1. First contact band (tip) is visible past the first header contact
2. Window between each header contact is clear
3. Ninth contact band is not visible

Not fully inserted

4. First contact band (tip) is not visible past the first header contact
5. Window between each header contact is partially blocked by contact band
6. Ninth contact band is visible

Figure 4. Correct versus incorrect extension insertion (IPGs with compatible header)



Fully inserted

1. Window between each header contact is clear
2. Eighth contact band is not visible

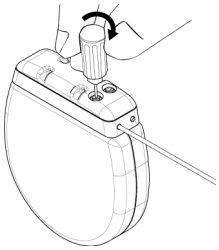
Not fully inserted

3. Window between each header contact is partially blocked by contact band
4. Eighth contact band is visible

5. Use the clinician programmer app to communicate with the IPG, and test the impedance to ensure that the extension is fully inserted. See the clinician's manual for the clinician programmer app for instructions.
6. Turn the torque wrench clockwise to tighten the setscrew until the torque wrench clicks.

   NOTE: After removing the torque wrench, check the septum to ensure it has closed. If the septum did not close, gently reseat the septum flaps.

Figure 5. Tighten the setscrew clockwise



7. Repeat steps 2 through 6 for the other extension.

   NOTE: In case only one extension is used with the IPG, insert a compatible port plug into the unused IPG port.

Placing the IPG

To place the IPG, follow these steps:

1. Insert the pocket sizer in the IPG pocket to ensure that it is large enough to accommodate the IPG and the excess extension length. Remove and discard the pocket sizer when finished.

   CAUTION: The pocket sizer is not intended for permanent, long-term implantation.

2. Carefully place the IPG into the pocket with the logo side facing the skin surface and at a depth not to exceed 4.0 cm (1.57 in).

   CAUTION: Do not place the IPG deeper than 4.0 cm (1.57 in) because the clinician programmer and patient controller may not communicate effectively with the IPG.

   NOTE: By implanting the IPG with the logo side facing the skin surface, you enhance the IPG's ability to detect a magnet.

3. Carefully coil any excess extension in loops with a diameter of at least 2.5 cm (1 in) and place it behind the IPG.

4. To stabilize the IPG within the pocket and minimize movement, pass sutures through the suture holes at the top of the IPG header and secure them to the connective tissue.

5. Before closing, use the clinician programmer app to communicate with the IPG. Test the impedance using the clinician programmer app to ensure that all implantable components are functional. See the clinician's manual for the clinician programmer app for instructions.

6. Close the IPG pocket incision. The IPG should be positioned away from the pocket incision suture line.

   CAUTION: Be careful to avoid puncturing the IPG header or extensions while closing the incision.

   WARNING: Do not use surgical staples to close the IPG pocket; use suture. Using

surgical staples may interfere with IPG communication to the programmer.

Replacing the IPG

To replace the IPG, follow these steps:

1. After ensuring that stimulation is turned off, open the IPG pocket per normal surgical procedure, and carefully remove the IPG from the pocket.

   CAUTION: Be extremely careful when using sharp instruments and electrocautery around the extension.

2. Insert the torque wrench into the IPG header septum, and loosen the setscrew by turning it counterclockwise.

3. Gently pull the extension from the IPG header. Clean and dry all contacts on the extensions, ensuring they are free of fluid and tissue.

   NOTE: If you need to remove the extension, make an incision above the extension connector assembly, disconnect the extension from the lead, and sever the distal end of the extension just proximal to the extension connector assembly. After removing the extension by carefully pulling it through the IPG pocket, place the new extension by following the instructions in the extension packaging.

4. Insert the extension into the new IPG.

5. Tighten the setscrew clockwise until the torque wrench clicks.

6. Remove the torque wrench and ensure the septum is closed.

7. Repeat the steps in “Placing the IPG” (page 14).

8. Return any explanted components to St. Jude Medical. Refer to “Disposing of Explanted Components” (page 15) for more information.

Disposing of Explanted Components

Explanted St. Jude Medical™ components should be returned to St. Jude Medical for proper disposal. To return an explanted component, place it in a container or bag marked with a biohazard label and coordinate the return with your St. Jude Medical representative or Technical Support.

Checking the Status of the IPG Battery

The IPG contains a nonrechargeable battery. The amount of time that the battery will provide active stimulation depends on the patient’s stimulation settings and daily usage time. To check the status of the IPG battery, use the clinician programmer app or patient controller app. For more information about this function, refer to the clinician’s programming manual and the user’s guide for the patient controller app. For information about estimating longevity of the IPG battery, see the appropriate appendix in this manual.

NOTE: IPG battery status is available one day after first using the clinician programmer app to program the IPG.

The following list provides general information about the battery status:

- A low-battery warning will appear on the clinician programmer app or patient controller app when the battery is approaching its end of service.
- Stimulation will automatically stop when the battery cannot support stimulation.

Technical Support

For technical questions and support for your product, use the following information:

- +1 855 478 5833 (toll-free within North America)
- +1 651 756 5833

For additional assistance, call your local St. Jude Medical representative.

Appendix A: Product Specifications

NOTE: Not all models are available in all countries. Contact your local representative for more information.

Storage Specifications

Store the components in this kit according to the following conditions.

Table 1. Storage conditions for components

Temperature	-20°C–60°C (-4°F–140°F)

Product Materials

The following materials are intended to come into contact with tissue.

Table 2. Product materials for IPG kit

Component	Material
IPG	Titanium, silicone rubber
Pocket sizer	Polybutylene terephthalate
Port plug	Polysulfone

NOTE: These components are not made with natural rubber latex.

IPG Specifications

The St. Jude Medical Infinity™ IPGs have the following physical specifications.

Table 3. IPG specifications

Model	6660	6662
	6661*	6663*
Height	5.55 cm (2.19 in)	6.68 cm (2.63 in)
Length	4.95 cm (1.95 in)	5.02 cm (1.98 in)
Thickness	1.34 cm (0.53 in)	1.35 cm (0.53 in)
Weight	48.9 g (1.7 oz)	58.3 g (2.1 oz)
Volume	30.4 cm^3 (1.9 in^3)	38.6 cm^3 (2.4 in^3)
Power source	Carbon monofluoride/silver vanadium oxide cell	
Connector strength	10 N (Models 6660, 6662) 5 N (Models 6661, 6663)	
Program storage capacity	15 programs	

* Denotes models with compatible headers

The IPG has the following operating parameters.

Table 4. Operating parameters for the IPG

Parameter	Range	Steps
Pulse width	20–500 µs	10 µs
Frequency	2–240 Hz	2 Hz
Amplitude	0–12.75 mA	0.05–1.00 mA

Compatibility Guidelines for IPGs with Compatible Headers

IPGs with compatible headers are compatible with the following Medtronic™ extensions available before May 5, 2015. (Medtronic is a trademark of Medtronic, Inc.)

Table 5. Compatible Medtronic extensions

Device	Model
Extension*	37085-40, 37085-60, 37085-95, 37086-40, 37086-60, 37086-95

* The specified extensions are connected to Medtronic DBS leads (Model 3387 or 3389) to ensure compatibility with the IPG.

WARNING: The use of Medtronic leads or extensions other than those specified in this table may increase risk to the patient, including the potential for tissue damage.

Appendix B: System Components and Accessories

The St. Jude Medical Infinity™ neurostimulation system includes the following components.

NOTE: Not all models are available in all countries. Contact your local representative for more information.

NOTE: The Model 6661 and 6663 IPGs are compatible only with the leads and extensions listed in "Compatibility Guidelines for IPGs with Compatible Headers" (page 17). They are not compatible with St. Jude Medical™ leads and extensions.

NOTE: Traditional leads are compatible only with traditional extensions. Leads for the St. Jude Medical Infinity™ DBS system are compatible only with extensions for the St. Jude Medical Infinity™ DBS system. The Model 1149 lead boot is compatible only with traditional leads.

IPGs

6660 St. Jude Medical Infinity™ 5 implantable pulse generator

6661 St. Jude Medical Infinity™ 5 implantable pulse generator

6662 St. Jude Medical Infinity™ 7 implantable pulse generator

6663 St. Jude Medical Infinity™ 7 implantable pulse generator

IPG Accessories

1101 Torque wrench

1111 Port plug

Programmers and Controllers

3874 St. Jude Medical™ Clinician Programmer App

3875 St. Jude Medical™ Patient Controller App

Programmer and Controller Accessories

1210 Patient magnet

6884 DBS patient manual and magnet

Leads and Extensions

6100-series traditional leads

6100-series leads for the St. Jude Medical Infinity™ DBS system

6300-series traditional extensions

6300-series extensions for the St. Jude Medical Infinity™ DBS system

Lead and Extension Accessories

1100-series stylets

1140 DBS lead stop

1149 4-CH lead protection boot

1190 Tunneling tool, 0.125-in diameter

1191 Tunneling tool, 0.156-in diameter

1803 Lead and extension insertion tool

6010 Guardian™ burr hole cover system

Adapters

2303 Legacy MDT pocket adapter, 25 cm (use only with Infinity IPG model 6660 or 6662 and Medtronic extension model 7482 or 7483)

2311 8-channel adapter, M, 10 cm

2316 8-channel adapter, M, 60 cm

Trial System

6599 St. Jude Medical™ DBS External Pulse Generator

Trial System Accessories

1212 Coin cell batteries

1216 EPG header cap

1218 Carrying case

1917 Battery door

3014 Multilead trial cable

Appendix C: Battery Longevity Information

The longevity of the IPG battery depends on the following factors:

- Programmed settings, such as frequency, pulse width, amplitude, and number of active electrodes
- Program impedance
- Hours of stimulation per day
- Shelf life of the device between the dates of manufacture and implant
- Duration of communication sessions between the IPG and the patient controller or clinician programmer

To estimate battery longevity manually, perform the following steps.

1. Locate the energy factor for the desired stimulation parameters according to the lead impedance in the tables that follow these steps.

   NOTE: The parameters in the tables are for estimating device longevity. Some parameter combinations may result in a charge density greater than the limit of 30 $\mu C/cm^2$. When this charge density limit is reached, the clinician programmer app will display a warning. For additional information about high stimulation outputs and charge density limits, see "Warnings" (page 1).

   NOTE: If the desired parameters do not appear in the tables, estimate the energy factor by choosing a value between the listed energy factors for the closest parameters.

   NOTE: The following information for estimating battery longevity is based on IPG software version 1.1.2.1. To determine the software version of the IPG you have, view generator details using a clinician programmer or system information using a patient controller. Refer to those manuals for instructions. For help estimating battery longevity on an IPG with a different software version or for other help estimating longevity, contact Technical Support.

2. For an IPG using a bilateral lead configuration, determine the energy factor for each lead from the previous step, and add each of these values together.

3. Use the figures after the tables in this section to determine the estimated battery longevity by finding the energy factor from the previous steps on the curve for the appropriate model IPG.

   NOTE: The first figure shows the estimated battery longevity of a newly implanted IPG. The second figure shows the estimated longevity of an IPG battery after the low-battery warning—also called the elective replacement indicator (ERI)—first appears on the clinician programmer app or patient controller app when the battery is approaching its end of service.

Table 6. Energy factors for various stimulation parameters (500-ohm impedance)

		Pulse Width (µs)				
Amplitude (mA)	**Frequency (Hz)**	**60**	**90**	**120**	**250**	**500**
1	**120**	36	37	39	45	57
	180	50	52	54	63	81
	240	62	65	68	80	104
2	**120**	45	50	55	79	125
	180	62	71	78	114	182
	240	79	90	100	148	239
3	**120**	50	58	66	102	238
	180	71	83	95	148	353
	240	90	106	122	193	466
4	**120**	67	83	99	170	306
	180	96	120	144	250	454
	240	124	156	188	330	601
5	**120**	75	116	143	260	486
	180	128	169	209	385	724
	240	167	221	275	509	961
6	**120**	99	132	164	305	711
	180	145	193	242	453	1062
	240	188	253	318	599	1412
8	**120**	143	197	251	576	1117
	180	210	291	372	859	1670
	240	276	384	492	1141	2585
10	**120**	197	321	415	825	1846
	180	292	475	617	1232	2758
	240	385	629	818	1638	4123
12.75	**120**	320	458	595	1337	2917
	180	470	676	883	1995	4798
	240	619	894	1170	2653	6963

Table 7. Energy factors for various stimulation parameters (1000-ohm impedance)

		Pulse Width (µs)				
Amplitude (mA)	Frequency (Hz)	60	90	120	250	500
1	120	39	42	45	57	80
	180	54	58	62	80	115
	240	68	73	79	103	149
2	120	51	59	67	103	171
	180	72	84	96	149	251
	240	92	107	124	195	331
3	120	67	83	99	170	306
	180	96	120	144	250	454
	240	124	156	188	329	601
4	120	89	116	143	261	486
	180	129	170	210	386	724
	240	168	222	276	510	1143
5	120	116	157	197	373	826
	180	170	231	291	555	1233
	240	223	303	384	736	1640
6	120	150	207	264	510	1126
	180	220	305	390	759	1678
	240	289	402	516	1149	2503
8	120	241	338	435	948	1849
	180	351	496	642	1410	3035
	240	460	654	848	1873	4398
10	120	347	495	697	1400	2979
	180	509	791	1034	2088	4796
	240	671	1047	1370	3005	—
12.75	120	536	777	1090	2209	—
	180	792	1235	1621	—	—
	240	1122	1638	2154	—	—

Table 8. Energy factors for various stimulation parameters (1500-ohm impedance)

		Pulse Width (µs)				
Amplitude (mA)	Frequency (Hz)	60	90	120	250	500
1	**120**	39	42	45	57	80
	180	54	58	62	80	115
	240	68	73	79	103	149
2	**120**	56	67	78	125	216
	180	80	96	112	183	319
	240	102	123	145	239	421
3	**120**	76	96	116	204	442
	180	109	139	169	302	658
	240	141	181	222	466	873
4	**120**	113	150	188	353	669
	180	164	220	277	523	1138
	240	213	289	364	693	1510
5	**120**	153	206	260	553	1060
	180	219	300	423	818	1749
	240	285	392	556	1084	2325
6	**120**	209	290	371	723	1536
	180	303	425	546	1177	2494
	240	397	558	720	1562	3318
8	**120**	333	473	613	1315	2759
	180	487	698	908	1959	—
	240	642	922	1292	2790	—

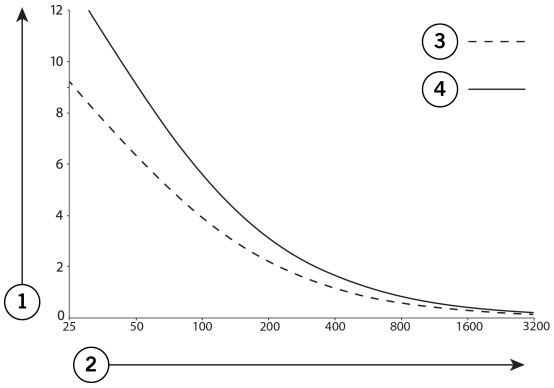
Table 9. Energy factors for various stimulation parameters (2000-ohm impedance)

		Pulse Width (µs)				
Amplitude (mA)	Frequency (Hz)	60	90	120	250	500
1	**120**	43	47	51	69	103
	180	60	66	72	98	150
	240	75	83	91	127	196
2	**120**	62	76	89	148	261
	180	89	109	129	217	387
	240	114	141	168	285	512
3	**120**	94	122	150	274	511
	180	135	178	220	405	868
	240	176	232	289	535	1150
4	**120**	144	192	240	452	949
	180	205	277	350	667	1412
	240	265	362	459	881	1875
5	**120**	198	272	346	669	1401
	180	286	397	508	1075	2089
	240	374	522	670	1426	3008
6	**120**	263	368	473	930	1946
	180	382	540	697	1486	3113
	240	501	711	921	1974	—

Table 10. Energy factors for various stimulation parameters (3000-ohm impedance)

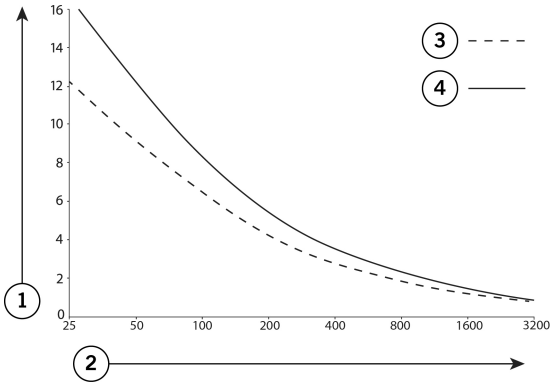
Amplitude (mA)	Frequency (Hz)	Pulse Width (µs) 60	90	120	250	500
1	**120**	45	51	56	80	126
	180	64	72	80	115	184
	240	80	91	102	149	241
2	**120**	75	94	113	195	354
	180	107	135	163	287	524
	240	138	175	213	378	790
3	**120**	128	169	209	385	724
	180	182	242	303	567	1179
	240	235	315	396	748	1564
4	**120**	193	262	332	637	1316
	180	277	382	487	944	1961
	240	361	501	641	1344	2793

Figure 6. Estimated battery longevity by energy factor for St. Jude Medical Infinity™ IPGs (from time of implant)



1. Estimated battery longevity (years)
2. Energy factor
3. Models 6660 and 6661
4. Models 6662 and 6663

Figure 7. Estimated battery longevity by energy factor for St. Jude Medical Infinity™ IPGs (from time of ERI)



1. Estimated battery longevity (months)
2. Energy factor
3. Models 6660 and 6661
4. Models 6662 and 6663

Appendix D: Regulatory Statements

This section contains regulatory statements about your product.

Disposal Guidelines for Battery-Powered Devices

This device contains a battery and a label is affixed to the device in accordance with European Council directives 2002/96/EC and 2006/66/EC. These directives call for separate collection and disposal of electrical and electronic equipment and batteries. Sorting such waste and removing it from other forms of waste lessens the contribution of potentially toxic substances into municipal disposal systems and into the larger ecosystem. Return the device to St. Jude Medical at the end of its operating life.

Statement of FCC Compliance

This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses, and can radiate radiofrequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna.
- Increase the separation between the equipment and receiver.
- Connect the equipment into an outlet on a circuit different from that to which the receiver is connected.
- Consult the dealer or an experienced radio/TV technician for help.

Operation is subject to the following two conditions:

- This device may not cause harmful interference.
- This device must accept any interference received, including interference that may cause undesired operation.

Modifications not expressly approved by the manufacturer could void the user's authority to operate the equipment under FCC rules.

Statement of Compliance With License-Exempt RSS Standard (Canada)

This device complies with Industry Canada license-exempt RSS standard(s). Operation is subject to the following two conditions: (1) this device may not cause interference, and (2) this device must accept any interference, including interference that may cause undesired operation of the device.

Identification Information for Product Registration

This device has a label that contains, among other information, a product identifier in the following format:

Table 11. Registration identification information

Identifier Type	Registration Identifier
FCC registration number	RIASJMRFC
Industry Canada (IC) registration number	IC: 8454A-M3660123

Wireless Technology Information

The following table summarizes the technical details of the Bluetooth® Smart wireless technology as it is implemented in the device.

Table 12. Bluetooth Smart wireless technology information

Antenna type	Embedded patch antenna in header
Antenna dimensions	8.1 mm x 5.1 mm x 4.9 mm
Modulation	GFSK
Magnetic field strength (at 2 m distance)	16.3 µA/m
Electric field strength (at 2 m distance)	6.1 mV/m
Output power (EIRP*)	1 mW (0 dBm) typical, 10 mW (+10 dBm) maximum
Range	1–2 m typical
Center frequency	2.44 GHz
Channel	40 logical channels
Bandwidth	2 MHz per channel
Data flow	Bi-directional
Protocol	Bluetooth Smart wireless technology
*EIRP = Equivalent isotropically radiated power	

Radio Transmitter, Cables, Transducers

The device contains a radio transmitter/receiver with the following parameters.

Radio transmitter parameters:

- Frequency (range): 2.4000 to 2.4835 GHz
- Bandwidth (-15dB): 2.398 to 2.4855 GHz
- Channel: 40 logical channels using AFH
- Modulation: GFSK
- Radiated output power: 10 mW (+10 dBm) maximum
- Magnetic field strength (at 2 m distance): 16.3 µA/m
- Duty cycle: Variable, but low (<5%)
- Semi-duplex capability

The radio receiver in the device is using the same frequency and bandwidth as the transmitter.

Cables and transducers:

Cables and transducers are not used during normal use of the device nor while programming the device.

Quality of Service for Wireless Technology

Bluetooth® Smart wireless technology enables communication between the generator and the clinician programmer or patient controller. The quality of the wireless communication link varies depending on the use environment (operating room, recovery room, and home environment).

After the clinician programmer or patient controller is paired with a generator, the Bluetooth wireless technology symbol is visible on the clinician programmer or patient controller in the upper right-hand corner of the screen. When the Bluetooth Smart wireless technology connection is not active, the symbol appears dimmed.

The quality of service (QoS) should allow wireless data to be transferred at a net rate of 2.5 kB/sec. Each connection interval includes a semi-duplex transmission with a required acknowledge, a transmission latency in each direction (2x), and a receive-to-transmit mode (RX-to-TX) time. Data is resent if not successfully received. Each key press may transmit up to 4 data packets with up to 20 bytes per packet, depending on the number of packets that need to be transmitted (i.e., if there is only one packet to transmit, only one packet will be transmitted). If the interference is high (e.g., the bit error rate exceeds 0.1%), the user may experience what appears to be a slow connection, difficulty pairing devices, and a need to decrease the distance between connected devices. For information on how to improve connection issues, please refer to “Troubleshooting for Wireless and Coexistence Issues” (page 28).

Wireless Security Measures

The wireless signals are secured through device system design that includes the following:

- The generator will encrypt its wireless communication.
- Only one patient controller or clinician programmer may communicate with the generator at the same time.

- A unique key for each unit that is checked during each transmission.
- Built-in pairing that specifies valid and legitimate pairing among units.
- Proprietary authentication in addition to the pairing procedure specified in Bluetooth® Smart wireless technology, which includes an element of proximity.
- A proprietary algorithm that detects and prevents an unauthorized user from attempting to pair with the generator.

Troubleshooting for Wireless and Coexistence Issues

If you experience issues with the wireless communication between the generator and the clinician programmer or patient controller, try the following:

- Decrease the distance between the devices
- Move the devices so they share line of sight
- Move the devices away from other devices that may be causing interference
- Close the clinician programmer or patient controller application, and turn the clinician programmer or patient controller off and on
- Wait a few minutes and try connecting again
- Do not operate other wireless devices (i.e., laptop, tablet, mobile phone, or cordless phone) at the same time

  NOTE: Wireless communications equipment, such as wireless home network devices, mobile and cordless telephones, and tablets, can affect the device.

Appendix E: Safety and Effectiveness Studies for Parkinson's Disease and Essential Tremor

This section includes information that supports the clinical use of this neurostimulation system.

Parkinson's Disease Study

Parkinson's Disease Study Design

Patients were treated between October 2005 and April 2009. The database for this premarket approval (PMA) reflected data collected through August 2010 and included 136 patients. There were 15 investigational sites.

The study was a prospective, multicentered, randomized, controlled clinical study, which compared patients randomized to receive immediate as compared to delayed stimulation. All patients in the trial were implanted. Patients who had a successful implant were randomized in a 3:1 ratio (active stimulation group or delayed stimulation control group). Patients remained in their assigned randomization group for 90 days. After 90 days, all patients received stimulation. Patients were followed for one year. After one year, patients were consented to a long-term follow-up study where they continued for a total of 5 years post-implant.

The study was not blinded, i.e., both investigators and patients were aware of the treatment assignment. Deep brain stimulation was used as an adjunct to anti-Parkinson's disease medications. Medication adjustments were made by the investigators at each site depending on the randomization assignment.

A Data Safety Monitoring Board (DSMB) was used to continuously review the adverse event data for the entire study duration. The DSMB was designed to alert the sponsor of any safety concerns or study execution concerns.

Parkinson's Disease Study Inclusion and Exclusion Criteria

Enrollment in the Parkinson's disease study was limited to patients who met the following selection criteria.

Inclusion Criteria

- Patient signed an informed consent.
- Patient was 18 to 80 years of age.
- Patient was diagnosed with Parkinson's disease for at least five (5) years according to standard practice.
- Patient experienced six (6) hours or more of daily "non-on time" illustrated by a dyskinesia diary as off time or moderate to severe dyskinesias due to Parkinson's disease during waking hours.
- Patient had a history of improvement of Parkinson's symptoms as a direct result of administering L-dopa to the patient with at least a 33% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor score.
- Patient was willing to maintain a constant dose of anti-Parkinson's disease medication that was indicated as best medical management for at least one month prior to study enrollment.
- Patient was available for appropriate follow-up times for the length of the study.
- Patient completed diary training, and each patient's diary response indicating their level of dyskinesia severity during training must agree with study personnel responses a minimum of 75% of the time.

Exclusion Criteria

- Patient was not a surgical candidate.
- Patient had any major illness or medical condition that in the opinion of the physician would interfere with participation in the study.
- Patient had untreated, clinically significant depression.
- Patient had an electrical or electromagnetic implant (e.g., cochlear prosthesis or pacemaker).
- Patient had any condition requiring repeated magnetic resonance imaging (MRI) scans.
- Patient had any condition requiring diathermy.
- Patient was taking anticoagulant medications.
- Patient had a prior surgical ablation procedure or any other previous neurosurgical procedure for the treatment of Parkinson's disease symptoms on either side of the brain.
- Patient had dementia that interferes with their ability to cooperate or comply with the study requirements or comprehend the informed consent as determined by the investigator.
- Patient abused drugs or alcohol.
- Patient had a history of cranial surgery.
- Patient had a history of seizures.
- Patient had any MRI noncompatible metallic implants that may interfere with the functioning of the device (e.g., aneurysm clips).
- Patient had a history of stimulation intolerance in any area of the body.
- Patient was a female who was lactating or who could bear children and either had a urine pregnancy test that was positive or was not using adequate contraception.
- Patient was a participant in a drug, device, or biologics trial within the preceding 30 days.

- Patient had confirmation of diagnosis of a terminal illness associated with survival less than 12 months.

Parkinson's Disease Study Follow-Up Schedule

All study participants were screened according to the criteria listed previously, and all participants signed an informed consent prior to undergoing any study procedures. The following table shows the baseline evaluations. Implantation was performed according to each individual site's standard procedures. Implant assessments are shown in the following table. Either one or two St. Jude Medical™ IPG devices were implanted based on the physician's decision. After all components of the system were implanted and prior to programming, patients were randomized to the active stimulation group or the control group. Patients in the active stimulation group were programmed to receive stimulation within 7 days after implant. Patients in the control group were not programmed to receive stimulation until after the 90 day follow-up visit assessment was complete. After the randomization visit, patients returned to clinic at 30 days, 90 days, 180 days, and 365 days post-implant. The following table shows the assessments required at each visit.

Table 13. Follow-up schedule

Procedures	Screening / Baseline	Implant	Randomization (Day 0)	Day 30 (±7 d)	Day 90 (±14 d)	Day 180 (±30 d)	Day 365 (±30 d)
Informed consent	X						
Neuro-psychological exam	X				X		X
History	X						
UPDRS	X				X	X	X
Hoehn & Yahr Staging	X				X	X	X
Schwab & England	X				X	X	X
PDQ-39	X					X	X
Pittsburgh Quality Sleep Index	X					X	X
Global outcome measure	X				X	X	X
Dyskinesia diary		X		X	X	X	X
Implant information		X					
Randomization			X				
Device information			X		X	X	X
Patient satisfaction						X	X
Adverse events		X	X	X	X	X	X

Clinical Endpoints

The safety endpoint compared the adverse event incidence rates between the active stimulation group and the control group throughout the duration of the study.

The primary effectiveness endpoint was a comparison of the increase in the duration of “on time” without dyskinesias or with nonbothersome dyskinesias as demonstrated by the change in diary responses after 90 days of stimulation with medication “on” compared to the control group. Nonbothersome dyskinesias were defi ned by the Hauser Dyskinesia Diary as “mild”, i.e., present but do not interfere with activities and daily functions.

The secondary effectiveness endpoints assessed at 90 days were a comparison of

- The percent of patients with an increase from baseline in “on time” without dyskinesias or with nonbothersome dyskinesias of at least 2 hours with medication “on”
- UPDRS motor scores in the medication “on” state
- Activities of daily living from the UPDRS and Schwab England scale
- Comparison of the Hoehn and Yahr Staging in the medication “on” state
- Global outcome evaluations by both the patient and caregiver
- Rate of patient satisfaction

Additional endpoints assessed at one year compared to the baseline include

- Reduction in Parkinson’s disease symptoms as demonstrated by the UPDRS motor scores in the medication on state with stimulation on through one year compared to baseline medication on and off scores
- Activities of daily living as determined from the UPDRS and Schwab England scale
- Total UPDRS scores and each individual component of the UPDRS in the medication on and off state with stimulation
- Quality of life as measured by the PDQ-39
- Pittsburgh Quality Sleep Index
- Hoehn and Yahr Staging in the medication on and off, stimulation on state
- Global outcome evaluations by the patient
- Levodopa reduction over time
- Patient satisfaction

Parkinson's Disease Prespecified Statistical Analysis Plan

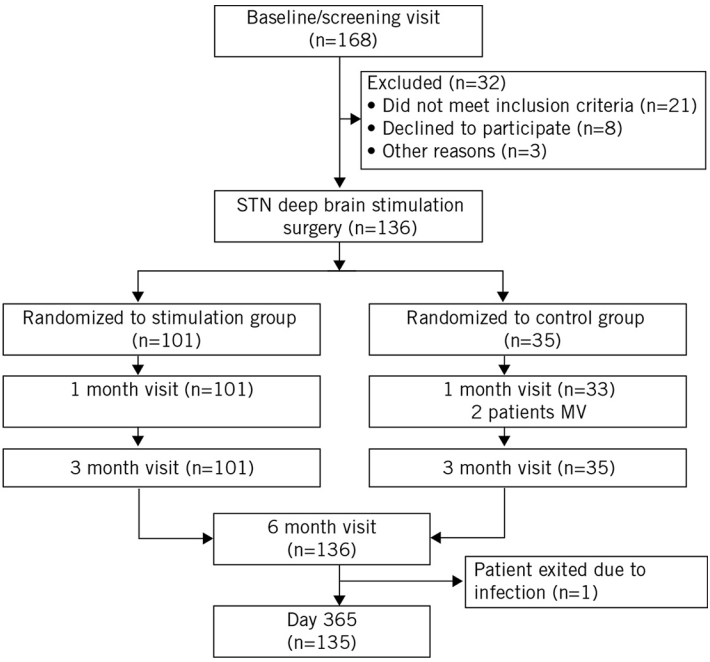
The primary hypothesis was a two-sided test of the difference in mean changes from baseline between the active stimulation group and the delayed stimulation control group at 90 days post-implant. The primary analysis was a two-way analysis of covariance that included the effects of treatment, study center, and baseline “on time”. The sample size of 136 was chosen to provide 80% power to detect a 3-hour difference in “on time” between treatment groups at the 0.05 level of significance. Missing data at 90 days were imputed by using data from the last available patient diary.

There was no prespecified method for multiplicity testing of the secondary endpoints. Therefore, 95% confidence intervals are provided for the secondary endpoints.

Accountability of Subject Cohort

A total of one hundred sixty-eight (168) were enrolled at 15 investigational sites. A total of 136 patients were implanted with the Libra™ or Libra*XP*™ deep brain stimulation system from October 2005 to April 2009. A total of 133 patients completed the 90 day visit for the primary endpoint analysis. A total of 135 patients completed the 12 month visit. A summary of the patient accounting is provided in the following figure.

Figure 8. Patient accounting



Parkinson's Disease Study Population Demographics and Baseline Parameters

A total of 136 patients were randomized in this study. The demographics of the study population are typical for a study evaluating Parkinson's disease patients in the United States.

Table 14. Demographic summary

	Stimulation Group (N=101)	Control Group (N=35)	*p*-value
Gender: n (%)			
Male	63 (62.4%)	21 (60.0%)	0.803
Female	38 (37.6%)	14 (40.0%)	
Race: n (%)			
Caucasian	91 (90.1%)	31 (88.6%)	0.755[1]
African American	1 (1.0%)	0 (0.0%)	
Hispanic	8 (7.9%)	3 (8.6%)	
Other	1 (1.0%)	1 (2.9%)	

Table 14. Demographic summary

	Stimulation Group (N=101)	Control Group (N=35)	*p*-value
Age (yr)			
Mean ± std	60.6±8.3	59.5±8.2	0.519
Range	41–78	41–76	
Weight (lb)			
Mean ± std	177.7±40.0	164.9±34.4	0.093
Range	95–298	98–226	
Height (in)			
Mean ± std	68.3±4.4	67.4±4.1	0.296
Range	59–79	62–76	
Years since symptom onset			
Mean ± std	12.1±4.9	11.7±4.1	0.684
Range	5–29	5–19	
[1] Caucasian vs. non-Caucasian			

The following stimulation parameters were used during the study.

Table 15. Programming parameters initially and at 1 year

Parameter	Initial Programming	1 Year
Left-side pulse		
Mean	72.5	74.0
Median	65	65
Left-side frequency		
N	101	133
Mean	147.9	151.5
Median	136.0	150.0
Range	100–200	40–200
Left-side amplitude		
N	101	133
Mean	1.55	2.31
Median	1.50	2.20
Range	0.2–5.0	0.5–5.0
Right-side pulse		
Mean	72.4	74.3
Median	65	65

Table 15. Programming parameters initially and at 1 year

Parameter	Initial Programming	1 Year
Right-side frequency		
N	101	133
Mean	147.3	151.1
Median	136.0	140.0
Range	100–210	40–202
Right-side amplitude		
N	101	133
Mean	1.40	2.32
Median	1.30	2.00
Range	0.05–4.0	0.5–4.5

Parkinson's Disease Study Safety Results

The analysis of safety was based on the 136 patients implanted in the trial. The safety profile was based on a comparison of adverse events that occurred during the randomized phase as well as a comparison of all adverse events that occurred through the last follow-up visit. The Data Safety Monitoring Board used their previous experience, knowledge of the literature, comments from the site and information from the clinical research staff to evaluate each event and classify them into the categories listed in the tables.

Patients were randomized in a 3:1 ratio to the stimulation or control group: 58.4% (59/101) of the subjects in the stimulation group had a total of 144 adverse events, and 45.7% (16/35) of the subjects in the control group had a total of 25 adverse events, as shown in the following table. There were no significant differences between the occurrence of adverse events in the stimulation group compared to the control group between implant and 90 days.

Table 16. Summary of the first occurrence of all adverse events during the first 90 days

Adverse Event	Stimulation Group (N=101) n (%)	Control Group (N=35) n (%)	*p*-value[1]
Number with at least 1 adverse event	59 (58.4%)	16 (45.7%)	0.238
Gait disorder including balance problem	14 (13.9%)	1 (2.9%)	0.115
Dysarthria	9 (8.9%)	0 (0.0%)	0.111
Edema	7 (6.9%)	0 (0.0%)	0.190
Disequilibrium	5 (5.0%)	1 (2.9%)	1.0
Dyskinesias	5 (5.0%)	1 (2.9%)	1.0
Infection	5 (5.0%)	1 (2.9%)	1.0
Preoperative pain, stress, or discomfort	6 (5.9%)	0 (0.0%)	0.338

Table 16. Summary of the first occurrence of all adverse events during the first 90 days

Adverse Event	Stimulation Group (N=101) n (%)	Control Group (N=35) n (%)	*p*-value[1]
Anxiety	4 (4.0%)	1 (2.9%)	1.0
Confusion	4 (4.0%)	1 (2.9%)	1.0
Depression	4 (4.0%)	0 (0.0%)	0.572
Headache	4 (4.0%)	1 (2.9%)	1.0
Intracranial hemorrhage	4 (4.0%)	1 (2.9%)	1.0
Paresthesia	4 (4.0%)	0 (0.0%)	0.572
Dysphasia	3 (3.0%)	1 (2.9%)	1.0
Lead migration	3 (3.0%)	0 (0.0%)	0.569
Psychiatric changes/distrubances	3 (3.0%)	0 (0.0%)	0.569
Sleep disturbances	3 (3.0%)	0 (0.0%)	0.569
Subcutaneous hemorrhage or seroma	3 (3.0%)	1 (2.9%)	1.0
Asthenia	2 (2.0%)	0 (0.0%)	1.0
Rigidity	2 (2.0%)	0 (0.0%)	1.0
Seizure or convulsions	2 (2.0%)	0 (0.0%)	1.0
Tremor	2 (2.0%)	1 (2.9%)	1.0
Cerebrospinal fluid leakage	1 (1.0%)	0 (0.0%)	1.0
Diarrhea	1 (1.0%)	0 (0.0%)	1.0
Dystonia	1 (1.0%)	0 (0.0%)	1.0
Hallucinations	1 (1.0%)	1 (2.9%)	0.450
Hearing disturbances	1 (1.0%)	0 (0.0%)	1.0
Increased salivation	1 (1.0%)	0 (0.0%)	1.0
Jolting or shocking sensations	1 (1.0%)	0 (0.0%)	1.0
Lead fracture	1 (1.0%)	0 (0.0%)	1.0
Motor fluctuations	1 (1.0%)	0 (0.0%)	1.0
Nausea	1 (1.0%)	0 (0.0%)	1.0
Persistent pain at IPG site	1 (1.0%)	1 (2.9%)	0.450
Visual disturbances	1 (1.0%)	0 (0.0%)	1.0
Abnormal thinking	0 (0.0%)	1 (2.9%)	0.257
Dementia	0 (0.0%)	1 (2.9%)	0.257
Pneumonia	0 (0.0%)	1 (2.9%)	0.257
Vomiting	0 (0.0%)	1 (2.9%)	0.257
Other	34	8	[2]
Total adverse events	144	25	[2]

[1] Fisher's Exact Test was used to compute *p*-values.

[2] No *p*-value is included since the event types are mixed.

A total of 18 patients, 13.9% (14/101) in the stimulation group and 11.4% (4/35) in the control group, experienced a serious adverse event during the first 90 days as shown in the following table. There was a total of 18 serious adverse events (SAEs) in the stimulation group and 7 in the control group.

Table 17. Summary of the first occurrence of serious adverse events during the first 90 days

Serious Adverse Event	Stimulation Group (N=101) n (%)	Control Group (N=35) n (%)	*p*-value[1]
Number with at least 1 serious adverse event	14 (13.9%)	4 (11.4%)	1.0
Intracranial hemorrhage	3 (3.0%)	1 (2.9%)	1.0
Infection	2 (2.0%)	1 (2.9%)	1.0
Lead migration	2 (2.0%)	0 (0.0%)	1.0
Motor fluctuations	1 (1.0%)	0 (0.0%)	1.0
Cerebrospinal fluid leakage	1 (1.0%)	0 (0.0%)	1.0
Confusion	1 (1.0%)	0 (0.0%)	1.0
Gait disorder including balance problems	1 (1.0%)	0 (0.0%)	1.0
Lead fracture	1 (1.0%)	0 (0.0%)	1.0
Pneumonia	0 (0.0%)	1 (2.9%)	0.257
Seizure or convulsions	1 (1.0%)	0 (0.0%)	1.0
Tremor	1 (1.0%)	0 (0.0%)	1.0
Other	4 (4.0%)	4 (11.4%)	0.204
Total serious adverse events	18	7	[2]

[1] Fisher's Exact Test was used to compute *p*-values.

[2] No *p*-value is included since the event types are mixed.

During the first 90 days of the study, 107 patients (78.7%) experienced a total of 409 adverse events.

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Total adverse events	**359**	**50**	**107**	
Accidental event	**22**	**4**	**22**	**16.2%**
Car accident	1		1	0.7%
Single event (fall/slip/trip)	13	1	12	9.5%
Fracture/dislocation/stitches/hit on head/injured finger	8	3	11	8.1%
Disease progression	**6**		**6**	**4.4%**
Gait disorder including balance problems	4		4	2.9%
Worsened Parkinson's disease	1		1	0.7%
Motor fluctuations	1		1	0.7%
General	**38**		**28**	**20.6%**
Headache	5		5	3.7%
Nausea/vomiting	5		4	2.9%
Weight gain/loss	4		4	2.9%
Edema	2		2	1.5%
Gait disorder including balance problems	1		1	0.7%
Sweating	1		1	0.7%
Other (pain/cramps [9], erectile dysfunction constipation, fever, weakness [3], fatigue [2], difficulty turning in bed, leg extra movement, and lightheadedness)	20		17	12.5%
Hardware-related	**10**	**4**	**13**	**9.6%**
Extension malfunction	4		4	2.9%
IPG malfunction	2	1	3	2.2%
Jolting or shocking sensations	2		2	1.5%
Lead migration	1	1	2	1.5%
Erosion		1	1	0.7%
Lead malfunction (lead break due to blow on the head)		1	1	0.7%
Pain at connection	1		1	0.7%

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Medication-related	**27**		**18**	**13.2%**
Edema	5		4	2.9%
Sleep disturbances	4		4	2.9%
Confusion	2		1	0.7%
Gait disorder including balance problems	2		1	0.7%
Increased salivation	2		2	1.5%
Jolting or shocking sensations (tingling in foot at night)	1		1	0.7%
Anxiety	1		1	0.7%
Diarrhea	1		1	0.7%
Disequilibrium	1		1	0.7%
Dystonia	1		1	0.7%
Hallucinations	1		1	0.7%
Motor fluctuations	1		1	0.7%
Tremor	1		1	0.7%
Psychiatric changes/disturbances	1		1	0.7%
Other (erectile dysfunction, fatigue, and facial swelling)	3		3	2.2%
Parkinson's disease symptoms	**36**	**3**	**29**	**21.3%**
Gait disorder including balance problems	5	2	7	5.1%
Dysarthria	7		7	5.1%
Sleep disturbances	4		4	2.9%
Asthenia	2		2	1.5%
Disequibrium	2		2	1.5%
Dysphagia	2		2	1.5%
Dystonia	2		2	1.5%
Amnesia	1		1	0.7%
Bradykinesia	1		1	0.7%
Depression	1		1	0.7%
Dyskinesias	1		1	0.7%
Rigidity	1		1	0.7%
Other (pain [2], coughing, hypotension [2], worsening of Parkinson's disease features, torn rotator cuff, and leg "gives out")	7	1	6	4.4%

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Pre-existing event	**4**	**1**	**5**	**3.7%**
Pain	1	1	2	1.5%
Anxiety	1		1	0.7%
Difficulty breathing	1		1	0.7%
Sleep apnea	1		1	0.7%
Pre-existing event — worsened	**18**	**1**	**18**	**13.2%**
Depression	10	1	10	7.4%
Hallucinations	3		3	2.2%
Anxiety	1		1	0.7%
Gait disorder including balance problems	1		1	0.7%
Psychiatric changes/disturbances	1		1	0.7%
Seizure or convulsions	1		1	0.7%
Other (increased stuttering)	1		1	0.7%
Stimulation-related	**32**		**21**	**15.4%**
Dysarthria	7		6	4.4%
Disequilibrium	3		3	2.2%
Gait disorder including balance problems	3		2	1.5%
Paresthesia	3		3	2.2%
Anxiety	2		2	1.5%
Dysphasia	2		2	1.5%
Postoperative pain, stress, or discomfort	2		2	1.5%
Psychiatric changes/disturbances	2		2	1.5%
Confusion	1		1	0.7%
Depression	1		1	0.7%
Dystonia	1		1	0.7%
Dyskinesias	1		1	0.7%
Edema	1		1	0.7%
Hearing disturbances	1		1	0.7%
Increased salivation	1		1	0.7%
Jolting or shocking sensations	1		1	0.7%

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Surgery-related	**44**	**16**	**37**	**27.2%**
Infection	4	5	7	5.1%
Confusion	4	1	5	3.7%
Intracranial hemorrhage	1	4	5	3.7%
Edema	3		3	2.2%
Subcutaneous hemorrhage or seroma	3		3	2.2%
Anxiety	2		2	1.5%
Dysphasia	2		2	1.5%
Headache	2		2	1.5%
Persistent pain at device site	2		2	1.5%
Postoperative pain, stress, or discomfort	2		2	1.5%
Psychiatric changes/disturbances	2		2	1.5%
Seizure or convulsions	1	1	2	1.5%
Abnormal thinking	1		1	0.7%
Apathy	1		1	0.7%
Cerebrospinal fluid leakage		1	1	0.7%
Dementia	1		1	0.7%
Disequilibrium	1		1	0.7%
Dysarthria	1		1	0.7%
Gait disorder including balance problems	1		1	0.7%
Hallucinations	1		1	0.7%
Lead migration		1	1	0.7%
Paresthesia	1		1	0.7%
Pneumonia		1	1	0.7%
Tremor	1		1	0.7%
Visual disturbances	1		1	0.7%
Other (fatigue [2], numbness, increased somnolence, dysphagia, urosepsis, urinary retention, and DVT)	6	2	6	4.4%

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Titration-related	**35**	**2**	**22**	**16.2%**
Dyskinesias	10		7	5.1%
Dysphasia	1		1	0.7%
Gait disorder including balance problems	7		7	
Rigidity	2		2	1.5%
Disequilibrium	1		1	0.7%
Dysarthria	2		2	1.5%
Motor fluctuations		1	1	0.7%
Dystonia	1		1	0.7%
Paresthesia	1		1	0.7%
Psychiatric changes/disturbances	2		2	1.5%
Sleep disturbances	2		2	1.5%
Other (foot drop, fatigue [2], increased Parkinson's disease symptoms, increased freezing, symptomatic orthostasis, and pain)	6	1	7	5.1%
Unable to determine	**13**	**1**	**9**	**6.6%**
Depression	4		4	2.9%
Disequilibrium	2		1	0.7%
Hallucinations	1		1	0.7%
Psychiatric changes/disturbances		1	1	0.7%
Other (dry mouth [2], illusion, pressure ulcer, sores, and weakness)	6		3	2.2%
Unrelated event	**74**	**18**	**53**	
Anxiety	1		1	0.7%
Disequilibrium	1		1	0.7%
Edema	1		1	0.7%
Hearing disturbance	1		1	0.7%
Infection		1	1	0.7%
Paresthesia	2		2	1.5%
Pneumonia	1		1	0.7%
Urinary incontinence	1		1	0.7%
Tremor		1	1	0.7%

Table 18. Frequency of all adverse events during 1 year study by DSMB classification (all AEs include serious AEs and nonserious AEs)

Adverse Event	AE	SAE	Number of Patients	Incidence Rate
Other (pain [2/17 SAE], arthritis [1/2 SAE], prostate enlarged, diagnosed with cancer [1/3 SAE], flu/cold/URI [5], cyst, UTI [3/10 SAE], bruising, low platelets, hair texture change, photophobia, bronchitis [2], elevated cholesterol, diverticulitis, anemia, infection in mouth, hernia repair, atrial flutter, teeth breaking [2], noise, sciatica [3], cervical myelopathy, spinal stenosis, congestive heart failure, cholecystitis, hip surgery, fatigue, hospitalization to rule out stroke, wrist surgery [2], carpal tunnel, coughing, dermatitis, phlebitis, torn muscle, gastroparesis, rotator cuff repair, open eustachian tube, shoulder surgery, abdominal mass, PICC blockage, diabetes, conversion of left foot, neck sprain, tachycardia, and overactive bladder)	66	16	48	35.3%

Device Revisions

The following table provides a summary of device revisions through one year. In addition to the revisions, one patient was explanted.

Table 19. Device revision summary

Revision	Patients Implanted N=136 n (%)
Lead	4 (2.9%)
Extension	7 (5.1%)
IPG	7 (5.1%)

Deaths

There were 3 deaths in the long-term follow-up study. The cause of the deaths were unrelated to the device and included sepsis secondary from a UTI, cancer, and multiple infections that started with osteomyelitis of the big toe.

Neuropsychological Testing

Neuropsychological testing was done at baseline and at 90 days to compare the assessments in the stimulation and control groups. The following table provides these results.

Table 20. Neuropsychological testing summary at 90 days

Characteristic	StimulationGroup		Control Group		*p*-value
	Baseline	90 days	Baseline	90 days	
Dementia rating scale					
Attention	10.9 (2.2)	10.9 (2.1)	10.6 (2.6)	10.8 (2.1)	0.945
Initiation	9.5 (2.3)	9.1 (2.8)	9.6 (2.7)	8.3 (3.1)	0.079
Construction	9.3 (1.7)	9.4 (1.4)	9.4 (1.9)	9.1 (2.0)	0.156
Conceptualization	9.2 (2.2)	9.1 (2.0)	8.9 (2.6)	9.2 (2.2)	0.719
Memory	9.1 (3.0)	9.4 (3.2)	8.7 (3.1)	9.2 (2.9)	0.781
Stroop					
Word	38.8 (11.3)	37.4 (10.6)	38.3 (11.5)	38.7 (10.5)	0.214
Color	39.5 (10.3)	37.4 (10.7)	38.0 (11.1)	37.3 (10.7)	0.308
Color-word	44.4 (9.4)	41.5 (9.1)	43.6 (11.4)	42.0 (10.2)	0.458
Intereference	47.7 (6.9)	45.9 (7.9)	46.9 (8.3)	46.7 (8.1)	0.432
Delis-Kaplan					
Letter fluency	10.6 (4.2)	9.1 (3.7)	10.2 (4.5)	9.3 (4.7)	0.642
Category fluency	10.6 (3.8)	8.7 (3.6)	9.9 (3.6)	8.6 (3.6)	0.459
Switching fluency	10.4 (3.9)	9.2 (4.1)	11.1 (2.9)	9.2 (3.8)	0.696
Switching accuracy	10.2 (3.6)	9.5 (3.9)	10.9 (2.9)	9.2 (3.5)	0.417
Wisconsin (WCST)					
Categories	2.71 (1.50)	2.54 (1.58)	3.13 (1.41)	3.13 (1.45)	0.269
Perseverative					
Raw scores	11.1 (7.4)	10.4 (6.5)	10.5 (6.6)	9.2 (6.0)	0.452
T-scores	46.5 (13.8)	47.5 (13.2)	46.1 (11.4)	49.5 (12.6)	0.442
Nonperseverative					
Raw scores	9.1 (5.8)	10.2 (6.1)	7.8 (5.3)	8.7 (5.0)	0.538
T-scores	45.5 (13.3)	42.9 (13.2)	47.9 (10.6)	44.8 (9.7)	0.791
Trail making A	44.6 (11.6)	43.1 (12.4)	40.3 (14.4)	40.0 (12.2)	0.960
Trail making B	41.6 (12.6)	40.7 (14.3)	39.2 (12.4)	36.7 (15.7)	0.388
Hopkins verbal learning					
Total recall	39.1 (11.5)	40.0 (11.3)	36.6 (10.8)	38.3 (10.6)	0.837
Delayed recall	40.5 (12.8)	39.3 (13.0)	39.0 (10.8)	38.7 (11.5)	0.921
Retention	44.7 (14.3)	42.6 (13.2)	42.9 (11.4)	43.9 (12.7)	0.397
Recognition	41.2 (12.4)	42.5 (11.5)	43.6 (13.3)	44.8 (13.3)	0.430

Table 20. Neuropsychological testing summary at 90 days

Characteristic	StimulationGroup		Control Group		*p*-value
	Baseline	90 days	Baseline	90 days	
Wechsler memory					
Logical memory I	9.7 (3.7)	9.9 (3.6)	10.1 (2.7)	10.2 (2.3)	0.760
Logical memory II	10.3 (3.4)	10.9 (3.4)	10.6 (2.9)	10.8 (3.1)	0.616
Family pictures I	8.9 (3.6)	9.6 (3.2)	8.6 (2.4)	8.5 (3.0)	0.069
Family pictures II	9.0 (3.4)	9.8 (3.3)	8.6 (2.9)	8.9 (3.4)	0.229
Hamilton depression[1]					
Total T-score	66.1 (13.2)	57.4 (13.7)	69.3 (13.7)	66.2 (11.9)	0.005
Frontal systems behavior					
Apathy	64.8 (18.3)	61.3 (16.1)	69.0 (16.8)	65.8 (14.2)	0.484
Disinhibition	56.6 (18.3)	55.6 (15.2)	60.4 (13.4)	60.3 (14.7)	0.284
Executive dysfunction	62.4 (16.0)	59.7 (14.1)	64.4 (17.6)	65.4 (13.3)	0.102
Total	64.4 (18.2)	61.2 (15.8)	68.3 (14.8)	66.4 (13.6)	0.372
NOTE: An increase in score represents an improvement, except the test noted with [1]. [1] indicates a decrease in score represents an improvement.					

Neuropsychological testing was also done at 12 months. The following table provides a comparison of the neuopsychological testing results from baseline to 12 months.

Table 21. Neuropsychological testing summary at 12 months

Characteristic	Baseline	12 months	*p*-value
Dementia rating scale			
Attention	10.9 (2.0)	10.9 (2.5)	0.918
Initiation	9.5 (2.4)	8.9 (2.8)	0.010
Construction	9.4 (1.6)	9.3 (1.7)	0.493
Conceptualization	9.1 (2.2)	9.5 (2.4)	0.076
Memory	9.2 (2.9)	9.4 (2.9)	0.419
Stroop			
Word	38.8 (11.2)	35.3 (11.8)	<0.001
Color	39.1 (10.6)	35.2 (11.1)	<0.001
Color-word	44.7 (9.2)	41.6 (10.2)	<0.001
Interference	47.9 (7.0)	46.9 (8.3)	0.257

Table 21. Neuropsychological testing summary at 12 months

Characteristic	Baseline	12 months	*p*-value
Delis-Kaplan			
Letter fluency	10.5 (4.3)	9.1 (4.0)	<0.001
Category fluency	10.4 (3.7)	8.5 (3.6)	<0.001
Switching fluency	10.7 (3.5)	9.0 (3.9)	<0.001
Switching accuracy	10.5 (3.4)	9.2 (3.9)	0.001
Wisconsin (WCST)			
Categories	2.82 (1.49)	2.64 (1.7)	0.191
Perseverative			
Raw scores	11.1 (7.5)	10.7 (6.3)	0.571
T-scores	46.1 (12.9)	48.1 (12.8)	0.122
Nonperseverative			
Raw scores	8.8 (5.8)	9.8 (6.0)	0.069
T-scores	46.0 (12.4)	44.4 (12.2)	0.248
Trail making A	43.4 (12.6)	42.6 (13.0)	0.388
Trail making B	41.6 (11.8)	40.3 (14.0)	0.231
Hopkins verbal learning			
Total recall	38.5 (11.2)	39.4 (11.4)	0.391
Delayed recall	40.7 (12.2)	40.3 (13.0)	0.761
Retention	45.0 (13.4)	44.6 (13.2)	0.749
Recognition	41.9 (12.6)	43.1 (12.6)	0.299
Wechsler memory			
Logical memory I	9.9 (3.4)	10.5 (3.2)	0.014
Logical memory II	10.6 (3.2)	11.2 (3.3)	0.007
Family pictures I	8.8 (3.3)	9.4 (3.5)	0.019
Family pictures II	8.9 (3.3)	9.7 (3.5)	0.003
Hamilton depression[1]			
Total T-score	66.9 (13.3)	60.2 (14.5)	<0.001
Frontal systems behavior			
Apathy	65.5 (17.5)	64.8 (16.2)	0.624
Disinhibition	58.1 (17.4)	58.1 (16.9)	0.970
Executive dysfunction	62.7 (16.0)	61.3 (15.0)	0.332
Total	65.2 (17.1)	63.6 (16.8)	0.261

NOTE: An increase in score represents an improvement, except the test noted with [1]. [1] indicates a decrease in score represents an improvement.

Parkinson's Disease Study Effectiveness Results

The analysis of effectiveness was based on the 136 evaluated patients at the 90-day time point. Key effectiveness outcomes are presented in the tables in this section.

As shown in the following table, the primary endpoint was met at 90 days with a statistically significant (p=0.003) improvement in "on" time without dyskinesias or with nonbothersome dyskinesias for the stimulation group (4.27 hours of "on" time) compared to the control group (1.77 hours of "on" time). One patient in the control group did not have diary information at the 90-day visit because the nursing personnel misplaced the 90-day diary information, so the 1-month information was used for this analysis. In addition, two patients in the stimulation group were missing the 90-day diary information, so the 1-month information was used for this analysis. Thus, the stimulation group improved the "on" time without dyskinesias or with nonbothersome dyskinesias by a mean of 2.51 hours in comparison to the control group.

Table 22. Mean baseline and change from baseline to 90 days in the duration of "on" time (hours) without dyskinesias or with bothersome dyskinesias

	Stimulation Group (N=101)	Control Group (N=34)	*p*-value
Baseline			
Mean ± std		7.4±2.5	0.262
Range	0–14.8	3.0–13.8	
90 days			
Mean ± std	11.2±4.5	8.9±2.9	
Range	0–18.8	3–13.8	
Change from baseline[2]			
Mean	4.27	1.77	0.003
Difference 95% (CI)	2.51 (0.87–4.16)		

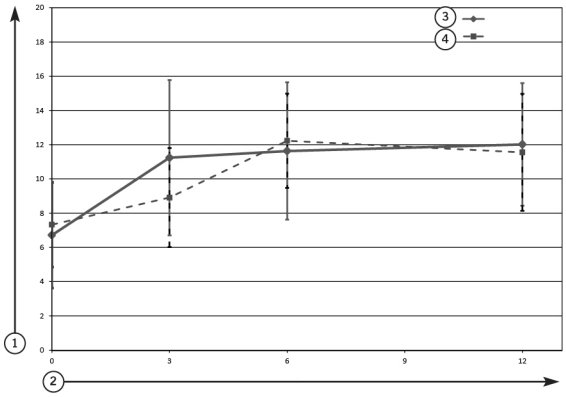
[1] The one-month visit was carried forward to 90 days for patients who were missing month 3.

[2] Adjusted for study site and baseline "on" time.

NOTE: An increase in hours represents an improvement.

See the following figure for results of the "good quality 'on' time" over the study duration.

Figure 9. Duration of "good quality 'on' time"



1. On time (hours)
2. Months
3. Stimulation
4. Control

Secondary Endpoints

This section provides a summary of the results of the secondary endpoints. Since a multiplicity adjustment procedure was not prespecified for the secondary endpoints, the results are presented with 95% CIs instead of *p*-values. In addition, several of the secondary endpoints could be assessed under various conditions, i.e., medication on/off and stimulation on/off. In some cases, the condition for assessment of the endpoints was not prespecified. Therefore, multiple tables for the same assessment are included to address this concern.

A secondary analysis of the primary endpoint was performed as a responder analysis. A responder was defined as an increase from the baseline of 2.0 hours or more in “on” time. The stimulation group demonstrated a 72.3% responder rate, and the control group demonstrated a 38.2% responder rate, with an odds ratio of 4.70 (1.96–11.28).

Table 23. Number of responders

	Stimulation Group (N=101)	Control Group (N=34)
Responders: n (%)[1]	73 (72.3%)	13 (38.2%)
Odd ratio (95% CI)	4.70 (1.96–11.28)	
[1] Increase of "on" time from baseline of 2 hours or greater		

The stimulation group demonstrated a greater improvement in Parkinson's disease symptoms as measured by the UPDRS Motor Examination at 90 days from baseline compared to the control group as demonstrated in the following tables.

Table 24. Change from baseline to 90 days in the UPDRS Motor Examination with medication "off" at baseline compared to medication "off" and stimulation "on" in stimulation group and stimulation "off" in control group

	Stimulation Group	Control Group
Baseline		
N	99	35
Mean ± std	40.8±10.8	44.1±14.0
90 days		
Mean ± std	24.8±10.1	40.4±11.6
Change[1]		
Mean	-16.1	-2.1
Difference 95% (CI)	-14.0 (-17.5, -10.5)	
[1] Adjusted for study site and baseline **NOTE:** A decrease in score represents an improvement.		

Table 25. Change from baseline to 90 days in the UPDRS Motor Examination with medication "on" at baseline compared to medication "on" and stimulation "on" in stimulation group and stimulation "off" in control group

	Stimulation Group	Control Group
Baseline		
N	99	35
Mean ± std	18.3±9.5	17.8±10.1
90 days		
Mean ± std	15.1±8.2	22.3±10.5
Change		
Mean	-3.01	4.37
Difference 95% (CI)	-7.38 (-10.18, -4.57)	
NOTE: A decrease in score represents an improvement.		

The stimulation group demonstrated an improvement in Schwab and England ADL assessment when the assessment was performed with medication "on" at baseline compared to the medication "on" and stimulation "on" condition at 90 days as demonstrated in the following table.

Table 26. Mean baseline and change from baseline to 90 days in the Schwab and England activities of daily living

	Stimulation Group	Control Group
Baseline		
N	99	35
Mean ± std	77.6±16.8	76.5±16.3
90 days		
N	99	34
Mean ± std	86.1±11.41	76.8±17.7
Change		
Mean	8.8	-0.5
Difference 95% (CI)	9.3 (4.4, 15.3)	
Results are medication "on" at baseline compared to medication and stimulation "on" at 90 days. [1] Adjusted for study site and baseline **NOTE:** An increase in score represents an improvement.		

The stimulation group demonstrated a greater improvement in the Hoehn and Yahr Scale at 90 days from baseline compared to the control group when the assessment was performed under the medication "off" baseline score compared to the medication "off" and stimulation "on" condition at 90 days.

Table 27. Baseline and 90 days Hoehn and Yahr staging mean results medication "off" at baseline, medication "off" at 90 days, and stimulation "on" at 90 days

	Stimulation Group	Control Group
Baseline		
N	99	35
Mean ± std	2.94±0.80	3.30±0.89
90 days		
Mean ± std	2.38±0.67	3.14±0.95
Change[1]		
Mean	-0.64	-0.07
Difference 95% (CI)	-0.57 (-0.81 -0.32)	
[1] Adjusted for study site and baseline score **NOTE:** A decrease in score represents an improvement.		

However, minimal improvement was seen on the Hoehn and Yahr Scale when the assessment was performed with the medication "on" at baseline compared to the medication "on" and stimulation "on" condition at 90 days.

Table 28. Baseline and 90 days Hoehn and Yahr staging mean results medication "on" at baseline, medication "on" and stimulation "on" at 90 days

	Stimulation Group	Control Group
Baseline		
N	96	35
Mean ± std	2.15±0.49	2.39±0.64
90 days		
Mean ± std	2.13±0.65	2.44±0.76
Change[1]		
Mean	-0.11	0.11
Difference 95% (CI)	-0.23 (-0.46, 0.01)	
[1] Adjusted for study site and baseline score **NOTE:** A decrease in score represents an improvement.		

A comparison of the stimulation and control groups on the global outcome measures were performed at 90 days. These assessments were performed by the examiner, caregiver, and patients as shown in the following table.

Table 29. Global outcome measures at 90 days

	StimulationGroup n (%)		Control Group n (%)	
	Baseline	90 days	Baseline	90 days
Examiner	N=101		N=35	
No disability	0 (0.0%)	5 (5.0%)	1 (2.9%)	0 (0.0%)
Mild disability	17 (16.8%)	62 (61.4%)	3 (8.6%)	7 (20.0%)
Moderate disability	50 (49.5%)	31 (30.7%)	15 (42.9%)	18 (51.4%)
Marked disability	28 (27.7%)	2 (2.0%)	10 (28.6%)	6 (17.1%)
Severe disability	6 (5.9%)	1 (1.0%)	6 (17.1%)	4 (11.4%)
Caregiver	N=85	N=77	N=28	N=27
No disability	2 (2.0%)	8 (10.4%)	0 (0.0%)	1 (3.7%)
Mild disability	11 (10.9%)	38 (49.4%)	5 (14.3%)	3 (11.1%)
Moderate disability	33 (32.7%)	24 (31.2%)	11 (31.4%)	13 (48.2%)
Marked disability	32 (31.7%)	6 (7.8%)	7 (20.0%)	8 (29.6%)
Severe disability	7 (6.9%)	1 (1.3%)	5 (14.3%)	2 (7.4%)

Table 29. Global outcome measures at 90 days

	StimulationGroup n (%)		Control Group n (%)	
	Baseline	90 days	Baseline	90 days
Patient	N=101		N=35	
No disability	4 (4.0%)	9 (8.9%)	1 (2.9%)	1 (2.9%)
Mild disability	17 (16.8%)	54 (53.5%)	5 (14.3%)	5 (14.3%)
Moderate disability	40 (39.6%)	30 (29.7%)	12 (34.3%)	19 (54.3%)
Marked disability	30 (29.7%)	6 (5.9%)	11 (31.4%)	7 (20.0%)
Severe disability	10 (9.9%)	2 (2.0%)	6 (17.1%)	3 (8.6%)

Additional Endpoints

This section provides the results of additional endpoints (assessments performed through one year). Because a multiplicity adjustment procedure was not prespecified for these endpoints, the results are presented with 95% CIs instead of *p*-values.

After the 90-day visit, all patients received stimulation. The UPDRS activities of daily living, motor examination, complications, and total scores were assessed at 12 months. The motor examination of the UPDRS (also known as UPDRS Part III) demonstrated a reduction over time through one year as compared to baseline the medication "off" condition compared to the medication "off"/stimulation "on" for both groups as shown in the following tables.

Table 30. Change from baseline through 12 months in the UPDRS with medication "off" at baseline and medication "off" at 12 months and stimulation "on" at 12 months

UPDRS Component	Baseline[1]	12 Months	
		Actual	Change
Activities of daily living			
N	121	115	115
Mean ± std	22.1±7.2	12.7±6.8	-9.4±8.5
95% confidence interval			-10.2 to -8.6
Motor examination			
N	136	130	130
Mean ± std	41.6±11.8	17.5±10.2	-24.1±13.9
95% confidence interval			-25.4 to -22.8
Complications			
N	130	125	125
Mean ± std	8.93±3.77	4.32±2.46	-4.61±4.04
95% confidence interval			-4.99 to -4.23

Table 30. Change from baseline through 12 months in the UPDRS with medication "off" at baseline and medication "off" at 12 months and stimulation "on" at 12 months

UPDRS Component	Baseline[1]	12 Months	
		Actual	Change
Total			
N	116	109	109
Mean ± std	76.8±18.3	37.9±16.8	-38.4±21.8
95% confidence interval			-40.4 to -36.4

[1] Patients with a value at 3, 6, or 12 months

NOTE: A decrease in score represents an improvement.

Table 31. Change from baseline through 12 months in the UPDRS with medication "on" at baseline and medication "on" at 12 months and stimulation "on" at 12 months

UPDRS Component	Baseline[1]	12 Months	
		Actual	Change
Activities of daily living			
N	118	112	112
Mean ± std	9.4±5.7	12.6±6.8	3.22±6.87
95% confidence interval			2.57 to 3.87
Motor examination			
N	135	130	130
Mean ± std	18.2±9.6	17.5±10.2	-0.8±11.1
95% confidence interval			-1.8 to 0.2
Complications			
N	125	121	121
Mean ± std	9.00±3.55	4.35±2.49	-4.69±3.91
95% confidence interval			-5.06 to -4.32
Total			
N	111	105	105
Mean ± std	39.6±13.3	38.3±16.9	-1.6±17.3
95% confidence interval			-3.3 to 0.1

[1] Patients with a value at 3, 6, or 12 months

NOTE: A decrease in score represents an improvement.

At one year, there was an improvement in the mean Schwab and England ADL score as shown in the following table.

Table 32. Mean baseline and change from baseline to 12 months in the Schwab and England activities of daily living

	Baseline	12 Months	
		Actual	Change[1]
N	134	133	133
Mean ± std	77.2±16.6	83.5±14.2	6.39±20.9
95% confidence interval			4.58 to 8.20
Medication "on" at baseline, and medication and stimulation "on" at 12 months **NOTE:** An increase in the score represents an improvement.			

The stimulation system demonstrated improvement in quality of life through one year as measured by the Parkinson's disease quality of life assessment questionnaire (PDQ-39) as shown in the following table. Stimulation provided improvement in the total quality of life score, as well as in the individual components: mobility, activities of daily living, functional well-being, stigma, cognitive impairment, and bodily discomfort.

Table 33. Change from baseline at 12 months in the PDQ-39 components and total score

Component	Baseline	12 Months	
		Actual	Change
Mobility N	136	135	135
Mean ± std	58.6±18.3	48.5±19.0	-10.3±19.4
95% confidence interval			-12.0 to -8.6
Activities of Daily Living			
N	134	132	132
Mean ± std	57.3±15.4	45.1±14.7	-12.3±16.8
95% confidence interval			-13.8 to -10.8
Emotional and Well-Being			
N	131	129	129
Mean ± std	44.2±15.8	40.1±15.5	-4.0±14.5
95% confidence interval			-5.3 to-2.7
Stigma			
N	136	135	135
Mean ± std	46.1±20.3	33.8±15.1	-12.4±18.9
95% confidence interval			-14.0 to -10.8

Table 33. Change from baseline at 12 months in the PDQ-39 components and total score

Component	Baseline	12 Months	
		Actual	Change
Cognitive Impairment			
N	135	134	134
Mean ± std	44.3±15.5	38.1±13.9	-6.2±15.6
95% confidence interval			-7.5 to -4.9
Bodily Discomfort			
N	136	135	135
Mean ± std	58.7±18.8	46.8±18.9	-11.9±22.4
95% confidence interval			-13.8 to -10.0
Total Score			
N	136	135	135
Mean ± std	50.6±11.6	42.5±11.2	-8.2±12.0
95% confidence interval			-9.2 to -7.2
[1] Patients with medication "on" at baseline and 12 months **NOTE:** A decrease in score represents an improvement.			

The stimulation system demonstrated improvement in sleep quality and fewer disturbances through 12 months as demonstrated by the Pittsburgh Sleep Quality Index (PSID) as shown in the following table.

Table 34. Change from baseline at 12 months in the PSID

	Baseline	12 Months	
		Actual	Change
N	136	135	135
Mean ± std	9.68±4.34	7.50±4.00	-2.16±4.09
95% confidence interval			-2.51 to -1.81
NOTE: A decrease in score represents an improvement.			

The following tables compare the Hoehn Yahr scores at 6 and 12 months.

Table 35. Baseline vs. 3, 6, and 12 months Hoehn and Yahr staging results medication "off" at baseline, medication "off" at 3, 6, and 12 months, stimulation "on" at 3, 6, 12 months

Stage	Baseline (N=133)	6 Months (N=133)	12 Months (N=131)
0	0 (0.0%)	1 (0.8%)	0 (0.0%)
1	0 (0.0%)	3 (2.3%)	2 (1.5%)
1.5	0 (0.0%)	2 (1.5%)	1 (0.8%)
2	25 (18.8%)	65 (48.9%)	63 (48.1%)
2.5	30 (22.6%)	29 (21.8%)	24 (18.3%)
3	41 (30.8%)	24 (18.1%)	28 (21.4%)
4	29 (21.8%)	6 (4.5%)	9 (6.9%)
5	8 (6.0%)	3 (2.3%)	4 (3.1%)

NOTE: A decrease in stage represents an improvement.

Table 36. Baseline vs. 3, 6, and 12 months Hoehn and Yahr staging results medication "off" at baseline, medication "off" at 3, 6, and 12 months, stimulation "on" at 3, 6, 12 months

Stage	Baseline (N=130)	6 Months (N=130)	12 Months (N=129)
0	1 (0.8%)	1 (0.8%)	2 (1.6%)
1	3 (2.3%)	10 (7.7%)	8 (6.2%)
1.5	3 (2.3%)	3 (2.3%)	2 (1.6%)
2	82 (63.1%)	72 (55.4%)	79 (61.2%)
2.5	22 (16.9%)	26 (20.0%)	22 (17.1%)
3	17 (13.1%)	17 (13.1%)	12 (9.3%)
4	1 (0.8%)	0 (0.0%)	2 (1.6%)
5	1 (0.8%)	1 (0.8%)	2 (1.6%)

NOTE: A decrease in stage represents an improvement.

Global outcome was assessed by the examiner, caregiver, and patient at 12 months as shown in the following table.

Table 37. Global outcome measures at 12 months

	Baseline n (%)	12 Months n (%)
Examiner	N=136	N=135
No disability	1 (0.7%)	4 (3.0%)
Mild disability	20 (14.7%)	80 (59.3%)
Moderate disability	65 (47.8%)	44 (32.6%)
Marked disability	38 (27.9%)	5 (3.7%)
Severe disability	12 (8.8%)	2 (1.5%)
Caregiver	N=113	N=108
No disability	2 (1.5%)	1 (0.9%)
Mild disability	16 (11.8%)	55 (50.9%)
Moderate disability	44 (32.4%)	35 (32.4%)
Marked disability	39 (28.7%)	13 (12.0%)
Severe disability	12 (8.8%)	4 (3.7%)
Patient	N=136	N=135
No disability	5 (3.7%)	7 (5.2%)
Mild disability	22 (16.2%)	70 (51.9%)
Moderate disability	52 (38.2%)	44 (32.6%)
Marked disability	41 (30.1%)	12 (8.9%)
Severe disability	16 (11.8%)	2 (1.5%)

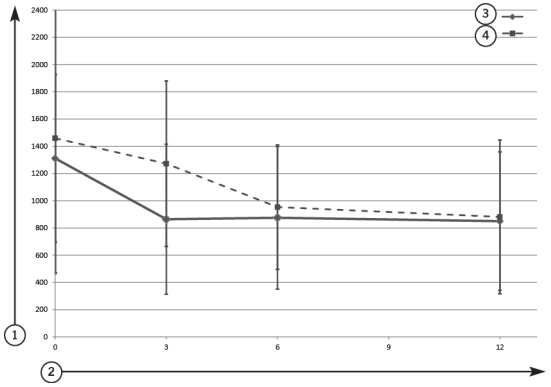
Patient satisfaction was assessed at 6 months and one year as shown in the following table.

Table 38. Patient satisfaction

Assessment	6 Months n/N (%)	1 Year n/N (%)
How satisfied are you?		
Very satisfied	68/135 (50.4%)	82/135 (60.7%)
Satisfied	50/135 (37.0%)	39/135 (28.9%)
Indifferent	6/135 (4.4%)	6/135 (4.4%)
Non satisfied	10/135 (7.4%)	5/135 (3.7%)
Very unsatisfied	1/135 (0.7%)	3/135 (2.2%)
You would undergo this process again?	125/136 (91.9%)	124/135 (91.9%)
You would recommend this deep brain stimulation system to someone else?	128/135 (94.8%)	128/134 (95.5%)

Mean changes in the total daily dose were compared between the treatment groups at 90 days by an analysis of covariance, using the baseline daily dosage as a covariate. The data demonstrate that after stimulation was initiated, the active stimulation group experienced a decrease in patient-administered daily levodopa medication dose requirements as compared to the control group. Continuing effect of stimulation demonstrated a decrease in levodopa dosage that was maintained for the 12-month study. Results are shown in the following graph.

Figure 10. Levodopa equivalent dosage over time



1. Levadopa equivalent dosage (mg)
2. Months
3. Stimulation
4. Control

Ninety-five (95) percent of patients indicated they would recommend this deep brain stimulation system to others at 6 months, and 96% of patients indicated they would recommend this deep brain stimulation system to others at 12 months.

Study Limitations

The study has several limitations. The study was not blinded and patients were informed of their random allocation to a control group or to the stimulation group. Therefore, the study design could have reduced expectations and the possible influence of a placebo effect in the control group. Because of the absence of blinding, the cause and the magnitude of benefit in the control group cannot be precisely interpreted. Disappointment about being randomly assigned to the delayed-stimulation group might have resulted in a nocebo effect.

Additional limitations of the one year data include the open label design. Open label studies may cause an overestimation of the treatment effect in investigator and subject ratings. In addition, subjects may modify their adjunctive medications which would confound interpretation of the one year data. Only one patient did not complete the one year study; thus missing data from this study was minimized and did not impact the results.

Essential Tremor Study

Essential Tremor Pivotal Clinical Study Design

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the St. Jude Medical™ deep brain stimulation system for the treatment of essential tremor of the upper extremities. This section includes a summary of the clinical study.

Study Design

Patients were treated between October 2005 and September 2012. The database for this premarket approval (PMA) reflected data collected through October 2013. A total of 150 patients with disabling medication-refractory upper extremity essential tremor were enrolled from 12 investigational sites. A total of 127 patients were implanted with the St. Jude Medical deep brain stimulation system.

This study was designed as a prospective, multicentered study for 365 days in duration from device implantation. The duration for the original study was one year. After one year, patients were consented to the long-term follow-up study where they continued follow up for a total of 5 years post-implant. There was no control group in this study. The primary analysis was evaluated by one independent blinded reviewer. At baseline and day 180, the Clinical Rating Scale for Tremor (CRST) evaluation session was video recorded for analysis by an independent evaluator unaware of the functioning of the device (i.e., the evaluator did not know if the patient on the video was being assessed at the baseline visit prior to the device implant or at the 180-day visit after implantation and whether the device was on or off at that assessment).

The Data Safety Monitoring Board (DSMB) reviewed all adverse events to classify all events into the appropriate category. The following categories were used: hardware-related, surgery-related, stimulation-related, and unrelated events to surgery or device. The DSMB used their previous experience, knowledge of the literature, comments from the site, and information from the clinical research staff to evaluate each event and classify it into the appropriate category.

Essential Tremor Study Clinical Inclusion and Exclusion Criteria

Enrollment in the tremor study was limited to patients who met the following selection criteria.

Inclusion Criteria

- Patient signed an informed consent.
- Patient was over 18 years of age.
- Patient was diagnosed with essential tremor for at least 3 years.
- Patient had a disabling medical-refractory, upper-extremity tremor with no evidence of supraspinal central nervous system disease or injury (tremor not adequately controlled by medications for at least three [3] months before implant).
- Patient had a postural or kinetic tremor severity score of at least 3 out of 4 on the extremity intended for treatment on the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor.
- Patient maintained a constant dose of anti-tremor medication that was indicated as best medical management for one (1) month prior to enrollment in the study.
- Patient was available for appropriate follow-up times for the length of the study.

Exclusion Criteria

- Patient was not surgical candidate.
- Patient had other clinically or medically significant diseases.
- Patient had any neurological injury or disease other than essential tremor.
- Patient had any condition requiring repeated magnetic resonance imaging (MRI) scans.
- Patient had any condition requiring diathermy.
- Patient was taking anticoagulant medications.
- Patient had untreated, clinically significant depression.
- Patient had an electrical or electromagnetic implant (cochlear prosthesis, pacemaker, etc.).
- Patient had a prior thalamotomy or surgical ablation procedure in either side of the brain.

- Patient had dementia that interfered with their ability to cooperate or comply with study requirements or comprehend the informed consent (mini-mental exam score less than 24).
- Patient abused drugs or alcohol.
- Patient had botulinum toxin injections within six (6) months prior to enrollment.
- Patient had a history of cranial surgery.
- Patient had a history of seizures.
- Patient had any metallic implants that may interfere with the functioning of the device (e.g., aneurysm clips).
- Patient had a history of stimulation intolerance in any area of the body.
- Patient was a female who could bear children and either had a urine pregnancy test that was positive or was not using adequate contraception.

Essential Tremor Study Follow-Up Schedule

The following table shows the baseline evaluations. Implantation was performed according to each individual site's standard procedures. Implant assessments are shown in the table. Stimulation was turned on the same day as the implant. Patients returned to the clinic at 90 days, 180 days, and 365 days post implant. The following table shows the assessments required at each visit.

Table 39. Follow-up schedule

Procedures	Screening/Baseline	Implant	Day 90 (±14 d)	Day 180 (±30 d)	Day 365 (±30 d)
Informed consent	X				
Demographics/history	X				
BDI-II	X				X
Mini mental state exam	X				X
Essential tremor diagnostic criteria	X				
Target extremity and maximum tremor position	X				
CRST	X[1]		X (stim on and off)	X[1] (stim on and off)	X (stim on and off)
QUEST	X		X	X	X
SF-36	X		X	X	X
Global outcomes measure	X		X	X	X
Implant and device information		X			
Patient satisfaction			X	X	X
Adverse events		X	X	X	X

[1] Assessment videotaped

Clinical Endpoints

The primary safety endpoint was the rate of device-related or procedure-related adverse events within 6 months following the initial implant. The secondary safety endpoint was a summary of the rate of the first occurrence of all adverse events and device- and procedure-related adverse events within 6 months following the initial unilateral implant with exact one-sided 95% upper confidence bounds.

The primary effectiveness endpoint was the difference in the postural or kinetic tremor score of the target limb between stimulation on and stimulation off at the 180-day visit. Postural and kinetic tremor scores were assessed by the Clinical Rating Scale for Tremor (CRST) (Fahn, Tolosa, Marin Tremor Rating Scale) scale.

All patients were assessed by videotape by the same independent rater. An independent rater, who was unaware of the device functioning and patient timeline, assessed the postural and tremor score used for this analysis. The measure was analyzed by a two-sided paired t-test at the 0.05 level of significance. In addition, a two-sided 95% confidence interval was calculated for the mean difference. All patients with available data at the 180-day visit were included in this analysis.

Secondary endpoints were assessed at 180 days and 365 days with medication “on”. These endpoints included

- Reduction in postural or kinetic tremor of the nontarget limb in essential tremor patients who received a bilateral implant in the medication “on” state with stimulation “on” versus stimulation “off” at one year.
- Percent of patients who achieve a 2-point reduction in the postural or kinetic tremor scores at 180 days.
- For patients who undergo bilateral implantation, the percent of patients who achieve a 2-point reduction in the postural or kinetic tremor scores at 180 days and at 1 year in both extremities.
- Percent of patients whose treatment with deep brain stimulation is successful. Success is defined as those patients who have a minimum of a 2-point reduction in postural or kinetic tremor scores and show an improvement in activities of daily living at 180 days.
- For patients who undergo bilateral implantation, the percent of patients whose treatment with deep brain stimulation is successful. Success is defined as those patients who have a minimum of a 2-point reduction in postural or kinetic tremor scores and show an improvement in activities of daily living at 180 days and 1-year in both extremities.
- Reduction in the total CRST scores.
- Improvement in activities of daily living from the appropriate section from the CRST.
- Reduction in each of the components of the total CRST scores.
- Improvement in the quality of life measure as determined by the Short Form questionnaire (SF-36) and the Quality of Life in Essential Tremor (QUEST) questionnaire.
- Improvement of patient and caregiver Global Ratings.
- Percent of patients utilizing the patient amplitude control option.
- Range of amplitude permitted.
- Rate of patient satisfaction.

Essential Tremor Study Success Criteria

The primary safety endpoint analysis compared the rate of device-related or procedure-related adverse events within 6 months post-implant compared to a historical control of 38.1%. (This rate was reported in the product labeling for the Medtronic Activa™ device for the tremor indication).

The secondary safety analysis summarized the rates of time to the first device- or procedure-related adverse events within 6 months of the initial unilateral implant using one-sided 95% upper confidence bounds.

The sample size was driven by the safety endpoint and chosen to provide 64% power to detect a noninferiority window of 0.10 when comparing against a historical device-related or procedure-related adverse event rate of 38.1%. All patients with available data at the 180-day visit were included in this analysis.

For effectiveness, study success was defined as superiority of the reduction in the blinded evaluation of postural or kinetic tremor of the target limb in essential tremor patients on medication with stimulation "on" versus stimulation "off" at 180 days using the postural and kinetic tremor scores of the Clinical Rating Scale for Tremor (CRST) (Fahn, Tolosa, Marin Tremor Rating Scale) scale.

The primary effectiveness endpoint hypothesis was tested by a two-sided paired t-test at the 0.05 level of significance comparing the mean difference between stimulation "on" and stimulation "off" at 180 days post-implant. A two-sided 95% confidence interval was also calculated for the mean difference between when stimulation "on" and stimulation "off" at 180 days post-implant. The proportion of responders was calculated with an exact 95% confidence interval, where a responder was defined as a patient with a 2-point reduction in kinetic tremor or postural tremor.

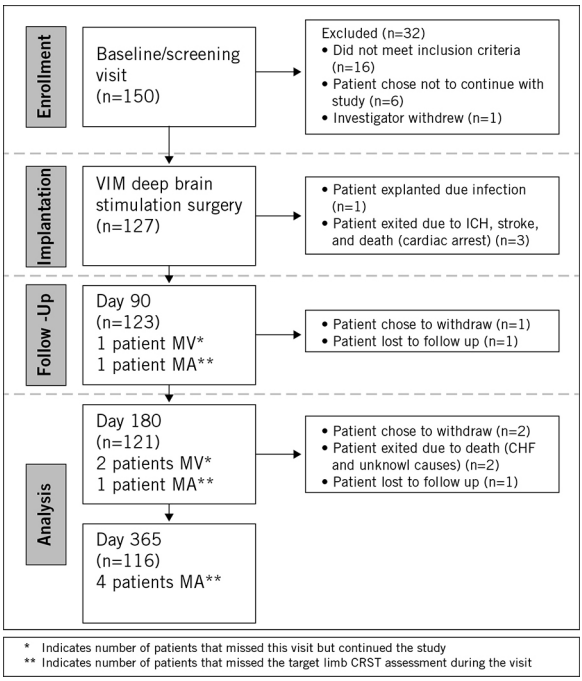
The secondary effectiveness endpoint analysis comparing the CRST second-side implant on the second-side limb change from baseline to 180 days of stimulation to the nontarget side was performed using a paired t-test at the 0.05 significance level.

The additional secondary effectiveness endpoint analysis comparing postural or kinetic tremor scores between stimulation "on" and stimulation "off" following 180 days of stimulation was performed using a paired t-test at the 0.05 significance level and included all patients with available data at each visit. In addition, a responder analysis was completed, in which a responder was defined as a patient with a 2-point reduction in kinetic or postural tremor between stimulation "off" and stimulation "on" following 180 days of stimulation. This analysis calculated the proportion of responders and summarized with an exact 95% confidence interval. A multiplicity adjustment procedure was not prespecified for the secondary endpoints. Therefore, 95% confidence intervals are provided for the secondary endpoints.

Essential Tremor Study Accountability of PMA Cohort

A total of 150 patients were screened and 127 patients were implanted at 12 investigational sites. A total of 123 patients completed the 90-day visit. A total of 121 patients completed the 180-day visit and a total of 116 patients completed the 365-day visit. The following figure summarizes the patient accounting.

Figure 11. Summary of patient accounting



Essential Tremor Study Population Demographics and Baseline Parameters

A total of 127 patients were implanted with the Libra™ deep brain stimulation system with the majority being Caucasian. The demographics of the study population are typical for a study evaluating essential tremor patients in the United States.

The mean age was 65 years (range 36 to 80). There were 69 males and 58 females. The mean time since onset of essential tremor was 29.1 years, and the mean time since initial diagnosis of essential tremor was 14.8 years prior to enrollment in the study. 110 patients were right-hand dominant, and the remaining 17 patients were left-hand dominant. At baseline only, 20 of 127 patients (15.7%) were on anti-tremor medication.

Table 40. Study population demographics

	Not Implanted (N=21)	Implanted (N=127)
Gender: n (%)		
Male	12 (57.1%)	69 (54.3%)
Female	9 (42.9%)	58 (45.7%)
Age (yr)		
Mean ± std	63.2±8.2	64.6±9.6
Range	45–81	36–80
Height (in)		
Mean ± std	67.0±3.6	68.1±6.5
Range	62–73	60–125
Weight (lb)		
Mean ± std	181.2±47.5	190.3±47.0
Range	114–250	85–333
Race: n (%)		
Caucasian	22 (100%)	124 (97.6%)
African American	0 (0.0%)	1 (0.8%)
Hispanic	0 (0.0%)	2 (1.6%)
Years since initial diagnosis of essential tremor		
Mean ± std	11.9±9.9	14.8±11.8
Range	3–47	0–52

The following table provides the stimulation parameters that were used in the study.

Table 41. Summary of programming for patients upon finishing the study visit

Parameter	Initial Programming	90 Days	180 Days	365 Days
Target side pulse: n (%)				
Mean	88.3	93.7	95.0	95.9
Median	91.0	91.0	91.0	91.0
Targeted side frequency				
N	127	122	118	116
Mean	153.2	159.8	162.0	163.9
Median	150.0	160.0	164.0	170.0
Range	124–208	100–210	120–218	120–238

Table 41. Summary of programming for patients upon finishing the study visit

Parameter	Initial Programming	90 Days	180 Days	365 Days
Targeted side amplitude				
N	127	122	118	116
Mean	1.86	2.39	2.49	2.58
Median	1.80	2.28	2.38	2.33
Range	0.25–5.3	0.55–8.0	0.75–6.5	0.85–6.5

Amplitude control provides the ability for the patient to adjust stimulation intensity within a specified range as set by the clinician. During the study, 32 patients were given the ability to control their amplitude.

Essential Tremor Study Safety Results

The analysis of safety was based on the 127 patients implanted in the trial. The safety profile was based on a comparison of adverse events that occurred through the 180-day period following implant to a historical control, as well as a comparison of all adverse events that occurred through the last follow-up visit. The Data Safety Monitoring Board used their previous experience, knowledge of the literature, comments from the site, and information from the clinical research staff to evaluate each event and classify it into the categories listed in the tables.

The statistical hypothesis for the primary safety endpoint was met. The primary safety endpoint was the rate of device-related or procedure-related adverse events within 6 months following the initial implant. All such adverse events, rated as probably or definitely related to the device or the procedure, were counted for 180 days following surgery or until the day of the second implant, whichever came first. In addition, rates of the first occurrence of all adverse events and device and procedure related adverse events within 6 months following the initial unilateral implant were summarized along with exact one-sided 95% upper confidence bounds. Rates of the first occurrence of all adverse events and device- and procedure-related adverse events that occurred subsequent to the second implant were presented separately.

Forty patients (31.5%) had a device- or procedure-related adverse event that occurred within 180 days of the initial implant. The one-sided 95% upper confidence bound on this proportion is 38.9%, which is less than 10 percentage points more than the comparator rate of 38.1%. Hence the primary safety hypothesis is rejected and the device- or procedure-related adverse event rate is not inferior to the comparator rate of 38.1%.

A total of 55 adverse events occurred in the first 180 days of initial implant and prior to second implant. These events were classified as probably or definitely procedure or device related by the investigator. No unanticipated adverse event occurred during the study. The following table shows these results.

Table 42. Summary of device- or procedure-related adverse events within 180 days of initial implant and prior to the second implant (N=127 patients), events rated as probably or definitely related

Adverse Event	n	%	Upper 95% Confidence Bound
Patients with one or more events	40	31.5	38.9
Abnormal thinking	1	0.8	3.7
Deep brain stimulation system malfunction	2	1.6	4.9
Diminished tremor relief	1	0.8	3.7
Dysarthria	4	3.1	7.1
Dystonia	2	1.6	4.9
Gait disorder including balance problem	2	1.6	4.9
Headache	4	3.1	7.1
Infection	2	1.6	4.9
Intracranial hemorrhage	3	2.4	6.0
Intermittent stimulation	1	0.8	3.7
Jolting or shocking sensations	10	7.9	13.0
Paresis	1	0.8	3.7
Paresthesia	1	0.8	3.7
Peristent pain at IPG site	2	1.6	4.9
Postoperative discomfort	2	1.6	4.9
Postoperative pain	1	0.8	3.7
Stroke	1	0.8	3.7
Subcutaneous hematoma	1	0.8	3.7
Visual disturbances	1	0.8	3.7
Weakness	1	0.8	3.7
Other[1]	12	9.4	14.9
Totals	55	NA	NA

[1] Patients with one or more "other" adverse events

Table 43. Summary of all adverse events within 180 days of initial implant or the second implant (N=127 patients)

Adverse Event	n	%	Upper 95% Confidence Bound
Abnormal thinking	1	0.8	3.7
Anxiety	2	1.6	4.9
Aphasia	3	2.4	6.0
Confusion	3	2.4	6.0
Deep brain stimulation system malfunction	2	1.6	4.9
Death	1	1.6	4.9
Depression	6	4.7	9.1
Diminished tremor relief	4	3.1	7.1
Disequilibrium	5	3.9	8.1
Dysarthria	17	13.4	19.4
Dysphasia	2	1.6	4.9
Dystonia	3	2.4	6.0
Gait disorder including balance problem	8	6.3	11.1
Headache	12	9.4	14.9
Infection	8	6.3	11.1
Intracranial hemorrhage	3	2.4	6.0
Intermittent stimulation	1	0.8	3.7
Jolting or shocking sensations	13	10.2	15.8
Loss of stimulation	1	0.8	3.7
Paresis	2	1.6	4.9
Paresthesia	3	2.4	6.0
Persistent pain at IPG site	2	1.6	4.9
Postoperative discomfort	4	3.1	7.1
Postoperative pain	2	1.6	4.9
Seizure	1	0.8	3.7
Stroke	1	0.8	3.7
Subcutaneous hematoma	1	0.8	3.7
Visual disturbances	6	4.7	9.1
Urinary incontinence	1	0.8	3.7
Weakness	3	2.4	6.0
Other	58	45.7	53.4
Totals	179	NA	NA

A total of 327 adverse events in 97 (76%) subjects occurred during the study, as shown in the following table.

Table 44. Summary of all adverse events classified by the Data Safety Monitoring board (N=127 patients)

Adverse Event	Number of Events
Total adverse events	**327**
Stimulation-related	**65**
Resolved when reprogrammed	42
Persistent events (12 speech disturbances, 3 gait/postural disorder; 1 cognitive changes; 1 dysphagia, and 1 tinnitus)	18
Transient events (2 gait disorder, 2 shocking or jolting sensation, and 1 dysphagia)	5
Surgery-related	**67**
Postoperative pain/discomfort/redness	17
Headache	8
Cognitive changes (transient)	7
Misplaced lead (4 revised and 2 nonrevised)	6
Infection	5
Intracranial hemorrhage (2 symptomatic [1 persistent and 1 transient], 1 nonsymptomatic)	3
Paresis (symptomatic and transient)	2
Wound dehiscence	2
Pocket hematoma	2
Seizure (transient)	1
Stroke (symptomatic and persistent)	1
Intracranial edema (symptomatic and transient)	1
Worsening of pre-existing condition (dystonia and possible TIA)	2
Dysarthria (persistent)	1
Other (2 visual disturbances, 1 air embolism, 1 diminished appetite, 1 drainage, 1 handwriting worse, 1 skin tear, 1 UTI, and 1 vivid dreaming)	9
Hardware-related	**22**
Battery check	9
Extension malfunction	6
IPG malfunction	4
Gait disorder including balance problem	1
Shocking or jolting sensation	1
Hemiparesis (right)	1
Deleted due to duplicate	4
Unrelated to study or surgery	**169**

All Serious Adverse Events

A total of 34 serious adverse events occurred in 29 patients during the study. No unanticipated device-related effects occurred during the study. The events included 3 deaths, 8 infections, 3 intracranial hemorrhages, 2 paresis, 1 seizure, and 1 stroke. The following table shows the results.

Table 45. Summary of serious adverse events (N=127 patients)

Serious Adverse Event	Number of Events
Total serious adverse events	**34**
Surgery-related events causing hospitalization or prolonged hospitalization (3 infections, 3 intracranial hemorrhages, 2 wound dehiscence, 1 air embolism, 1 intracranial edema paresis, 1 pneumocephalus, 1 seizure, 1 stroke, and 1 worsening of pre-existing condition)	14
Device-related event causing hospitalization (Right hemiparesis [weakness])	1
Unrelated to study or surgery	**19**
Death (2[1] cardiac-related and 1 unknown)	3
Hospitalization due to other medical conditions/events	16

[1] One additional subject had a cardiac arrest during preoperative testing.

All Adverse Events Following the Second Implant

Thirty-nine (39) patients had their second side implanted approximately 180 days after the first side implant. The most common adverse event report after the second side was dysarthria with 9 (7%) patients reporting. The following table shows the results.

Table 46. Summary of all adverse events after second implant (N=39)

Adverse Event	n	%	Upper 95% Confidence Bound
Aphasia	1	0.8	3.7
Ataxia	1	0.8	3.7
Confusion	2	1.6	4.8
Death	1	0.8	3.7
Depression	6	4.7	9.0
Disequilibrium	1	0.8	3.7
Dysarthria	9	7.0	11.9
Dysphagia	1	0.8	3.7
Gait disorder including balance problem	2	1.6	4.8
Headache	1	0.8	3.7
Infection	1	0.8	3.7

Table 46. Summary of all adverse events after second implant (N=39)

Adverse Event	n	%	Upper 95% Confidence Bound
Jolting or shocking sensations	3	2.3	5.9
Loss of stimulation	2	1.6	4.8
Paresis	1	0.8	3.7
Paresthesia	1	0.8	3.7
Postoperative pain	1	0.8	3.7
Visual disturbances	1	0.8	3.7
Other	20	15.6	21.9
Total	55	NA	NA

Device Revisions

The following table provides a summary of device revisions through one year. In addition to the revisions, three patients were explanted during the study.

Table 47. Device revision summary

Revision	Patients Implanted N=127 n (%)
Lead	6 (4.7%)
Extension	9 (7.1%)
IPG	6 (4.7%)

Deaths

Two deaths were related to cardiac events. One death was due to unknown causes.

Back Depression Inventory II

The Beck Depression Inventory II (BDI-II) is a clinical rating scale designed for detecting depression based on the Diagnostic and Statistical Manual of Mental Health Disorders—Fourth Edition (DSM–IV) criteria. This widely used scale consists of 21 items to assess the intensity of depression in clinical and normal patients. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression. The following table provides a comparison of the mean BDI-II scores from baseline to 12 months.

Table 48. Baseline and change from baseline in the BDI-II

Baseline	
N	112
Mean ± std	8.8±7.6
Minimal depression (score 0–13): n (%)	85 (75.9%)
Mild depression (score 14–19): n (%)	15 (13.4%)
Moderate depression (score 20–28): n (%)	10 (8.9%)
Severe depression (score 29–63): n (%)	2 (1.8%)
365 days	
Mean ± std	15.1±8.2
N	112
Mean ± std	6.8±7.1
Mean change ± std	-2.0±6.3
p-value	0.001
95% confidence interval	-3.2, -0.8
Minimal depression (score 0–13): n (%)	94 (83.9%)
Mild depression (score 14–19): n (%)	9 (8.0%)
Moderate depression (score 20–28): n (%)	7 (6.3%)
Severe depression (score 29–63): n (%)	2 (1.8%)

NOTE: A decrease in score represents an improvement.

Mini Mental State Exam

The following table provides a comparison of the mean Mini Mental State Exam (MMSE) scores from baseline to 12 months.

Table 49. Baseline and change from baseline to day 365 in the MMSE

Baseline	
N	110
Mean ± std	29.2±1.2
365 days	
N	110
Mean ± std	29.1±1.4
Mean change ± std	-0.1±1.2
p-value	0.23
95% confidence interval	-0.4, 0.1

NOTE: Score must be greater than 24. Lower scores may indicate a negative effect on mental status.

Essential Tremor Study Effectiveness Results

The analysis of effectiveness was based on the 127 patients evaluated at the 180-day visit. Key effectiveness outcomes are presented in the following tables. The primary effectiveness endpoint was based on the postural tremor score of the target limb between stimulation "on" and stimulation "off" at the 180-day visit, as measured by the blind reviewer.

Among the 127 implanted patients, 118 had site-physician assessments at 180 days. Among these 118 patients, 87 had blinded assessments with stimulation "off" and 86 had blinded assessments with stimulation "on" for the primary endpoint at 180 days, resulting in 76 patients with data for both stimulation "on" and stimulation "off." The mean difference at day 180 in the postural tremor score of the target limb between stimulation "on" and stimulation "off" is -1.25±1.26, which is statistically significant (p<0.001). The study demonstrated a successful primary endpoint, as shown in the following table and figure.

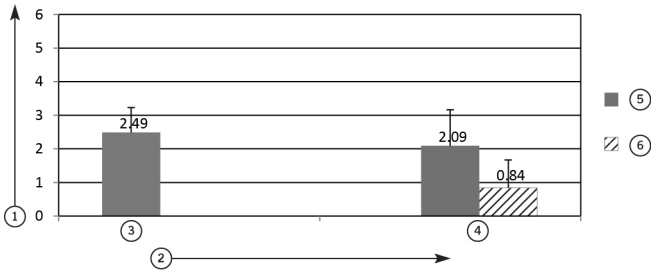
Table 50. Mean target limb severity score (CRST) with stimulation "off" and "on," as assessed by the blind reviewer

Day 180	
N	76
Stimulation off, mean ± std	2.09±1.07
Stimulation on, mean ± std	0.84±0.83
Mean difference ± std	-1.25±1.26
p-value	<0.001
95% confidence interval	-1.54, -0.96

NOTE: A decrease in score represents an improvement.

NOTE: At baseline only 20/127 (15.7%) of the patients were on anti-tremor medication.

Figure 12. Mean target limb severity score (CRST) with stimulation on and off as assessed by the blind reviewer (statistical difference found between stimulation on versus stimulation off at day 180 [p<0.001])



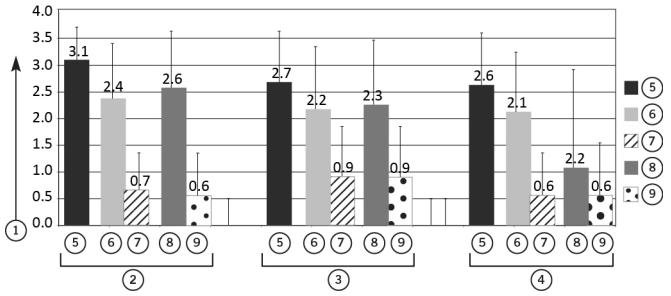
1. CRST score
2. Visit
3. Baseline
4. Day 180
5. Target side stim off
6. Target side stim on

Secondary Endpoints

The following secondary endpoints were also assessed at 180 days and 365 days. Since a multiplicity adjustment procedure was not prespecified for these endpoints, the results are presented with 95% confidence intervals instead of *p*-values.

The Clinical Rating Scale for Tremor (CRST) is a rating tool to assess the severity of postural, isometric, kinetic, and task-specific tremor in the dominant and nondominant sides of the head, trunk, and limbs of patients with essential tremor. The CRST utilizes a 0- to 4-point scale where 0 indicates a nonsymptomatic (normal) and 4 indicates the most severe rating of the patient's tremor symptoms. The following figure shows the results from the CRST for the target limb severity, the patient's handwriting, and the patient's pouring abilities on and off stimulation.

Figure 13. Mean target limb severity, handwriting and pouring scores (assessed by the CRST) at baseline compared to day 365 with stimulation on and off, as assessed by the site physician



1. CRST score
2. Target side severity
3. Handwriting
4. Pouring
5. Baseline
6. Day 180 stim off
7. Day 180 stim on
8. Day 365 stim off
9. Day 365 stim on

Target Limb Severity Score, Assessed by Site Investigator

The target limb was identified at baseline. The site physician evaluated the target limb according to the CRST. The mean target limb severity score at baseline was 3.10. The mean difference in the target limb severity score at each study visit is -2.34 at 90 days, -2.42 at 180 days, and -2.48 at 365 days. Additionally, target limb severity scores were compared between stimulation "on" and stimulation "off" at each visit, by the site physician. The mean difference between stimulation "on" and stimulation "off" at each visit is -1.66 at 90 days, -1.74 at 180 days, and -1.94 at 365 days. The following table shows the results.

Table 51. Mean target limb severity score (CRST) with stimulation off, stimulation on, and change from off to on, as assessed by the site physician

Baseline	
N	122
Mean ± std	3.10±0.62
Day 90	
N	121
Stimulation off, mean ± std	2.41±0.98
Stimulation on, mean ± std	0.75±0.78
Mean difference ± std	-1.66±1.07
95% confidence interval	-1.85, -1.47
Change from baseline on, mean ± std	-2.34±0.99
95% confidence interval	-2.52, -2.16
Day 180	
N	118
Stimulation off, mean ± std	2.41±0.96
Stimulation on, mean ± std	0.67±0.70
Mean difference ± std	-1.74±1.10
95% confidence interval	-1.94, -1.54
Change from baseline on, mean ± std	-2.42±0.97
95% confidence interval	-2.60, -2.25
Day 365	
N	112
Stimulation off, mean ± std	2.55±1.12
Stimulation on, mean ± std	0.62±0.79
Mean difference ± std	-1.94±1.16
95% confidence interval	-2.15, -1.72
Change from baseline on, mean ± std	-2.48±0.96
95% confidence interval	-2.66, -2.30

This responder analysis was done to compare the baseline evaluation with all visits. Comparing the rating from the baseline target limb score to the visit with stimulation, at the day-180 visit, 83.1% of patients responded, and at day 365, 86.6% of the patients responded. Another responder analysis was also done to evaluate the patients both with stimulation on and off at the same visit. At the day-180 visit when the assessment of the physician is compared between the stimulation on and off, 58.5% of patients responded at day 180 and 64.3% responded at day 365. The difference in these two responder analyses accounts for the carryover effects of stimulation and the time it takes for stimulation to be optimized. Results are in the following table. All results demonstrate the positive improvement that stimulation has on a patient's upper limb that allows for more use and control of the limb.

Table 52. CRST target limb responder analysis[1] between stimulation off and stimulation on and between baseline and stimulation on, as assessed by the site physician

Day 180	
Between stimulation off and stimulation on	
n/N (%)	69/118 (58.5%)
95% confidence interval	49.0%, 67.5%
Between baseline and stimulation on	
n/N (%)	98/118 (83.1%)
95% confidence interval	75.0%, 89.3%
Day 365	
Between stimulation off and stimulation on	
n/N (%)	72/112 (64.3%)
95% confidence interval	54.7%, 73.1%
Between baseline and stimulation on	
n/N (%)	97/112 (86.6%)
95% confidence interval	78.9%, 92.3%

[1] A reduction of 2 or more points

Table 53. Number of subjects with a 2-point reduction in CRST target limb, as assessed by the site physician

Day 180	
Between baseline and stimulation off	
n/N (%)	0/118 (0.0%)
Between baseline and stimulation on	
n/N (%)	98/118 (83.1%)
Day 365	
Between baseline and stimulation off	
n/N (%)	0/112 (0.0%)
Between baseline and stimulation on	
n/N (%)	97/112 (86.6%)

The following table provides the percent of patients whose treatment with deep brain stimulation is successful. Success is defined as those patients who have a minimum of a 2-point reduction in postural or kinetic tremor scores and show an improvement in activities of daily living at 180 days.

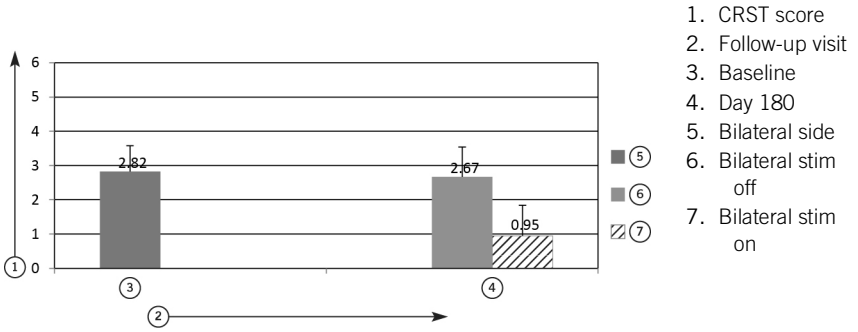
Table 54. Successful treatment with deep brain stimulation, as defined per protocol

n/N (%)	98/118 (83.1%)
95% confidence interval	75.0%, 89.3%

Bilateral Stimulation

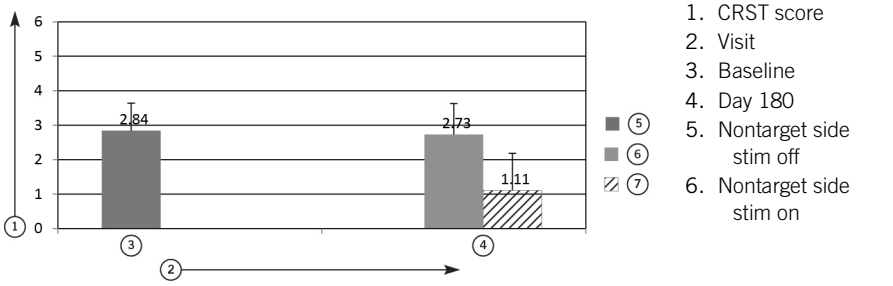
For those patients who had bilateral stimulation, the site physician evaluated the patient's nontarget side after 180 days of bilateral stimulation. At baseline, the mean nontarget limb severity score for bilateral stimulation was 2.82. This severity score decreased after stimulation, and the mean severity score after 180 days of stimulation is 0.95. Additionally, the nontarget limb severity scores were compared between stimulation on and stimulation off after 180 days of stimulation by the site physician. The mean difference between stimulation on and stimulation off is -1.72. The following figure shows these results, which demonstrate the positive improvement of bilateral stimulation.

Figure 14. Mean nontarget limb severity score (CRST) at baseline compared to day 180 with bilateral stimulation on and off, as assessed by the site physician



For those patients who had bilateral stimulation, the site physician evaluated the patient's nontarget side after 180 days with only the second-side system on. At baseline, the mean nontarget limb severity score for nontarget side stimulation was 2.84. The mean decreased to -1.73 at day 180. Additionally, the nontarget limb severity scores were compared between stimulation on and stimulation off after 180 days of stimulation with only the second-side system on, by the physician. The mean difference between stimulation on and stimulation off is -1.62. The following figure shows these results, which demonstrate the positive improvement that was achieved when the second side is implanted and stimulated.

Figure 15. Mean nontarget limb severity score (CRST) at baseline compared to day 180 with single-side stimulation on and off, as assessed by the site physician (nontarget-side stimulation)



Patients with bilateral implants who had a 2-point reduction in tremor scores and an improvement in ADLs at 6 months based on investigator scoring was 29/43 (67.4%).

Table 55. Investigator assessment of patients with bilateral implants

2-point reduction in tremor scores and an improvement in ADLs	
n/N (%)	29/43 (67.4%)
95% confidence interval	52.5%, 79.6%

Overall Motor Score as Measured by the CRST

The motor score adds all the responses to the tremor assessment for questions 1 through 9 of the CRST (whether or not the specific side is being treated). From the assessment of the site physician, the mean overall motor score at baseline was 16.9, and the changes at days 180 and 365 were -9.4 and -9.3, respectively. All results suggest a positive improvement stimulation has on a patient's motor symptoms. The following table shows the results.

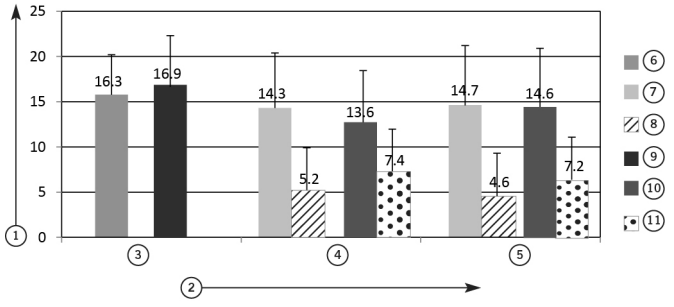
Table 56. Mean total motor score (CRST) with stimulation off, stimulation on, and change from off to on, as assessed by the site physician

Baseline	
N	122
Mean ± std	16.9±5.9
Day 180	
N	116
Stimulation off, mean ± std	13.6±6.9
Stimulation on, mean ± std	7.4±4.1
Mean difference ± std	-6.2±4.8
95% confidence interval	-7.0, -5.3
Change from baseline on, mean ± std	-9.4±4.9
95% confidence interval	-10.3, -8.5
Day 365	
N	112
Stimulation off, mean ± std	14.6±8.8
Stimulation on, mean ± std	7.2±5.0
Mean difference ± std	-7.4±6.6
95% confidence interval	-8.6, -6.1
Change from baseline on, mean ± std	-9.3±5.6
95% confidence interval	-10.3, -8.2
NOTE: A decrease in score represents an improvement.	

Activities of Daily Living as Measured by the CRST

The activity of daily living (ADL) score adds all the responses to questions 15 through 21 of the CRST. As assessed by the site physician, the ADL score at baseline was 16.3. This ADL score had a mean decrease of -11.1 at day 180 and a mean decrease of -11.5 at day 365. Additionally, ADL scores were compared between stimulation on and stimulation off at each visit, by the physician. The mean difference was -9.1 at day 180, and the mean difference was -10.0 at day 365. All results demonstrate the positive improvement stimulation has on a patient's activities of daily living. The following figure shows the results.

Figure 16. Activities of daily living (ADL) and total motor score (TMS) with stimulation off and stimulation on at day 180 and day 365 as assessed by the site physician by the CRST



1. CRST score
2. Stim on vs. stim off at each visit
3. Baseline
4. Day 180
5. Day 365
6. ADL
7. ADL stim off
8. ADL stim on
9. TMS
10. TMS stim off
11. TMS stim on

Individual Component Scores of the CRST

The following table shows the individual components of the CRST.

Table 57. Individual component scores of the CRST

CRST Score	Day	Baseline Mean	Off-Stim Mean	On-Stim Mean	Change (On-Baseline)	Lower 95% CI	Upper 95% CI
Face	90	0.24	0.23	0.12	-0.12	-0.21	-0.04
	180	0.24	0.14	0.06	-0.17	-0.26	-0.08
	365	0.24	0.22	0.12	-0.12	-0.21	-0.02
Tongue (resting)	90	0.20	0.11	0.04	-0.16	-0.25	-0.06
	180	0.20	0.16	0.04	-0.14	-0.23	-0.04
	365	0.20	0.12	0.05	-0.11	-0.20	-0.02
Tongue (postural)	90	0.67	0.39	0.24	-0.43	-0.57	-0.28
	180	0.67	0.42	0.19	-0.45	-0.60	-0.30
	365	0.67	0.38	0.14	-0.47	-0.62	-0.32
Voice	90	1.15	0.86	0.50	-0.66	-0.80	-0.52
	180	1.15	1.03	0.47	-0.64	-0.79	-0.49
	365	1.15	1.05	0.58	-0.50	-0.68	-0.33
Head (resting)	90	0.42	0.27	0.11	-0.31	-0.43	-0.19
	180	0.42	0.21	0.12	-0.30	-0.42	-0.18
	365	0.42	0.35	0.12	-0.29	-0.42	-0.16

Table 57. Individual component scores of the CRST

CRST Score	Day	Baseline Mean	Off-Stim Mean	On-Stim Mean	Change (On-Baseline)	Lower 95% CI	Upper 95% CI
Head (postural)	90	0.93	0.63	0.41	-0.52	-0.66	-0.37
	180	0.93	0.68	0.32	-0.59	-0.73	-0.45
	365	0.93	0.76	0.25	-0.64	-0.79	-0.48
Upper target (resting)	90	0.75	0.44	0.10	-0.63	-0.74	-0.51
	180	0.75	0.51	0.05	-0.71	-0.84	-0.58
	365	0.75	0.52	0.15	-0.56	-0.69	-0.44
Upper target (postural)	90	2.61	1.88	0.41	-2.18	-2.31	-2.05
	180	2.61	1.82	0.32	-2.30	-2.43	-2.16
	365	2.61	1.86	0.33	-2.24	-2.38	-2.11
Upper target (action)	90	3.01	2.40	0.76	-2.26	-2.43	-2.09
	180	3.01	2.35	0.73	-2.27	-2.44	-2.10
	365	3.01	2.60	0.63	-2.37	-2.54	-2.19
Upper nontarget (resting)	90	0.57	0.48	0.35	-0.21	-0.34	-0.07
	180	0.57	0.55	0.42	-0.15	-0.30	-0.01
	365	0.57	0.51	0.40	-0.11	-0.26	0.04
Upper nontarget (postural)	90	2.13	1.93	1.84	-0.28	-0.46	-0.10
	180	2.13	2.02	1.76	-0.37	-0.55	-0.19
	365	2.13	1.90	1.59	-0.48	-0.67	-0.29
Upper nontarget (action)	90	2.58	2.36	2.22	-0.37	-0.55	-0.20
	180	2.58	2.44	2.27	-0.30	-0.47	-0.13
	365	2.58	2.54	2.13	-0.42	-0.63	-0.21
Trunk (resting)	90	0.10	0.04	0.02	-0.08	-0.15	-0.01
	180	0.10	0.08	0.02	-0.08	-0.15	-0.02
	365	0.10	0.10	0.02	-0.09	-0.17	-0.01
Trunk (postural)	90	0.14	0.11	0.07	-0.07	-0.15	0.01
	180	0.14	0.14	0.06	-0.08	-0.16	0.01
	365	0.14	0.19	0.07	-0.06	-0.17	0.05
Right lower (resting)	90	0.13	0.11	0.07	-0.05	-0.11	0.02
	180	0.13	0.12	0.05	-0.08	-0.15	-0.02
	365	0.13	0.11	0.05	-0.09	-0.15	-0.02
Right lower (postural)	90	0.35	0.18	0.12	-0.24	-0.36	-0.12
	180	0.35	0.21	0.10	-0.25	-0.36	-0.13
	365	0.35	0.32	0.08	-0.27	-0.38	-0.17
Right lower (action)	90	0.32	0.23	0.14	-0.18	-0.31	-0.06
	180	0.32	0.20	0.09	-0.24	-0.33	-0.15
	365	0.32	0.35	0.11	-0.21	-0.31	-0.12

Table 57. Individual component scores of the CRST

CRST Score	Day	Baseline Mean	Off-Stim Mean	On-Stim Mean	Change (On-Baseline)	Lower 95% CI	Upper 95% CI
Left lower (resting)	90	0.09	0.06	0.07	-0.01	-0.07	0.05
	180	0.09	0.08	0.03	-0.07	-0.13	-0.01
	365	0.09	0.06	0.01	-0.09	-0.15	-0.03
Left lower (postural)	90	0.25	0.19	0.16	-0.10	-0.19	-0.01
	180	0.25	0.20	0.15	-0.10	-0.20	-0.01
	365	0.25	0.32	0.18	-0.09	-0.21	0.03
Left lower (action)	90	0.26	0.16	0.12	-0.14	-0.24	-0.04
	180	0.26	0.23	0.15	-0.12	-0.22	-0.02
	365	0.26	0.30	0.20	-0.07	-0.18	0.03
Drawing A right	90	2.34	1.89	0.91	-1.44	-1.64	-1.25
	180	2.34	1.93	0.81	-1.50	-1.69	-1.31
	365	2.34	1.93	0.84	-1.49	-1.69	-1.28
Drawing A left	90	2.40	2.20	1.85	-0.53	-0.73	-0.34
	180	2.40	2.26	1.92	-0.47	-0.67	-0.28
	365	2.40	2.19	1.83	-0.53	-0.75	-0.32
Drawing B right	90	2.58	2.15	1.04	-1.55	-1.74	-1.35
	180	2.58	2.18	0.97	-1.58	-1.79	-1.38
	365	2.58	2.18	0.99	-1.58	-1.78	-1.38
Drawing B left	90	2.65	2.39	2.09	-0.55	-0.74	-0.36
	180	2.65	2.49	2.15	-0.49	-0.68	-0.30
	365	2.65	2.47	2.11	-0.51	-0.73	-0.29
Drawing C right	90	2.26	1.98	0.93	-1.34	-1.56	-1.13
	180	2.26	1.97	0.88	-1.35	-1.56	-1.13
	365	2.26	1.94	0.78	-1.47	-1.69	-1.25
Drawing C left	90	2.41	2.29	1.97	-0.43	-0.62	-0.24
	180	2.41	2.35	2.02	-0.39	-0.58	-0.19
	365	2.41	2.22	1.98	-0.41	-0.62	-0.19
Pouring right	90	2.46	2.22	0.80	-1.68	-1.88	-1.48
	180	2.46	2.04	0.66	-1.81	-2.02	-1.59
	365	2.46	2.06	0.68	-1.78	-1.99	-1.57
Pouring left	90	2.28	2.17	1.80	-0.49	-0.71	-0.27
	180	2.28	2.17	1.72	-0.56	-0.77	-0.34
	365	2.28	2.24	1.65	-0.63	-0.86	-0.39
Speaking	90	0.95	0.71	0.45	-0.50	-0.64	-0.37
	180	0.95	0.76	0.46	-0.47	-0.63	-0.32
	365	0.95	0.79	0.43	-0.51	-0.68	-0.34

Table 57. Individual component scores of the CRST

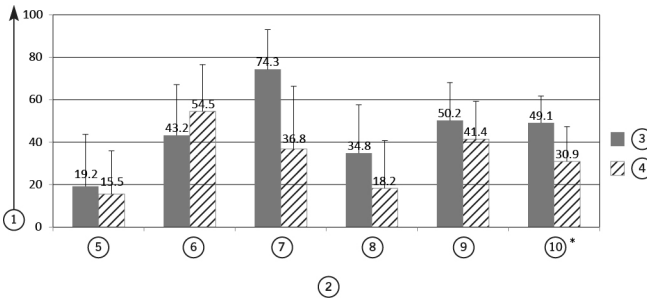
CRST Score	Day	Baseline Mean	Off-Stim Mean	On-Stim Mean	Change (On-Baseline)	Lower 95% CI	Upper 95% CI
Feeding	90	2.39	2.08	0.64	-1.75	-1.93	-1.58
	180	2.39	2.19	0.64	-1.75	-1.94	-1.57
	365	2.39	2.20	0.57	-1.82	-1.99	-1.65
Liquids to mouth	90	3.10	2.60	0.78	-2.33	-2.53	-2.12
	180	3.10	2.59	0.81	-2.29	-2.51	-2.07
	365	3.10	2.69	0.63	-2.43	-2.64	-2.22
Hygiene	90	2.33	1.99	0.61	-1.73	-1.93	-1.53
	180	2.33	2.02	0.57	-1.77	-1.98	-1.56
	365	2.33	2.15	0.63	-1.68	-1.90	-1.46
Dressing	90	2.15	1.66	0.60	-1.56	-1.75	-1.37
	180	2.15	1.80	0.68	-1.49	-1.70	-1.28
	365	2.15	1.86	0.61	-1.52	-1.74	-1.31
Writing	90	2.84	2.58	1.01	-1.83	-2.04	-1.62
	180	2.84	2.61	0.97	-1.86	-2.06	-1.65
	365	2.84	2.60	0.86	-1.99	-2.21	-1.77
Working	90	2.50	2.20	0.93	-1.57	-1.77	-1.37
	180	2.50	2.35	1.05	-1.45	-1.66	-1.24
	365	2.50	2.39	0.91	-1.55	-1.78	-1.33

Quality of Life in Essential Tremor (QUEST)

The QUEST questionnaire is a self-administered questionnaire, which consists of 30 items scored in 5 specific domains (physical, psychosocial, communication, hobbies/leisure, work/finances) and an overall summary index, as well as a patient assessment of tremor severity in specific body parts.

At baseline, the overall summary index mean was 49.1. This overall summary index mean improved at each study visit. All results demonstrate the positive improvement stimulation has on a patient's quality of life. The following figure shows the results.

Figure 17. QUEST questionnaire evaluation at baseline and day 365



1. Score
2. Subscale scores
3. Baseline
4. Day 365
5. Communication
6. Hobbies/leisure
7. Physical
8. Psychosocial
9. Work/finances
10. Summary index mean (* significant change from baseline $p<0.005$)

SF-36

The SF-36 is a general health status questionnaire designed to measure the patient's quality of life. The SF-36 is a self-administered questionnaire, which consists of 36 items addressing 11 domains of health. The 11 domains are summarized into a physical and mental component score. The following table shows these results.

Table 58. Baseline and change from baseline in the SF-36 components and individual domains

	Physical Component Summary	Mental Component Summary
Baseline		
N	123	123
Mean ± std	45.62±9.49	50.11±10.9
Day 365		
N	108	108
Mean ± std	45.6±9.79	52.21±10.15
Mean difference baseline vs. 365 day	-0.02	2.1
95% CI	-2.5, 2.4	-0.6, 4.8
NOTE: An increase in score represents an improvement.		

A comparison of the caregiver and patient global assessments from baseline to days 180 and 365 are provided in the following tables.

Table 59. Global assessment by caregiver

Baseline	
N	68
No disability: n (%)	0 (0.0%)
Mild disability: n (%)	2 (2.9%)
Moderate disability: n (%)	15 (22.1%)
Marked disability: n (%)	32 (47.1%)
Severe disability: n (%)	19 (27.9%)
Day 180	
N	66
No disability: n (%)	21 (31.8%)
Mild disability: n (%)	26 (39.4%)
Moderate disability: n (%)	11 (16.7%)
Marked disability: n (%)	6 (9.1%)
Severe disability: n (%)	2 (3.0%)
Day 365	
N	70
No disability: n (%)	25 (35.7%)
Mild disability: n (%)	28 (40.0%)
Moderate disability: n (%)	11 (15.7%)
Marked disability: n (%)	4 (5.7%)
Severe disability: n (%)	2 (2.9%)

Table 60. Global assessment by patient

Baseline	
N	123
No disability: n (%)	2 (1.6%)
Mild disability: n (%)	3 (2.4%)
Moderate disability: n (%)	27 (22.0%)
Marked disability: n (%)	59 (48.0%)
Severe disability: n (%)	32 (26.0%)

Table 60. Global assessment by patient

Day 180	
N	118
No disability: n (%)	35 (29.7%)
Mild disability: n (%)	50 (42.4%)
Moderate disability: n (%)	21 (17.8%)
Marked disability: n (%)	11 (9.3%)
Severe disability: n (%)	1 (0.9%)
Day 365	
N	110
No disability: n (%)	38 (34.6%)
Mild disability: n (%)	45 (40.9%)
Moderate disability: n (%)	20 (18.2%)
Marked disability: n (%)	6 (5.5%)
Severe disability: n (%)	1 (0.9%)

Subject's satisfaction with the device was assessed at day 180 and 365 as shown in the following table.

Table 61. Satisfaction with the deep brain stimulation system's functioning and ability to control symptoms

Day 180	
N	118
Very satisfied: n (%)	77 (66.3%)
Satisfied: n (%)	28 (23.7%)
Indifferent: n (%)	4 (3.4%)
Not satisfied: n (%)	5 (4.2%)
Very unsatisfied: n (%)	4 (3.4%)
Day 365	
N	110
Very satisfied: n (%)	76 (69.1%)
Satisfied: n (%)	22 (20.0%)
Indifferent: n (%)	2 (1.8%)
Not satisfied: n (%)	7 (6.4%)
Very unsatisfied: n (%)	3 (2.7%)

Study Limitations

The study has several limitations. With the exception of the primary effectiveness endpoint, the study assessments were performed in an open-label manner. Open-label studies may cause an overestimation of the treatment effect in investigator, caregiver, and subject ratings. The majority of the patients did not use deep brain stimulation as an adjunct to medications to control their tremor. However, over time, adjunct medications may be used which would confound interpretation of the year data. Missing data from the study could also contribute to the uncertainty. However this is minimized because overall the study lost/discontinued less than 10% of the total sample. If missing data did occur during the study, in many cases there was backup data collected. For example, if the blinded reviewer was unable to review the data, the investigator also rated the data during the visit so effectiveness data was able to be captured.

Overall Conclusions from Clinical Data

Parkinson's Disease Study

One hundred thirty-six (136) patients were implanted at 15 U.S. sites. Thirty-six (36, 28.3%) patients experienced a total of 50 serious adverse events during the one-year study. One hundred and seven (107, 78.7%) patients experienced an adverse event during the one-year study. A total of 5 intracranial hemorrhages occurred during this study. Three out of five hemorrhages occurred during microelectrode recording and only one out of five patients experienced long-term effects due to the event. There were also three deaths. The majority of adverse events were reversible and determined by the DSMB to be a combination of stimulation/medication/titrating-related, which were all expected by the nature of how deep brain stimulation is programmed. As the device is programmed, physicians tend to reduce medications which allows for a balance between stimulation and medication to optimize the patients therapy. While this optimizing occurs, the patients tend to need programming or medication adjustments to individualize their therapy.

There were no significant differences between the occurrence of adverse events in the stimulation group compared to the control group between implant and 90 days. In addition, there were no unanticipated adverse device effects.

The primary effectiveness endpoint was met at 90 days with a statistically significant (p=0.003) improvement in “on” time without dyskinesias or with nonbothersome dyskinesias for the stimulation group (4.27 hours of “on” time) compared to the control group (1.77 hours of “on” time).

The secondary analyses supported the primary effectiveness endpoint. The stimulation group demonstrated a 72.3% responder rate and the control group demonstrated a 38.2% responder rate. In addition, stimulation improved Parkinson’s disease symptoms, severity of Parkinson’s disease symptoms, and activities of daily living in the medication off baseline compared to medication off stimulation on condition. However, the improvement was not found when the assessments were performed in the medication on baseline compared to the medication on stimulation on condition. Improvements in Parkinson’s disease symptoms were sustained through one year as measured by the UPDRS components of motor examination and complications in the medication off baseline compared to medication off stimulation on condition. Data suggests that compared to the baseline, there were improvements in quality of life, sleep quality, and sleep disturbances through one year in patients with the stimulation system.

Patient’s global outcome measures were positive after 6 months and 12 months of stimulation with 58.8% and 57.1% respectively, indicating no to mild disability. Patient’s assessments indicated mild to marked improvement over time for up to 83.2% of the patients after stimulation was activated. After one year, 89.6% of the patients noted they were either satisfied or very satisfied with their therapy. Finally, 95% and 96% of patients indicated they would recommend

this deep brain stimulation system to others at 6 months and 12 months, respectively.

The Parkinson's Pivotal Study demonstrated safety and effectiveness for the use of the St. Jude Medical™ deep brain stimulation system for the adjunctive treatment for reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease in patients not adequately controlled by medication.

It is difficult to discern prior to surgery the amount of improvement the patient may experience after deep brain stimulation. The symptom improvement may take time to allow for stimulation parameters to be optimized. Deep brain stimulation does not cure the patient of Parkinson's disease; however, it does help manage motor symptoms such as tremor, rigidity, bradykinesia, and dyskinesia.

Essential Tremor Study

A total of 150 patients with disabling medication-refractory upper extremity essential tremor were enrolled from 12 investigational sites. A total of 127 patients were implanted with the St. Jude Medical™ deep brain stimulation system.

The primary safety endpoint, which was a comparison of the rate of device-related or procedure-related adverse events within 6 months post-implant compared to a historical control rate of 38.1%, was met. In addition, the safety profile through one year was consistent with that of a deep brain stimulation device. No unanticipated adverse event occurred during the study.

The study's primary endpoint was successful, with the stimulation on performing significantly better in postural or kinetic tremor reduction than stimulation off at day 180. In addition, the secondary endpoint of nontarget and bilateral side CRST scores showed tremor reduction at day 180 compared to the baseline.

The CRST also evaluated patients' total motor, handwriting, and pouring score at all visits. Stimulation on performed better in all categories and at all visits than stimulation off.

The QUEST evaluated the quality of life by the subjects across five different domains. The results obtained in this study were better in most of the domains at each time point. Likewise, the SF-36 evaluated the quality of life by the subjects across 11 domains, summarized into a total score as well as the physical and mental component subscores. The mental component score performed better at day 365, and the physical component score performed better at day 90.

Statistically significant results in the primary endpoint demonstrate the effectiveness of the device in treating tremors of the upper extremities in patients with essential tremor. The secondary endpoints are supportive of and provide further evidence of the effectiveness of deep brain stimulation (unilateral or bilateral) placement in the VIM for the treatment of tremors.

It is difficult to discern prior to surgery the amount of improvement the patient may experience after deep brain stimulation. The symptom improvement may take time to allow for stimulation parameters to be optimized. Deep brain stimulation does not cure the patient of the tremor; however, it does help manage the tremors for the patient to lead a more normal life.

Conclusions Drawn from the Studies

The nonclinical laboratory testing performed on the deep brain stimulation leads, extensions, IPG, clinician programmer, patient controller, and accessories demonstrate that the individual components, as well as the combined system, are reliable and that the probable benefits to health from the use of the device outweigh any probable injury or illness from such use. Furthermore, the nonclinical laboratory studies conducted by St. Jude Medical, when considered with the clinical experience, provides assurance that this neurostimulation system is safe and effective when used to treat Parkinson's disease and essential tremor.

Appendix F: Summary of Clinical Effectiveness of GPi Stimulation for Parkinson's Disease

In lieu of providing a clinical data set for Infinity™ DBS System, the sponsor provided a technological comparison (including a comparison of the technology, surgical procedures, and instructions for use) of the Infinity DBS Stimulation System to the Medtronic Activa Parkinson's Control Therapy which was approved under P960009/S007 for GPi stimulation. The purpose of the technological comparison was to establish sufficient similarity of the two DBS devices such that FDA could apply Section 216 of the Food and Drug Modernization Act (FDAMA), i.e., the "six-year rule," to assess the effectiveness profile of Infinity DBS.

According to FDA's "Guidance on Section 216 of the Food and Drug Modernization Act of 1997" available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073709.pdf, FDA may choose to utilize the publicly available detailed SSED of a previously approved device to support approval of a PMA for a new device if the applicant provides "a detailed justification of how the information in the earlier SSED applies to the applicant's device" and if the applicant is able "to describe how the devices are similar enough to allow for the data from the earlier device to apply to the new device."

Technical Comparison

For the purposes of establishing sufficient similarity of Infinity DBS System and the Medtronic Activa Parkinson's Control Therapy, the sponsor provided a technical comparison of the two devices. Deep brain stimulation (DBS) systems work by sending electrical stimulation from an implanted neurostimulator to leads in the brain where the current is dispersed through electrodes into the brain tissue in order to activate neurons in specific brain regions. The clinical response of stimulation varies depending on the brain target and the orientation of the DBS lead within the target. As part of DBS programming, the clinician can adjust the combination of parameters, including amplitude, pulse width, frequency and electrode configuration, to tailor the stimulation field to the needs of each patient. By comparing the Volume of Tissue Activation (VTA) of the Infinity DBS System to the Medtronic Activa Parkinson's Control Therapy, it was determined that the Infinity DBS System stimulates, and thus activates, neurons in the same area of the brain that was shown to be safe and effective for the Medtronic Activa Parkinson's Control Therapy approved in P960009/S007.

VTA modeling was been used to estimate the degree of neuronal activation and by extension the degree of stimulation efficacy (Butson & McIntyre, 2005). The modeled Abbott 8-channel segmented, and 4-channel non-segmented leads were able to achieve a comparable VTA shape when compared the Medtronic lead. In all the modeled scenarios the percent deviation of the VTAs of the Abbott leads from the VTA of the Medtronic lead was between 7.41% (meaning greater coverage for Abbott leads) and -4.26%. The results show that parameters of the Infinity DBS System can be varied to achieve a VTA comparable to that achieved by the Medtronic Activa Parkinson's Control Therapy approved in P960009/S007; the range of deviation is acceptable. These results also demonstrate that a desired VTA can be achieved by adjusting stimulation parameters on any of the three lead models (Abbott 4-channel non-segmented, Abbott 8-channel segmented, Medtronic lead models 3387 and 3389).

The clinical response of stimulation varies depending on the brain target and the orientation of the DBS lead within the target. As part of DBS programming, the clinician can adjust the combination of parameters, including amplitude, pulse width, frequency and electrode configuration, to tailor the stimulation field to the needs of each patient. Parameters can be adjusted to achieve a

desired VTA, with shaping customized on a patient-by-patient basis.

The Infinity DBS System demonstrated the capability to replicate at least the same output as the Medtronic Activa Parkinson's Control Therapy system indicating it can provide comparable efficacy. Though the waveforms of Infinity and Soletra differ in their method of charge balancing, they both have the capability to inhibit and excite action potentials. For parameters that differ between the devices, the Infinity DBS System helps to ensure safety by providing a charge density limit and preventing charge imbalance conditions. The Abbott Medical Parkinson's study of STN stimulation provides further assurance of the safety of the additional parameters provided by the Infinity device. The study was used to support the safety of DBS at therapeutic levels for Parkinson's disease. Although patients in the study were implanted in the STN, both the STN and GPi are grey matter nuclei that can be stimulated to treat some of the symptoms of Parkinson's disease.

The Infinity DBS System and the Medtronic Activa Parkinson's Control Therapy system leads, and extensions are clinically equivalent. Although there are differences in some physical aspects, those differences have been demonstrated not to impact the safe and effective delivery of the stimulation to the targeted location. A comparison of accessories establishes that there are no differences that impact the safety and effectiveness of the respective systems during use for a GPi target location. The instructions for use are equivalent regarding implant procedures, device programming and other instructions for use. The devices also have equivalent labeling for contraindications, warnings, precautions, and adverse events.

Effectiveness Conclusions

The sponsor provided adequate evidence of the sufficient similarity of the Infinity DBS System with regard to its technological characteristics as described in Section IX(B). Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control Therapy approved under P960009/S007 is directly applicable towards establishing reasonable assurance of the effectiveness of the Infinity DBS System for GPi stimulation. As detailed in the SSED for the Medtronic Activa Parkinson's Control Therapy, prospective open-label studies of the Medtronic Activa Parkinson's Control Therapy demonstrated that "On" time improved between pre-implant and 12 months by an average of 6.7 hours for the subset of GPi patients whose data were verified against medical records. Additionally, for the subset of patients with either GPi or STN stimulation whose data were verified against medical records, symptoms of Parkinson's disease (UPDRS Total Motor Examination (TME) scores) improved for 56/117 patients while ON medication and symptoms of Parkinson's disease (UPDRS TME scores) improved for 102/117 patients while OFF medication.

Safety Conclusions

The sponsor performed a prospective, multi-center, randomized, controlled clinical study, which compared patients randomized to receive immediate as compared to delayed stimulation with DBS implanted in the STN which was used to support approval of the Brio Neurostimulation System under P140009. Additional details of these studies are provided in the SSED for P140009 that is available on the CDRH website. The Infinity DBS System was approved under P140009/S001 based on a similarity of technological characteristics to the Brio Neurostimulation System. Although the data were used to support the safety of DBS at the STN, findings have applicability to the safety of stimulation at the GPi because of similarity of the technological characteristics. Location of the stimulation is different, but stimulation-related adverse effects can be resolved at either of the grey matter locations by adjustments to stimulation parameters.

In P140009, the risks of the device for Parkinson's disease were based on a comparison of the adverse events during the randomized phase and long-term follow-up. There were no significant differences between the occurrence of adverse events in the Stimulation Group compared to the

Control Group between implant and 90 days. Thirty-six patients (36, 28.3%) experienced a total of 50 serious adverse events during the one-year study, and one hundred and seven patients (107, 78.7%) patients experienced at least one adverse event. A total of five intracranial hemorrhages occurred during this study. Three out of five hemorrhages occurred during microelectrode recording and only one out of five patients experienced long-term effects due to the event. There were also three deaths. The cause of these deaths were unrelated to the device and included sepsis secondary to UTI, cancer and multiple infections which started with osteomyelitis of the big toe. There were no unanticipated adverse device effects.

The sponsor also provided adequate evidence of the sufficient similarity of the Infinity DBS System with regard to its technological characteristics. Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control Therapy approved under P960009/S007 is directly applicable towards establishing reasonable assurance of the safety of the Infinity DBS System for GPi stimulation.

As detailed in the SSED for the Medtronic Activa Parkinson's Control Therapy, all 160 enrolled patients (both the STN and GPi) were evaluated for the occurrence of adverse events. One or more adverse events occurred in one hundred and fifty-four enrolled patients (154/160, 96.3%). Table 3 of the SSED lists adverse events for all patients reported during the clinical investigation by major category and subcategories. Over the entire study duration, 12/160 patients (7.5%) had intracranial hemorrhage; 17/160 patients (10.6%) had device-related infection; 16 patients (10.0%) had paresis/asthenia; and 13/160 patients (8.1%) had hemiplegia/hemiparesis. In addition to the adverse events collected through the 12 months of study follow-up, the sponsor has provided adverse event information for 100 patients at 2 years (60 STN and 40 GPi), 82 patients at 3 years (47 STN and 35 GPi), 38 patients at 4 years (17 STN and 21 GPi), and 16 patients at 5 years (4 STN and 12 GPi). FDA review of the safety data concluded that the probable benefits to health outweigh the probable risks.

Overall Conclusions

The data provided and its applicability to the Infinity DBS System support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With regard to reasonable assurance of the effectiveness of the Infinity DBS System, the sponsor provided adequate evidence of the sufficient similarity of technological characteristics of the Infinity DBS System and the Medtronic Activa Parkinson's Control Therapy. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control Therapy is directly applicable towards establishing reasonable assurance of the effectiveness of the Infinity DBS System for GPi stimulation.

With regard to reasonable assurance of the safety of the Infinity DBS System, the sponsor also provided adequate evidence of the sufficient similarity Abbott Medical Brio Neurostimulation System approved under P140009. Although the data were used to support the safety of DBS at the STN, this data have applicability to the safety of stimulation at the GPi because of similarity of the technological characteristics, although the location of the stimulation is different. The sponsor also provided adequate evidence of the sufficient similarity of the Infinity DBS System and the Medtronic Activa Parkinson's Control Therapy with regard to technological characteristics. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control Therapy is directly applicable towards establishing reasonable assurance of the safety of the Infinity DBS System for GPi stimulation.

In conclusion, given the available information identified above and its applicability to the Infinity DBS System, the data support that for the requested indications for use, the probable benefits for the Infinity DBS System outweigh its probable risks

Appendix G: Symbols and Definitions

The following symbols may be used in this document and on some of the products and packaging:

Table 62. Symbols and definitions

Symbol	Definition
	Caution, consult accompanying documents
	Consult instructions for use
	Follow instructions for use on this website
	Magnetic Resonance (MR) Unsafe, an item poses unacceptable risks to the patient, medical staff, or other persons within an MR environment
	Device contains a radio-frequency (RF) transmitter, which may cause RF interference with other devices near this device.
	Single use only
	Do not resterilize
	Expiration date
	Date of manufacture
	Manufacturing facility
	Temperature limits for storage conditions
	Humidity limits
	Pressure limits
	Do not use if the product sterilization barrier or its packaging is compromised
	Catalog number

Table 62. Symbols and definitions

Symbol	Definition
	Manufacturer
	Contents quantity
	Pulse generator
	Accessories
	Serial number
	Batch code
	Prescription use only
	Ethylene oxide gas sterilization
	Authorized European representative
	European conformity, affixed according to the relevant provisions of AIMD directive 90/385/EEC and RE directive 2014/53/EU Annex II. Hereby, St. Jude Medical declares that this device complies with the essential requirements and other relevant provisions of these directives. The full text of the European Union RE directive 2014/53/EU declaration of conformity is available at the following internet address: www.sjmglobal.com/euconformity.
	Australian Communications and Media Authority (ACMA) and New Zealand Radio Spectrum Management (RSM) Regulatory Compliance Mark (RCM)
	This equipment is certified for type certification pursuant of Article 38-24 of the Japan Radio Law

St. Jude Medical
6901 Preston Road
Plano, Texas 75024 USA
+1 855 478 5833
+1 651 756 5833

St. Jude Medical
Coordination Center BVBA
The Corporate Village
Da Vincilaan 11 Box F1
1935 Zaventem
Belgium
+32 2 774 68 11

sjm.com

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