SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name:	Stimulator, Electrical, Implanted, For Parkinsonian Tremor
Device trade name:	Brio Neurostimulation System
Device Procode:	MHY
Applicant's name and address:	St. Jude Medical 6901 Preston Road Plano, Texas, 75024
Date of Panel recommendation:	None
Premarket Approval Application (PMA) Number:	P140009
Date of FDA notice of approval:	June 12, 2015

II. INDICATIONS FOR USE

The St. Jude Medical (SJM) Deep Brain Stimulation (DBS) system is indicated for the following conditions:

- Bilateral stimulation of the subthalamic nucleus (STN) 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.

III. CONTRAINDICATIONS

This system is contraindicated for patients who:

- are unable to operate the system.
- test stimulation is unsuccessful

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)

IV. WARNINGS AND PRECAUTIONS

Please refer to the device labeling for a list of warnings and precautions.

V. DEVICE DESCRIPTION

The St. Jude Medical Brio Neurostimulation System consists of:

1. A 16-channel, rechargeable, implantable pulse generator (IPG) (Brio IPG, Model 6789);
2. A patient programmer (Brio Patient Programmer, Model 6860);
3. An external charging system (Brio LE Charger, Model 6722); and
4. A lead kit (Models 6142, 6143, 6144, 6145, 6146, 6147, 6148, 6149) and extension kit (Models 6345 and 6346).

The Brio Neurostimulation System is a rechargeable system designed to deliver low-intensity electrical pulses to nerve/tissue in various combinations of amplitude, pulse width, and frequency. The electrical pulses travel from an IPG, through the leads and extensions, to electrodes near selected brain targets in order to provide therapeutic stimulation. The IPG is powered by a hermetically sealed battery within a titanium case. It uses microelectronic circuitry to generate constant current electrical stimulation.

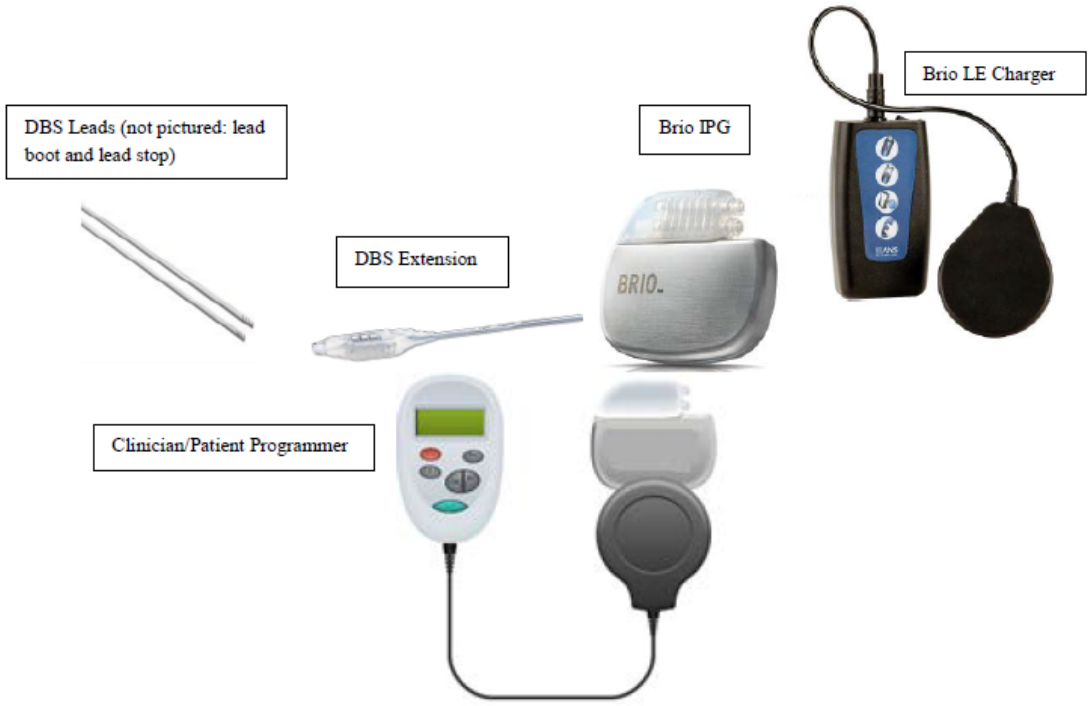


Figure 1: The Brio Deep Brain NeuroStimulation System

A. Implanted Components

- Brio IPG, Model 6789
  The Brio IPG Model 6789 is a programmable, 16 channel, rechargeable device that allows the connection of one or two leads with four electrodes. It is powered by a hermetically sealed battery within a titanium case. It uses microelectronic circuitry to generate constant current electrical stimulation. The Brio IPG is implanted in a subcutaneous pocket and receives near field telemetry communication via a wand connected to an external patient programmer. The Brio IPG stores programmed

information and delivers stimulation pulses to a selected combination of output electrodes on the connected lead. The stimulation output parameters are listed in Table 1 below:

Number of Programs	1
Number of Channels	16
Waveform	Charge Balanced Biphasic
Pulse Shape	Rectangular
Current or Voltage Regulated	Current
Maximum Current Amplitude @ 500 Ω	12.75mA
Maximum Output Voltage @ 500 Ω	< 6.5V
Pulse Width	50-500µS , 12.5µS steps
Frequency	2-240Hz, 2Hz steps
Current Path Options	Unipolar or bipolar

Table 1: Stimulation Output Parameters

- DBS Leads, Model 6142, 6143, 6144, 6145, 6146, 6147, 6148, 6149
  The DBS leads deliver electrical pulses to specific targets within the human brain. A DBS lead is comprised of four stimulating electrodes at its proximal end with edge-to-edge spacing defined to stimulate specific targets in the brain. Stranded conductor wires carry the current from the terminal end contacts to the stimulating electrodes. The conductor wires are further insulated and housed within a flexible sheath known as the lead body. The distal end of the lead contains 4 contacts that connect into the 4-channel extension.

	DBS Leads
Lead Length (cm)	25, 30, 35, 40
Lead Diameter (mm)	1.4
Number of Electrodes	4
Electrode Material	90% Platinum/ 10% Iridium
Electrode Spacing (edge-to-edge) (mm)	0.5 and 1.5
Array Length (mm)	6.5 or 10.5
Electrode Surface Area (mm^2)	2.1
Impedance (Ω)	15.15 (average)

Table 2: DBS Lead Specifications.

- DBS Extensions, Model 6345, 6346
  The DBS extension physically and electrically connects the lead to the IPG and delivers electrical pulses from the IPG to the implanted lead. A typical DBS extension is comprised of contact electrodes at one end (distal end) and a connector assembly at the proximal end. The electrodes at the distal end are defined with edge-to-edge spacing to mate with electrical contacts of the DBS IPG header. Stranded conductor wires carry the current from the IPG to the lead. The conductor wires are further insulated and housed within a flexible sheath known as the lead body.

B. External Components

- Brio LE Charger, Model 6722
  The battery charging system provides the capability to recharge the IPG battery while stimulation is either on or off. The charging system contains the following parts: AC line

cord, AC power supply, power cable, charger, and charger antenna. The chargers transmit RF energy through the charger antenna to the IPG battery to recharge it.

- Brio Patient Programmer, Model 6860
  The Brio Patient Programmer controls the creation and adjustment of all programming parameters for the Brio IPG. It is powered by three AAA batteries and communicates through the use of radio frequency signals from the programming wand to the implanted IPG. The programmer enables clinicians to create and modify programs for the IPG. It allows the patient the ability to adjust amplitude settings and turn the stimulation on and off. The shelf life of the patient programmer is 2 years.

Additionally the Brio Neurostimulation System includes the following accessories:

- A pocket sizer (used to check the IPG implant pocket);
- A torque wrench (used to tighten the setscrew on the connector assemblies of the IPG and extension) (Model 1101);
- Port plugs (used with the IPG to occupy unused lead ports in the header) (Model 1111);
- Lead stop (used to attach to the lead at a desired distance from the tip of the lead and set the depth of the implant) (Model 1140);
- Lead protection boot (protects the terminal end of the lead until the extension is attached) (Model 1149);
- Lead Stylet (Models 1143 and 1144);
- AAA battery pack (used to power the Patient Programmer) (Model 1254);
- Charger Accessory (Model 6720);
- AC power adapter and AC line cord (Models 3713 and 3714);
- Charger Antenna (Model 3717 and 3718);
- Programming Wand (used to program the IPG with stimulation parameters) (Model 1232); and
- Magnet (used turn on and off the IPG when the programming system is unavailable) (Model 1210).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is no cure for Parkinson's disease (PD) and essential tremor (ET). Therefore, the first-line therapy treatment is medication. The standard medical therapy for PD is levodopa combined with a peripheral decarboxylase inhibitor, such as carbidopa. Other medical therapy may be used as an adjunct to levodopa to treat the multiple symptoms of PD. In patients with ET, both primidone and propranolol reduce the magnitude of upper extremity and postural tremor. Levodopa, anticholinergic medications, dopamine agonists, and beta -blockers such as propranolol are effective drugs for rest tremor. However, these medications come with a variety of side effects. For example, chronic levodopa use can result in disabling motor fluctuations that further impair the patient's ability to function.

Surgical treatments are also available to PD and ET patients. Neurosurgical ablative procedures for the treatment of PD and ET are pallidotomy and thalamotomy. However, there is a risk of permanent neurological damage associated with the irreversible damage caused by these ablation procedures. The most disabling, permanent neurological complications reported include hemiparesis, dysarthria and dysphagia, and cognitive impairment.

Other Deep Brain Stimulation Devices are also currently marketed in the United States, these include: Activa® PC, Activa® RC, and Activa® SC Deep Brain Neurostimulation Systems.

VII. MARKETING HISTORY

The Brio Neurostimulation System including:

- Brio Implantable Pulse Generator (Model 6789);
- Brio Patient Programmer (Model 6860); and
- Brio LE Charger (Model 6722)

has not been marketed in any other country to date. However, the DBS Leads (Models 6142, 6143, 6144, 6145, 6146, 6147, 6148, 6149) and Extensions (Models 6345 and 6346) are CE marked and marketed in Europe since August 2008 for use in the indication of Parkinson's Disease. Additionally, there is a version of the Brio IPG (Model 6788), and a Brio Patient Programmer (Model 6856) and Brio Clinician Programmer (Model 6851) that are CE marked and marketed in Europe.

VIII. POTENTIAL ADVERSE DEVICE EFFECTS ON HEALTH

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 and/or cerebrospinal fluid abnormality; brain contusion; infection and/or inflammation; antibiotic anaphylaxis; skin disorder; edema; persistent pain at surgery site and/or IPG site; erosion; brachial plexus injury (nerves to chest, shoulder and arm); postoperative pain, stress, or discomfort; neuropathy (nerve degeneration); hemiparesis (muscular weakness or partial paralysis on one side of body); 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 possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture
    - Loss of therapeutic benefit as a result of change in electrode positions, loose electrical connections or lead/extension fracture
    - Initial jolt or tingling during stimulation/Jolting or shocking sensation
    - 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 pulse generator (IPG)
- Allergic or rejection response to implanted materials
- Persistent pain, tightness, or redness at the incision sites or general pain
- General erosion or local skin erosion over the pulse generator (IPG) or other device component
- Persistent pain, tightness or discomfort around the implanted parts (e.g., along the extension path in the neck)
- Impaired wound healing (e.g., incision site drainage) 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
- Rigidity (stiffness or inflexibility)
- Dyskinesia (fragmented or jerky movements)
- Worsening of motor fluctuations
- Tremor
- Abnormal gaitor incoordination
- Akinesia (absence of movement or freezing up)
- Bradykinesia (abnormally slow movement)
- Dysphagia (difficulty swallowing)
- Myoclonus (twitching or spasm of muscles)
- Neuropathy
- Neuralgia (acute nerve pain)
- Paresis (slight or partial paralysis)
- Hemiplegia (paralysis affecting one side of the body)
- Asthenia (lack or loss of strength)
- Ataxia (inability to coordinate voluntary muscular movements)
- Dystonia (involuntary distortions of trunk and limbs)
- Restless leg syndrome
- Disequilibrium
- Postural instability and/or increase in falls
- Headache
- Hearing and/or visual disturbances, including double vision, and loss or impairment of eye coordination
- Blepharospasm (involuntary eye winking)
- Eye apraxia (difficulty moving eye)
- Sensory deficit, including impairment of sensitivity/touch
- Supranuclear gaze palsy (gradual deterioration & death of selected brain areas)
- Cognitive impairment, including confusion, disorientation, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions, dementia or inability to act or make decisions
- Long term memory impairment
- Attention deficit
- Aphasia or dysphagia (loss or impairment of power to use or comprehend words)
- Dysarthria (difficulty articulating words)
- Hypophonia (weak voice)
- Drowsiness and/or increased sleepiness
- Sleep disturbance

- Psychiatric disturbances and/or mood changes
- Apathy (lack of feeling or emotion)
- Psychic akinesia (extreme passivity, apathy, & loss of self-motivation)
- Anxiety
- Irritability and/or fatigue
- Mania or hypomania (mild state of mania)
- Psychosis (defective or loss of reality)
- Aggression
- Emotional lability (involuntary laughing or crying)
- Depression or depression with suicide attempt
- Hypersexuality or increased libido
- Nausea and/or vomiting
- Sweating
- Sialorrhea (increased salivation)
- Respiratory distress (e.g., difficulty breathing)
- Decreased therapeutic response
- Urinary incontinence or retention
- GI changes (e.g. Diarrhea, Constipation, Nausea or vomiting)
- Weight changes (loss or gain)
- Cardiac dysfunction (e.g. Hypotension, hypertension, heart rate changes, or syncope)
- Fever
- Hiccups
- Cough
- Cramps
- Worsening existing medical conditions

IX. SUMMARY OF PRE-CLINICAL STUDIES

Verification testing was conducted to provide data to support the intended use of the device system. Testing was largely based on commonly recognized test methods and standards, such as International Standards Organization (ISO), European Standards (EN), and American Society of Testing and Materials (ASTM). All tests successfully met acceptance criteria per requirements.

A. Brio IPG

Test	Test Purpose	Acceptance Criteria
Electrical/ Leakage Current Verification and DC Imbalance	Verifies the magnitude of leakage currents and DC imbalance of the outputs of the IPG are within an acceptable range per ISO 14708-1: 2000	• The IPG outputs are electrically isolated to meet section 16.2 of EN 45502-1/ISO 14708-1 • The IPG stimulation outputs are DC balanced to meet section 3.2.3 of NS14
Electrical/ Output Characterization	Verify proper output (amplitude, pulse width, frequency, etc.) and detection parameters of the IPG function are within specified tolerances	The IPG stimulation output parameters: amplitude, pulse width, and frequency are within the specified tolerances across specified temperature and loading levels.
Electrical/Hardware Characterization	Verifies the proper functioning of the IPG Hardware. Hardware Verification testing is intended to verify that requirements related to the Brio IPG circuitry have been met.	Internal IPG circuits function within their specified limits.

Test	Test Purpose	Acceptance Criteria
Mechanical/ Hardware Verification	Verifies the mechanical testing of the Brio IPG. Testing included: • Test 1 Weight • Test 2 Operational Temperature/ Implantation Environment • Test 3 Drop Test • Test 4 Vibration Test • Test 5 Operating Pressure • Test 6 Heat Generation During Use • Test 7 Ultrasound • Test 8 Radiopaque Identification • Test 9 Connection retention Force • Test 10 Silicone Header adhesion to titanium. • Test 11 Temperature Shock	Testing demonstrated that all acceptance criteria was met.
Mechanical/ Hermeticity	Verifies Neurostimulator hermetic seal	Testing demonstrates that the hermetic seal has a leak rate no greater than 5 X 10^{-8} cc atm/sec during Helium Leak Testing
Electrical/Battery	• Battery Capacity Verification (Longevity). • Battery Qualification Testing under normal and sever conditions • Charge/Discharge Testing • Transportation Testing	• The IPG battery provides the specified time between the stimulation shutdown voltage and EOL voltage. • The IPG battery meets the specified shelf life. • The IPG battery meets the applicable sections of UN Transport of Dangerous Goods testing ST/SG/AC.10/11
Particulate Matter	Verify there is no unacceptable release of particulate matter when the device is used as intended	Per ISO 14708-3:2008
Firmware/System Verification Testing	• Patient Programmer Functional Verification • Program Creation, Selection, modification • IPG and Patient Programmer Error Notification and Handling • Stimulation Parameter Adjustment • Magnet Use • Stimulation Frequency Limitation • Pulse Width Limitation • Electrode Testing • Program Ramp and Ramp Time • Output Amplitude Testingprevent Stimulation Amplitude exceeding NS14 limitations	All tests successfully met acceptance criteria per requirements, including: • Programs successfully created by the programmer and saved to the generator. • Program data successfully created and changed. Different programs function as the active program. • Unsuccessful communication reports an error. • System inter-stim set Frequency is within tolerance. • Magnet turns stimulation on and off. • Stimulation frequency, pulse width, and amplitude limits are met per ANSI/AAMI NS 14 • Each electrode functioned as either an anode, cathode, or off. • System completed ramping within specification.
Firmware/ Communication Testing	• Patient Programmer and IPG Connection Testing • IPG Device Information Testing • Patient Programmer Host Control Mode • Patient Programmer Cycle and Bolus Mode	All tests successfully met acceptance criteria per requirements, including: • Programmer sends wake-up command to the generator. ACK received from the generator following a wake-up command upon power up. • Programmer displays IPG model number,

Test	Test Purpose	Acceptance Criteria
	• Bolus Lockout • IPG Functional Testing	serial number, hardware version, software version, and battery activation date. • Programs successfully written to the generator by the Rapid Programmer. • Cycle-On and Cycle- off times for a Cycle Mode Program can be programmed successfully. • No amplitude adjustment when IPG in bolus lockout. • Generator cycles amplitude on and off for a cycle program. Amplitude remains on for a continuous program.
Firmware/Battery Function and Charging Testing	• Battery Capacity Testing • ERI Accuracy Testing • Low Battery State Testing • Over Charging Prevention • Communication and Charging Zone Testing • Battery Charging • Battery Indicator TestingEOL State Testing	All tests successfully met acceptance criteria per requirements, including: • meet or exceed the battery capacity and longevity requirements; • The ERI time period is within the required accuracy limits of 10 years • The system notifies the user that the IPG requires a recharge; • System prevents charging when certain limits are reached; • The CHGR and IPG communicate throughout the Effective Charging Zone • The CHGR batteries have sufficient capacity to provide at least one full charge to the IPG battery • The system visually and audibly indicates an IPG charging error and turns off IPG charging • IPG battery enters the EOL state and prevents charging when the voltage reaches limit

Table 3: Brio IPG Verification Testing

B. Brio Patient Programmer

Test	Test Purpose	Acceptance Criteria
Patient Usability Validation	Validates the intended user population can effectively use the Brio Patient Programmer System	All tests successfully met acceptance criteria per requirements. Users completed the relevant tasks successfully, including regulating stimulation and checking IPG battery status.
Clinician Usability Validation	Validates that the intended user population (clinicians) can effectively use the Brio Patient Programmer System	All tests successfully met acceptance criteria per requirements. Users completed the relevant tasks successfully, including establishing communication with IPG, configuring leads and stimulation, reviewing and clearing charge density limit warning and checking impedance and battery status.
System Verification	Verifies that the Brio Patient Programmer complies with product requirements regarding • IPG functions • Programmer functions • Indicators • Error Handling • Stimulation Settings • Electrode Settings • Program Modes • Program Management	All tests successfully met acceptance criteria per requirements, including: • IPG Battery voltage level displayed appropriately. • Successful adjustment of amplitude and turning stimulation on or off. • Continuous charge limit indictor displays appropriately. • Attempted communication with an unsupported device reports an error. • Successful setting of frequency, pulse

Test	Test Purpose	Acceptance Criteria
	• Limits	width, and amplitude. • Successful setting of anode, cathode, or off for all electrodes. • Successful setting of magnet and stimulation mode. • Successful modification and display of saved programs. • Charge Limit warning message displayed appropriately.
Software Verification	Verifies functionality of the Patient Programmer Software, Patient Programmer Power On Self Test (POST) firmware including: • Hardware Diagnostic Error Handling • Memory Diagnostic Error Handling • Software Diagnostic Error Handling • Error Reporting	All tests successfully met acceptance criteria per requirements , including: • Successful completion of POST when no errors present. • Simulated Hardware errors generated and reported the expected diagnostic error codes. • Simulated Memory errors generated and reported the expected diagnostic error codes. • Simulated Software errors generated and reported the expected diagnostic error codes.
Mechanical Testing	Verifies that the Programmer and Wand meet requirements of EN45502-1 and EN60601-1 standards.	All tests successfully met acceptance criteria per requirements.

Table 4: Brio Patient Programmer Verification Testing

C. Brio LE Charger

Test	Test Purpose	Acceptance Criteria
Patient Usability Validation	Validates the intended user population can effectively use the Brio LE Charger.	All tests successfully met acceptance criteria per requirements. Users completed the relevant tasks successfully, including reviewing labeling, connecting system components, charging the IPG and charging the charger.
IPG Temperature During Charging	To verifiy that the outer surface of the IPG will not exceed specific temperature and exposure times during normal operation.	All tests successfully met acceptance criteria per requirements, including • IPG surface temperatures meet section 17 of ISO 14708-3
Effective Charging Zone Testing	To verify proper communication within the effective charging zone.	All tests successfully met acceptance criteria per requirements, including: • The charger and IPG communicate / charge throughout the effective charging zone defined in an internal SJM diagram.
Indicator Testing	To verify that all visual and audible indicators function as expected during power up and to verify that charging and reduced charging indicators are activated according to specification.	All tests successfully met acceptance criteria per requirements, including: • Charger indicates the "charging" and "reduced charging" states within the specified times.
Overcharging	To verify proper functioning of indicators which notify user of a fully charged battery and the cessation of charging at this point.	All tests successfully met acceptance criteria per requirements, including: • Charger turns off charging energy and gives a user indication when the IPG battery is fully charged.
Charging Current Limit	To verify that the Brio LE Charger shall limit the charging current	All tests successfully met acceptance criteria per requirements, including:

Test	Test Purpose	Acceptance Criteria
		• The IPG regulates its battery charging current to the specified level.
EOL State Verification	To verifiy functionality of the LE Charging System to recognize IPG EOL state and to prevent charging in this state.	All tests successfully met acceptance criteria per requirements, including: • The IPG battery enters the "EOL" state at a the specified voltage. • The IPG prevents charging when in the "EOL" state.
IPG Battery Overcharge Protection	To verify that Brio LE Charging System will prevent overcharging of the IPG Battery.	All tests successfully met acceptance criteria per requirements, including: • The IPG prevents charging of its battery above the specified voltage.
Electrical Safety Testing	To verify conformance to IEC 60601-1, CSA C22.2 No.601.1, and UL60601-1	All tests successfully met acceptance criteria per requirements, including: • The charger meets the applicable sections of IEC 60601-1, CSA C22.2 No.601.1 and UL60601-1.

Table 5: Brio LE Charger Verification Testing

D. DBS Leads and Extensions

Test	Test Purpose	Acceptance Criteria
Mechanical Verfication	To verify the following: • Use with various Brio System surgical accessories • Stylet Extraction • Lead Stop • Cannula Insertion • Lead trajectory • Electrical testing	All tests successfully met acceptance criteria per requirements, including: • Lead does not deviate from intended target. • Stylet removal below specification • No damage to lead after five insertion and removal cycles of the stylet. • Lead stop supports weight of lead • No damage to lead after five actuations of lead stop • Lead shall pass through insertion cannula without buckling • No damage to lead after 5 pass-through cycles of the cannula. • Lead remains within electrical specifications on drawing throughout testing.
Lead and Extension Flex Testing	To verifiy that the DBS Leads and Extensions conductors do not fatigue under flexural stressors.	All tests successfully met acceptance criteria per requirements, including: • Lead/Extension able to be coiled • Dry conductor resistance and leakage current specifications after flex testing • No damage to lead after flex cycling • No damage to extension after flex cycling
Lead and Extension Visibility Testing	To verify the visibility of the DBS leads and Extensions under x-ray/fluoroscopy	All tests successfully met acceptance criteria per requirements, including: • Visible when using x-ray fluoroscopy equipment. • When placed on a standard blue surgical drape and viewed at 18" under normal lighting conditions
Connector Assembly Lead Insertion/Extraction Force Testing	To verify insertion/extraction into boot and extension does not damage lead or extension.	All tests successfully met acceptance criteria per requirements, including: • Lead inserts into boot without buckling. • No damage to lead after five insertion and removal cycles into the lead boot. • Lead inserts into extension without buckling • No damage to lead or extension after five

Test	Test Purpose	Acceptance Criteria
		insertion and removal cycles.
Connector Assembly Lead Fixation Testing	To verify connector lead fixation force.	All tests successfully met acceptance criteria per requirements, including: • Lead withstands tensile load and remains within electrical specifications. • Extension connector assembly must retain lead when exposed to a load and remain within electrical specifications.
Particulate Matter Testing	To verify that no unacceptable release of particulate matter when the lead is used as intended.	All tests successfully met acceptance criteria per requirements per ISO 14708-3 section 14.2.

Table 6: DBS Leads and Extension Verification Testing

E. Biocompatiblity Testing

Biocompatibility of all patient-contacting components of the Brio Neurostimulation System was evaluated in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. The Brio IPG, DBS Leads and Lead Extensions are considered permanent (> 30 days) implants with tissue/bone contact. Biocompatibility of the Brio IPG was demonstrated by leveraging testing previously conducted on the Eon Mini IPG (P010032/S023 and P010032/S066). Leveraging this testing information was appropriate because the Brio IPG is identical to the Eon Mini IPG in terms of the patient-contacting materials, manufacturing and sterilization processes. Biocompatibility testing was conducted on the Brio DBS Lead and the Lead extension and is summarized in Table 7 below. All biocompatibility studies were conducted on the finished, sterilized devices in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. All pre-specified test acceptance criteria were met and all tests passed. The Brio Neurostimulation System also contains other implantable component with prolonged (24 hours – 30 days) tissue/bone contact and the components with limited (≤ 24 hours) skin contact. These components are either the identical components used for the Eon Mini System or use the same materials used for the permanently implantable components of the Brio Neurostimulation System.

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
DBS Lead and Lead Extension[a]			
Cytotoxicity (ISO 10993-5)	ISO MEM Elution Assay	Reactivity grade is not greater than mild reactivity (Grade 2)	PASS
Sensitization (ISO 10993-10)	ISO Guinea Pig Maximization Sensitization Test	Grades of <1 in the test group provided grades of < 1 are observed on the control animals. (If grades of ≥ 1 are noted on the control animals, then the reactions of the test animals which exceed most severe control reaction are presumed to be due to sensitization).	PASS
Irritation/Intracutaneous Reactivity (ISO 10993-10)	ISO Intracutaneous Reactivity Test	The difference between the test article and the control mean score is ≤ 1.0.	PASS
DBS Lead			
Systemic Toxicity (ISO 10993-11)	ISO Acute Systemic Toxicity Test	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	PASS
	Materials Mediated Rabbit Pyrogen Test	No rabbit shows an individual rise in temperature of 0.5°C or more above the baseline temperature.	PASS
Genotoxicity (ISO 10993-3)	Bacterial Mutagenicity Reverse Mutation Assay	There is less than 2-fold increase in the number of revertants when compared to the	PASS

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
	(Ames Test)	solvent controls in strains TA98, TA100, and WP2uvrA and less than 3-fold increase in the number of revertants when compared to the solvent control in strains TA1535 and TA1537.	
	Mouse Lymphoma Assay	The test article produces fewer than 90 mutants per 10^6 clonable cells over the background level.	PASS
	In Vivo Mouse Bone Marrow Micronucleus Assay	There is no statistically significant increase in the number of micronucleated polychromatic erythrocytes (PCEs) in the test group as compared to the concurrent negative control.	PASS
Implantation (ISO 10993-6)	13-Week Rabbit Subcutaneous Implantation Test	The test results are considered acceptable based on an overall interpretation of the degree of biocompatibility exhibited by the test article based on gross and microscopic analysis comparing test to control article (High density polyethylene), as well as clinical observations.	PASS
Combined Neuroimplantation/Chronic Toxicity Study (ISO 10993-6 and ISO 10993-11)	A 26-week intrathalamic implantation study was conducted in rats to assess potential neurotoxicity, local tissue responses as well as long-term systemic effects following implantation of the device. Implantation of the DBS lead was not found to produce any unexpected mortality, clinical observations, neurobehavioral deficits or changes in clinical pathology. Treatment-related microscopic changes observed in the brain occurred at a similar incidence and severity in animals of both sexes that received the DBS lead when compared to the animals that received the control device. The functional observational parameters and other clinical parameters were unaffected.		
Carcinogenicity (ISO 10993-3)	Adequately assessed by chemical characterization and genotoxicity testing on the final device and referencing data in a device master file		

[a] The testing performed on the DBS Lead, the data in the device master file, and the biocompatibility data on an U.S. marketed device were leveraged for assessment of acute systemic toxicity, subchronic toxicity, genotoxicity, implantation, chronic toxicity, and carcinogenicity potential of the lead extension.

Table 7: Biocompatibility Test Data on the Brio DBS Lead and Lead Extension

F. Sterilization

The Brio Neurostimulation System components that are provided sterile are terminally sterilized using a 100% ethylene oxide (EO) sterilization cycle. Validation of the sterilization process demonstrates a Sterility Assurance Level (SAL) of 10^{-6} and is in compliance with ANSI/AAMI/ISO 11135-1:2007. *Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices*. Sterilant residuals conform to the maximum allowable limits of EO) and Ethylene Chlorohydrin (ECH) residuals specified in ISO 10993-7: 2008. *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*. The product bacterial endotoxin limits for intrathecal devices was selected as 0.06 EU/mL or not more than 2.15 EU/device and device implant limits were tested at 20 EU/device. These limits were verified using Limulus Amebocye Lysate (LAL) testing.

G. Packaging and Shelf Life

Distribution Test was completed for the DBS Leads, DBS Extensions, IPG, Charger, Charger Accessories and Patient Programmer in accordance with ASTM D4169:2009. All acceptance criteria were met. The testing confirmed that the device packaging adequately protects the product during conditions that may be encountered during storage, shipping, and handling. The packaging design and testing of the packaging for the IPG, DBS Leads, and DBS Extensions complies with the requirements of BS EN ISO 11607-1:2009.

Shelf Life for the IPG, Leads and Extensions has been established as two (2) years from the date of manufacturing.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of the safety and effectiveness of deep brain stimulation (DBS) with the Libra device for the treatment of tremor due to essential tremor and as an adjunctive treatment for reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication in patients with Parkinson's disease in the US under IDE # G040051 and G040172 respectively. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
Pivotal (Parkinson's disease) G040172	Prospective, multi-center, randomized, controlled clinical study	Demonstrate the safety and effectiveness of the SJM Deep Brain Stimulation System providing bilateral stimulation to the Subthalamic Nucleus (STN) as an adjunctive treatment for reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication	15	136 subjects implanted/1 subject did not complete the study
Pivotal (Essential Tremor) G040051	Prospective, multi-centered clinical study	Demonstrate the safety and effectiveness of the SJM Deep Brain Stimulation System providing unilateral or bilateral stimulation to the ventral intermediate (VIM) nucleus of the thalamus implanted for the treatment of tremor due to essential tremor.	12	127 subjects implanted/ 11 subjects did not complete the study

Table 8: Description of Supporting Clinical Studies

X.1 Parkinson's Disease Study:

A. Parkinson's Disease Study Design

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

The study was a prospective, multi-center, 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 dayss. After 90 days, all patients received stimulation . Patients were followed for one year. After one year, patients were consented to the Long Term Follow-Up Study where they continued follow-up for a total duration of 5 years post-implant.

The study was not blinded, i.e. both investigators and patients were aware of the treatment assignment. DBS was used as an adjunct to anti-Parkinsonian 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 entire study duration. The DSMB was designed to alert the Sponsor of any safety concerns or study execution concerns.

B. Parkinson's Disease Study Clinical Inclusion and Exclusion Criteria

Enrollment in the PD study was limited to patients who met the following selection criteria:

Inclusion Criteria

1. Patient signed an informed consent;
2. Patient was 18 to 80 years of age;
3. Patient diagnosed with Parkinson's disease for at least five (5) years according to standard practice;
4. 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 (PD) during waking hours;
5. 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;
6. Patient was willing to maintain a constant dose of anti-Parkinson's disease medication indicated as best medical management for at least one month prior to study enrollment;
7. Patients were available for appropriate follow-up times for the length of the study; and
8. Patients 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

1. Patient was not a surgical candidate;
2. Patient had any major illness or medical condition that in the opinion of the physician would interfere with participation in the study;
3. Patient had untreated clinically significant depression;
4. Patient had an electrical or electromagnetic implant (e.g. cochlear prosthesis or pace maker);
5. Patient had any condition requiring repeated MRI scans;
6. Patient had any condition requiring diathermy;
7. Patients were on anticoagulant medications;
8. Patient had a prior surgical ablation procedure or any other previous neurosurgical procedure for the treatment of PD symptoms on either side of the brain;
9. Patient had dementia that interferes with their ability to co-operate or comply with study requirements or comprehend the informed consent as determined by the investigator;
10. Patient abused drugs or alcohol;
11. Patient had a history of cranial surgery;
12. Patients had a history of seizures;
13. Patient had any MRI non-compatible metallic implants that may interfere with the functioning of the device (e.g. aneurysm clips);
14. Patient had a history of stimulation intolerance in any area of the body;
15. Patient was a female that is lactating or of child bearing potential with a positive urine pregnancy test or not using adequate contraception; and
16. Patient was a participant in a drug, device, or biologics trial within the preceding 30 days;

17. Patient had confirmation of diagnosis of a terminal illness associated with survival <12 months.

C. Parkinson's Disease Study Follow-Up Schedule

All study participants were screened according to the criteria listed above and all participants signed an informed consent prior to undergoing any study procedures. The baseline evaluations are shown in Table 9. Implantation was performed according to each individual site's standard procedures. Implant assessments are shown in Table 9. Either one or two SJM IPG devices were implanted based on physician discretion. 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 assessments required at each visit are shown in Table ~~Table 9~~.

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	√						
Neuropsychological Exam	√				√		√
History	√						
UPDRS	√				√	√	√
Hoehn & Yahr Staging	√				√	√	√
Schwab & England	√				√	√	√
PDQ-39	√					√	√
Pittsburgh Quality Sleep Index	√					√	√
Global Outcome Measure	√				√	√	√
Dyskinesia Diary		√		√	√	√	√
Implant Information		√					
Randomization			√				
Device Information			√		√	√	√
Patient Satisfaction						√	√
Adverse Events		√	√	√	√	√	√

Table 9: Follow-up Schedule

D. 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. Non-bothersome dyskinesias were defined 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 non-bothersome 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; and
- Rate of patient satisfaction.

Additional endpoints assessed at one year as compared to baseline include:

- Reduction in Parkinson’s 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; and
- Patient satisfaction.

E. Parkinson’s Disease Study Pre-specified 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.

F. Accountability of PMA 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 LibraXP™ DBS 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 Figure 2.

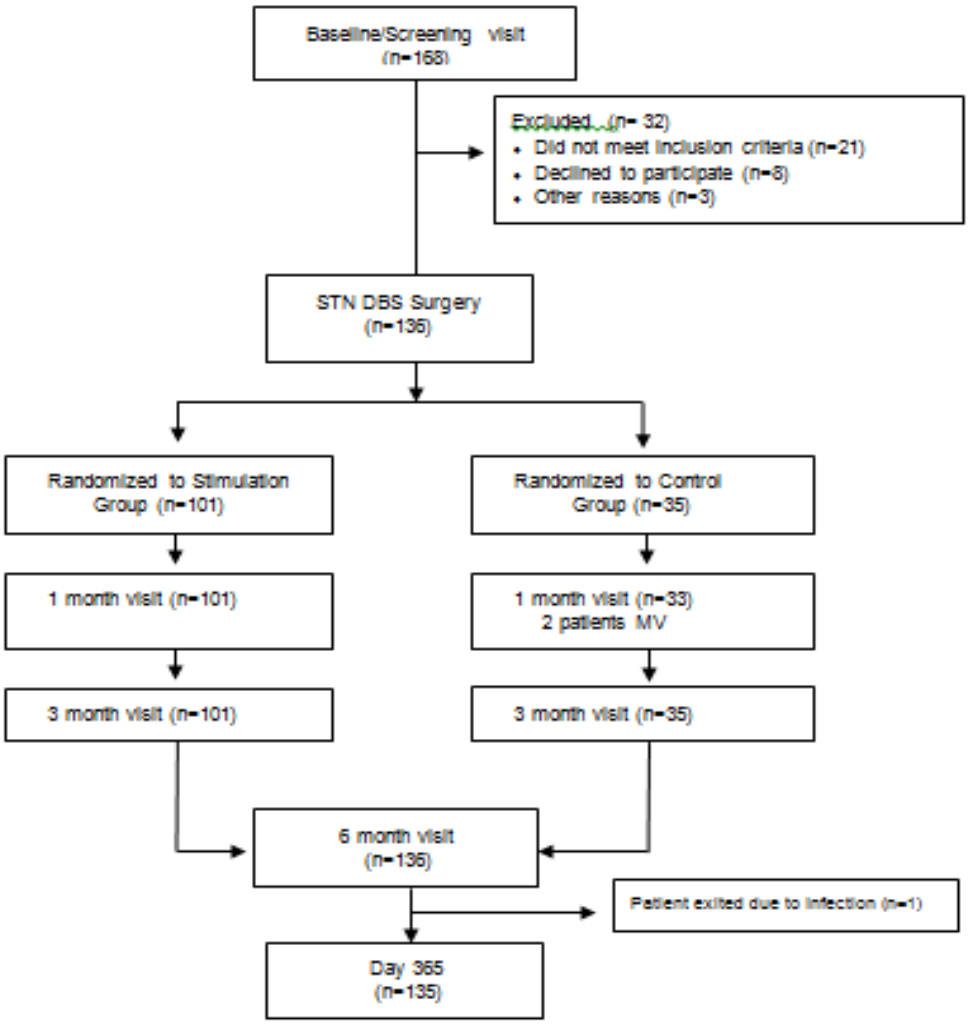


Figure 2: Patient Accounting

G. 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.

	Stimulation (N=101)	**Control (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%)	
Hispanic	8 (7.9%)	3 (8.6%)	
Other	1 (1.0%)	1 (2.9%)	
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

Table 7~~10~~: Demographic Summary

The following stimulation parameters were used during the study.

Parameter	Initial Programming	One 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
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

Table 11: Programming Parameters Initially and at One Year

H. 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 groups. 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. (Table 12). 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.

Adverse Event	Stimulation (N=101) n (%)	Control (N=35) n (%)	P Value*
Number with at least 1 AE	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
Post operative pain, stress, or discomfort	6 (5.9%)	0 (0.0%)	0.338
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/disturbance	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	*
Total AEs	144	25	**

*No p-value is included since the event types are mixed.
**Fisher's Exact Test used to compute P-values

Table 12: Summary of the First Occurrence of All Adverse Events During the First 90 Days

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 (Table 13). There were a total of 18 SAEs in the stimulation group and 7 in the control group.

Serious Adverse Event	Stimulation (N=101) n (%)	Control (N=35) n (%)	P-Value
Number with at least 1 SAE	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%)	1.0
Motor fluctuations	1 (1.0%)	0 (0%)	1.0
Cerebrospinal fluid leakage	1 (1.0%)	0 (0%)	1.0
Confusion	1 (1.0%)	0 (0%)	1.0
Gait disorder including balance problems	1 (1.0%)	0 (0%)	1.0
Lead fracture	1 (1.0%)	0 (0%)	1.0
Pneumonia	0 (0%)	1 (2.9%)	0.257
Seizure or convulsions	1 (1.0%)	0 (0%)	1.0
Tremor	1 (1.0%)	0 (0%)	1.0
Other	4 (4.0%)	4 (11.4%)	0.204
Total SAEs	18	7	*

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

Table 13: Summary of the First Occurrence of Serious Adverse Events During the First 90 Days

107 patients (78.7%) experienced a total of 409 adverse events during the first year of the study.

Adverse events	AEs	SAE	Number of patients	Incidence Rate
Total AEs	**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%**

Adverse events	AEs	SAE	Number of patients	Incidence Rate
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	0	1	1	0.7%
Lead Malfunction(lead break due to blow on the head)	0	1	1	0.7%
Pain at connection	1		1	0.7%
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%
PD 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%
Disequilibrium	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 PD features, torn rotator cuff, and leg “gives out”)	7	1*	6	4.4%
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%

Adverse events	AEs	SAE	Number of patients	Incidence Rate
Anxiety	2		2	1.5%
Dysphasia	2		2	1.5%
Post operative 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%
Increase salivation	1		1	0.7%
Jolting or shocking sensations	1		1	0.7%
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%
Post operative 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	0	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	0	1	1	0.7%
Paresthesia	1		1	0.7%
Pneumonia	0	1	1	0.7%
Tremor	1		1	0.7%
Visual disturbances	1		1	0.7%
Other (fatigue (2), numbness, increase somnolence, dysphagia, urosepsis, urinary retention, and DVT)	6	2	6	4.4%
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	0	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 PD 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%

Adverse events	AEs	SAE	Number of patients	Incidence Rate
Hallucinations	1		1	0.7%
Psychiatric changes/disturbances	0	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	0	1	1	0.7%
Paresthesia	2		2	1.5%
Pneumonia	1		1	0.7%
Urinary incontinence	1		1	0.7%
Tremor	0	1	1	0.7%
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 over active bladder	66	16	48	35.3%

Table 14: Frequency of All Adverse Events During 1 Year Study by DSMB Classification (All AEs include serious AEs and non serious AEs)

Device revisions

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

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

Table 15: Device Revision Summary

Deaths

There were 3 deaths in the long-term follow-up study. The cause of these deaths were unrelated to the device and include sepsis secondary from a UTI, cancer and multiple infections which 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.

	Stimulation		Control		
Characteristic	**Baseline**	**90 days**	**Baseline**	**90 days**	**P-value**
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
Interference	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
Non-perseverative					
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
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*					
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 test noted with *. * indicates a decrease in score represents an improvement.

Table 16: 90 Days Neuropsychological testing summary

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

Characteristic	Baseline	12-month	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
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
Non-perseverative			
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*			
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 test noted with *. * indicates a decrease in score represents an improvement.

Table 17: 12 Month Neuropsychological testing summary

I. Parkinson's Disease Study Effectiveness Results

The analysis of effectiveness was based on the 136 evaluable patients at the 90 day time point. Key effectiveness outcomes are presented in tables 18 to 34.

As seen in the table below, the primary endpoint was met at 90 days with a statistically significant (p=0.003) improvement in "on time" without dyskinesias or with non-bothersome 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 due to the nursing personnel miss-placing 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, Stimulation Group improves "on time" without dyskinesias or with non-bothersome dyskinesias by a mean of 2.51 hours as compared to the control group.

	Stimulation (N=101)	**Control (N=34)**	**P-Value**
Baseline			
Mean ± std	6.7 ± 3.1	7.4 ± 2.5	0.262
Range	0 – 14.8	3.0 – 13.8	
90 Days[1]			
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.

Table 18: Mean Baseline and Change from Baseline to 90 Days in the Duration of "on time" (hours) Without Dyskinesias or with Non-Bothersome Dyskinesias

See Figure 3~~Figure 3~~ for results of the "good quality "on" time over the study duration.

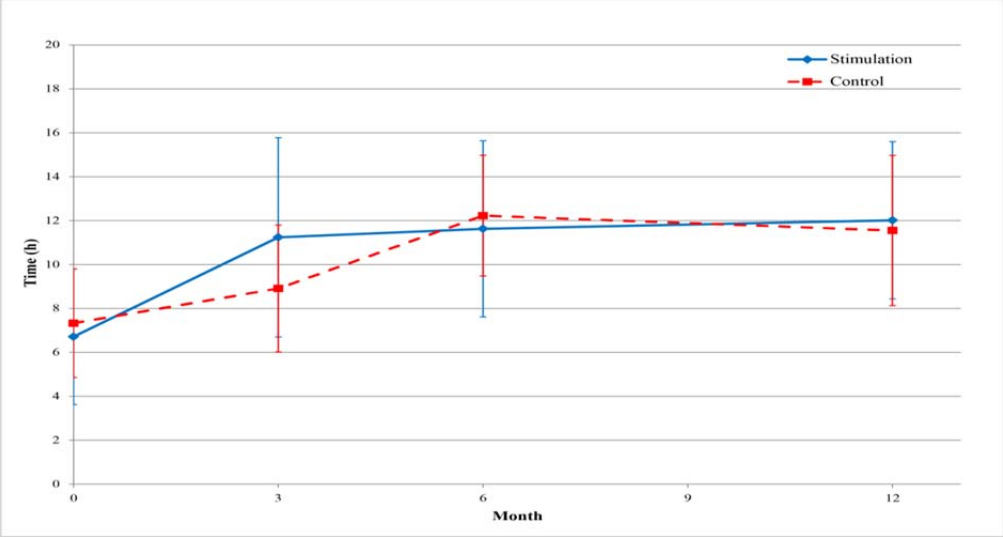


Figure 3: Duration of "Good Quality On Time"

Secondary Endpoints

This section provides a summary of the results of the secondary endpoints. Since a multiplicity adjustment procedure was not pre-specified for the secondary endpoints, the results are presented with 95% CIs instead of p-values. In addition, a number of the secondary endpoints could be assessed under various conditions, i.e. meds on/off and stim 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 baseline of 2.0 hours or more in "on time". The Stimulation Group demonstrated a 72.3% response rate and the Control Group demonstrated a 38.2% responder rate, with an odds ratio of 4.70 (1.96-11.28).

	Stimulation (N=101)	**Control (N=34)**
Responders: n (%)[1]	73 (72.3%)	13 (38.2%)
Odds Ratio (95% CI)	4.70 (1.96 – 11.28)	

[1] Increase of "on time" from baseline of 2 hours or greater

Table 19: Number of Responders

The Stimulation Group demonstrated a greater improvement in Parkinson's symptoms as measured by the UPDRS Motor Examination at 90 days from baseline compared to the Control Group as demonstrated in Table 20 and 21.

	Stimulation	**Control**
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 20: Change from Baseline to 90 Days in the UPDRS Motor Examination with Medications "off" at Baseline Compared to Medications"off" 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.

Table 21: Change from Baseline to 90 Days in the UPDRS Motor Examination with Medications "on" at Baseline Compared to Medications"on" and Stimulation "on" in Stimulation Group and Stimulation "off" in Control Group

The Stimulation Group demonstrated an improvement in the Schwab and England ADL assessement when the assessement was performed under the medication on at baseline compared to the medication on stimulation on condition at 90 Days demonstrated in Table 22.

	Stimulation	Control
Baseline		
N	99	34
Mean ± std	77.6 ± 16.8	76.5 ± 16.3
90 Days		
N	99	34
Mean ± std	86.1 ± 11.4	76.8 ± 17.7
Change[1]		
Mean	8.8	-0.5
Difference (95% CI)	9.3 (4.4, 15.3)	

Results are "on" medications 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.

Table 22: Mean Baseline and Change From Baseline to 90 Days in the Schwab and England Activities of Daily Living

The Stimulation Group demonstrated a greater improvement in Hoehn and Yahr Scale at 90 days from baseline compared to the Control when the assessement was performed under the medication off baseline score compared to the medication off stimulation on condition at 90 Days (Table 23). However, minimal improvement was seen in the Hoehn and Yahr scale when the assessment was performed under the medication on at baseline compared to the medication on stimulation on condition at 90 Days (Table 24).

	Stimulation	Control
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.

Table 23: Baseline and 90 Days Hoehn and Yahr Staging Mean Results Off Medication at Baseline, Off Medication at 90 Days, On Stimulation at 90 Days

	Stimulation	Control
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.

Table 24: Baseline and 90 Days Hoehn and Yahr Staging Mean Results On Medication at Baseline, On Medication and On Stimulation at 90 Days

A comparison of the stimulation and control groups on global outcome measures were performed at 90 Days. These assessments were performed by the examiner, caregiver and patients (Table 25).

	Stimulation n (%)		**Control n (%)**	
	Baseline	90 Days	Baseline	90 Days
Examiner	N=101		N=35	
No Disability	0	5 (5.0%)	1 (2.9%)	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%)	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%)
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%)

Table 25: Global Outcome Measures at 90 Days

Additional Endpoints

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

After the 90 Day visit, all patients recieved stimulation.The UPDRS activites 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 off medication condition compared to the off medication/on stimulation for both groups (Table 26).

UPDRS Component		Baseline*	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% CI			-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% CI			-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% CI			-4.99 to -4.23
Total	N	116	109	109
	Mean ± std	76.8±18.3	37.9±16.8	-38.4±21.8
	95% CI			-40.4 to -36.4

*Patients with a value at 3, 6 or 12 months.
Note: A decrease in score represents an improvement.

Table 26: 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*	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% CI			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% CI			-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% CI			-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% CI			-3.3 to 0.1

*Patients with a value at 3, 6 or 12 months.
Note: A decrease in score represents an improvement.

Table 27: 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

At one year, there was an improvement in the mean Schwab and England ADL score (Table 28).

	Baseline	12 Months	
		Actual	Change
N	134	133	133
Mean ± std	77.2 ± 16.6	83.5 ± 14.2	6.39 ± 20.9
95% CI			4.58 to 8.20

Medication "on" at Baseline and medication and Stimulation "on" at 12 Months
Note: An increase in score represents an improvement.

Table 28: Mean Baseline and Change From Baseline to 12 Months in the Schwab and England Activities of Daily Living

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 Table 29. 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.

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% CI			-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% CI			-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% CI			-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% CI			-14.0 to -10.8
Cognitive Impairment			
N	135	134	134
Mean ± std	44.3 ± 15.5	38.1 ± 13.9	-6.2 ± 15.6
95% CI			-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% CI			-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% CI			-9.2 to -7.2

Patients were ON Medications at baseline and 12 months.Note: A decrease in score represents an improvement.

Table 29: Change from Baseline at 12 Months in the PDQ-39 Components and Total Score

The stimulation system demonstrated improvement in sleep quality and fewer disturbances through 12 months as demonstrated by the Pittsburgh Sleep Quality Index as show in Table 30.

	Baseline	12 Months	
		Actual	Change
N	136	135	135
Mean ± std	9.68 ± 4.34	7.50 ± 4.00	-2.16 ± 4.09
95% CI			-2.51 to -1.81

Note: A decrease in score represents an improvement.

Table 30: Change from Baseline at 12 Months in the Pittsburgh Sleep Quality Index

The following table compares the Hoehn Yahr scores at 6 and 12 months (Table 31-32).

Stage	Baseline (N=133)	6 Months (N=133)	12 Months (N=131)
0	0 (0%)	1 (0.8%)	0 (0%)
1	0 (0%)	3 (2.3%)	2 (1.5%)
1.5	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 31: Baseline vs. 3, 6 and 12 Months Hoehn and Yahr Staging Results Off Medication at Baseline, Off Medication at 3, 6, and 12 Months, On Stimulation 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%)	2 (1.6%)
5	1 (0.8%)	1 (0.8%)	2 (1.6%)

Note: A decrease in stage represents an improvement.

Table 32: Baseline vs. 3, 6 and 12 Months Hoehn and Yahr Staging Results On Medication at Baseline, On Medication at 3, 6, and 12 Months, On Stimulation at 3, 6, and 12 Months

Global outcome was assessed by the examiner, caregiver and patient at one year (Table 33).

	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%)

Table 33: Global Outcome Measures at 12 Months

Patient satisfaction was assessed at 6 months and one year (Table 34).

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%)
Not Satisfied	10/135 (7.4%)	5/135 (3.7%)
Very Unsatisfied	1/135 (0.7%)	3/135 (2.2%)
You would undergo the process again	125/136 (91.9%)	124/135 (91.9%)
You would recommend this DBS system to someone else?	128/135 (94.8%)	128/134 (95.5%)

Table 34: Patient Satisfaction

Mean changes in total daily dose were compared between treatment groups at 90 Days by an analysis of covariance, using the baseline daily dose 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 demonstrates a decrease in levodopa medication dosage that was maintained for the 12 month study. Results are shown in the following Figure 4

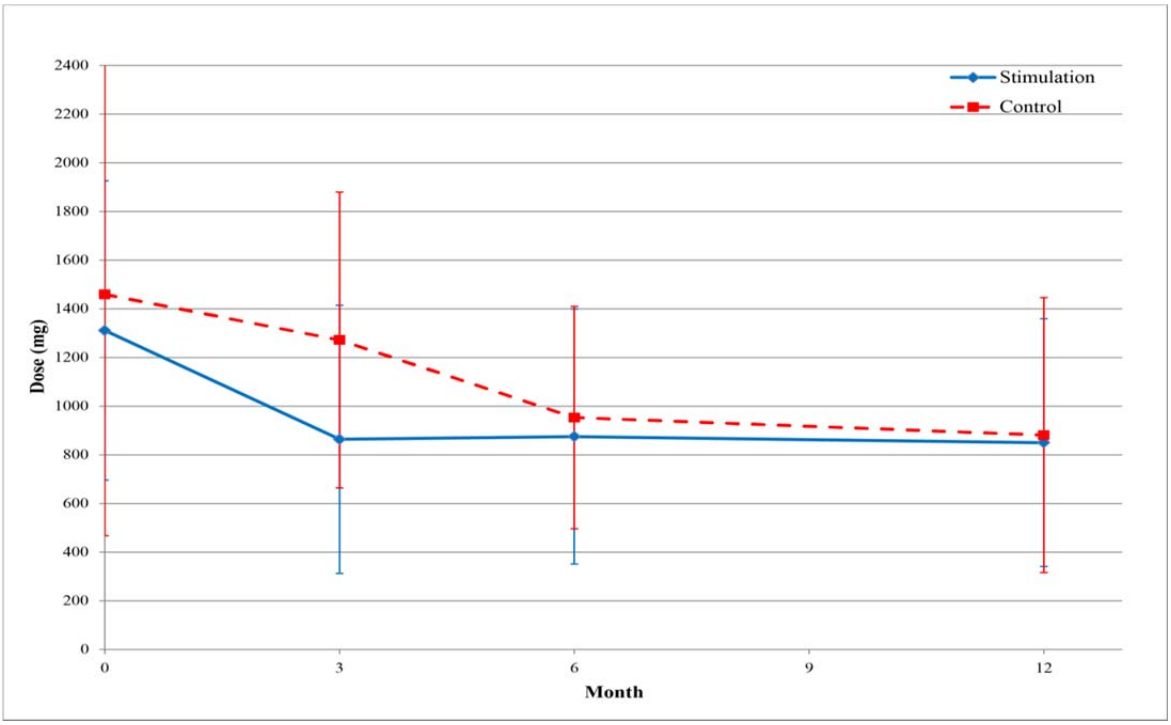


Figure 4: Levo Dopa Equivalent Dose

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.

X.2 Essential Tremor Study:

A. Essential Tremor Pivotal Clinical Study Design

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the SJM Deep Brain Stimulation (DBS) System for the treatment of essential tremor of the upper extremities. A summary of the clinical study is presented below.

B. Study Design

Patients were treated between October, 2005 and September, 2012. The database for this 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 SJM DBS Systems.

This study was designed as a prospective, multi-centered study for 365 days in duration from device implantation. The duration for the original study was for one year. After one year, patients were consented to the Long Term Follow-Up Study where they continued follow-up for a total follow-up duration 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 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 Day 180 visit after implantation and whether the device was on or off at that assessment).

The Data Safety Monitoring Board (DSMB) reviewed all AEs 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 them into the appropriate category.

C. 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

1. Patient signed an informed consent;
2. Patient was over 18 years of age;
3. Patient was diagnosed with essential tremor for at least 3 years;
4. 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);
5. Patient had a postural or kinetic tremor severity score of at least 3 out of 4 in the extremity intended for treatment on the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor;
6. Patient maintained a constant dose of anti-tremor medication indicated as best medical management for one (1) month prior to enrollment in study; and
7. Patient was available for appropriate follow-up times for the length of the study.

Exclusion Criteria

1. Patient was not surgical candidate;
2. Patient had other clinically or medically significant disease;
3. Patient had any neurological injury or disease other than essential tremor;
4. Patient had any condition requiring repeated MRI scans;
5. Patient had any condition requiring diathermy;
6. Patients on anticoagulant medications;
7. Patient had untreated clinically significant depression;
8. Patient had an electrical or electromagnetic implant (cochlear prosthesis, pacemaker etc);
9. Patient had a prior thalamotomy or surgical ablation procedure in either side of the brain;
10. Patient had dementia interfering with their ability to co-operate or comply with study requirements or comprehend the informed consent (mini-mental exam score <24);
11. Patient abused drugs or alcohol;
12. Patient had botulinum toxin injections in the six (6) months prior to enrollment;
13. Patient had a history of cranial surgery;
14. Patient had a history of seizures;
15. Patient had any metallic implants that may interfere with the functioning of the device (e.g. aneurysm clips);
16. Patient had a history of stimulation intolerance in any area of the body; and
17. Patient was a female of child bearing potential with a positive urine pregnancy test or not using adequate contraception.

D. Essential Tremor Study Follow-Up Schedule

The baseline evaluations are shown in **Error! Reference source not found.**~~Table 35: Follow-up Schedule~~. Implantation was performed according to each individual site's standard procedures. Implant assessments are shown in Table 35. Stimulation was turned on the same day as the implant. Patients returned to clinic at 90 days, 180 days and 365 days post implant. The assessments required at each visit are shown in **Error! Reference source not found.**~~Table 35~~.

Procedure	**Screening/ Baseline**	**Implant**	**Day 90 (± 14 d)**	**Day 180 (± 14 d)**	**Day 365 (± 30 d)**
Informed Consent	√				
Demographics/ History	√				
Beck Depression Inventory II	√				√
Mini Mental State Exam	√				√
ET Diagnostic Criteria	√				
Target Extremity & Maximum Tremor Position	√				
Clinical Rating Scale for Tremor (CRST)	√*		√ (Stim On & Off)	√ * (Stim On & Off)	√ (Stim On & Off)
Quality of Life in Essential Tremor (QUEST)	√		√	√	√
SF-36	√		√	√	√
Global Outcomes Measure	√		√	√	√
Implant & Device Information		√			
Patient Satisfaction			√	√	√
Adverse Events		√	√	√	√

*Assessment videotaped.

Table 35: Follow-up Schedule

E. 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).

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 medications "ON". These included:

- Reduction in postural or kinetic tremor of the non-target limb in essential tremor patients who received a bilateral implant in the "ON" medication 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 1-year in both extremities;
- Percent of patients whose treatment with DBS 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 DBS 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 (Troster et al. 2004);
- Improvement of patient and caregiver Global Ratings;
- Percent of patients utilizing the patient amplitude control option;
- Range of amplitude permitted;
- Rate of patient satisfaction.

F. 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 Activa™ device for the tremor indication.) The secondary safety analysis summarized the rates of time to first device related 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 non-inferiority 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 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 non-target 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 exact 95% confidence interval. A multiplicity adjustment procedure was not pre-specified for the secondary endpoints. Therefore, 95% confidence intervals are provided for the secondary endpoints.

G. 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. A summary of the patient accounting is provided in Figure 5.

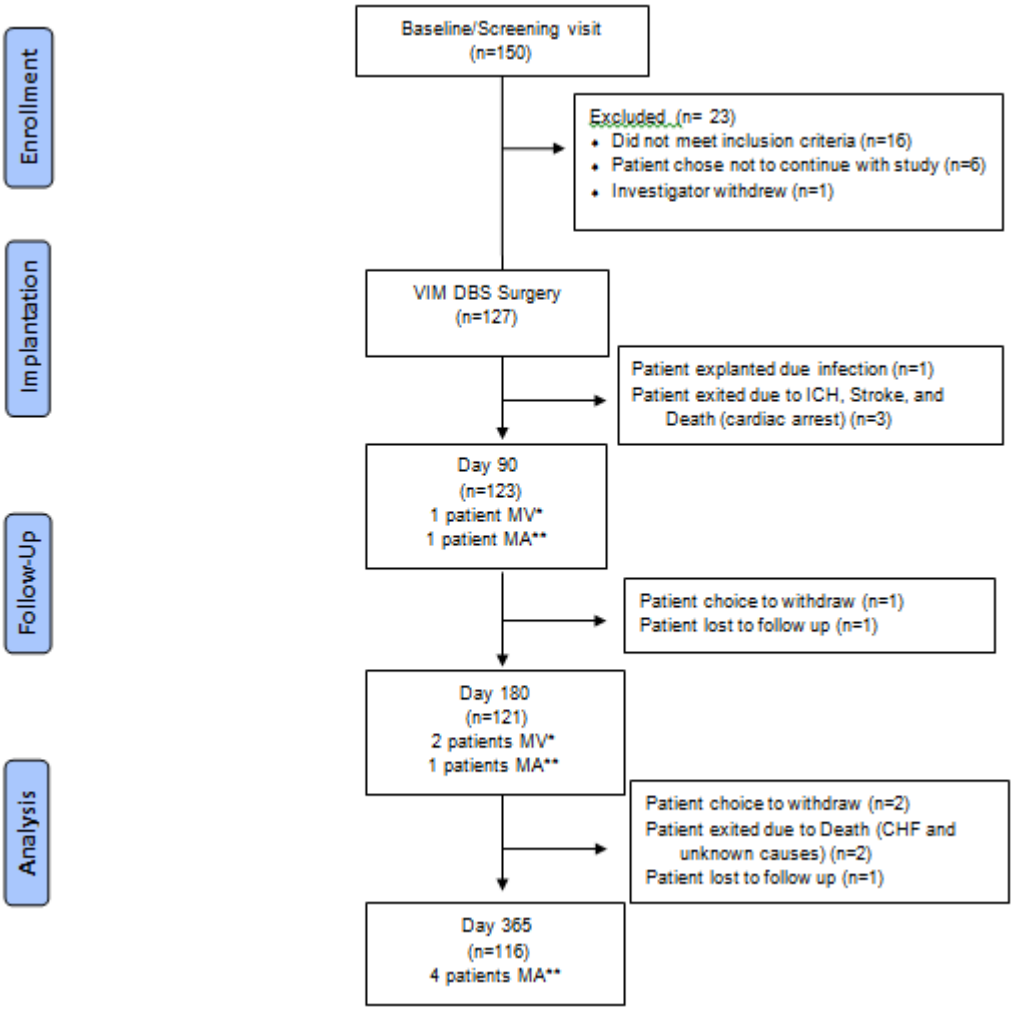


Figure 5: Patient Accounting

H. 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 36-80). 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 ET was 14.8 years prior to enrollment in the study. 110 patients were right hand dominant with the remaining 17 patients being left hand dominant. At baseline only 20/127 (15.7%) of the patients were on anti-tremor medication.

	Not Implanted (N=21)	Implanted (N=127)
Gender: n (%)		
Males	12 (57.1%)	69 (54.3%)
Females	9 (42.9%)	58 (45.7%)
Age		
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	1 (0.8%)
Hispanic	0	2 (1.6%)
Years since onset of tremor		
Mean ± std	24.4 ± 17.0	29.1 ± 17.4
Range	3 – 54	2 – 70
Years since initial diagnosis of ET		
Mean ± std	11.9 ± 9.9	14.8 ± 11.8
Range	3 – 47	0 - 52

Table 36: Study Population Demographics

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

Parameter	Initial Programming	90 days	180 Days	365 Days
Targeted 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
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

Table 37: Summary of Programming for Patients Upon Finishing the Study Visit

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 paitents were given the ability to control their amplitude.

I. 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 them 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 non-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. Results are shown in Table 38 below.

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
DBS 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
Persistent pain at IPG site	2	1.6	4.9

Adverse Event	n	%	Upper 95% Confidence Bound
Post operative discomfort	2	1.6	4.9
Post operative 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*	12	9.4	14.9
Totals	55	NA	NA

*Patients with one or more "other" adverse event

Table 38: 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
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
DBS 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

Adverse Event	n	%	Upper 95% Confidence Bound
Paresis	2	1.6	4.9
Paresthesia	3	2.4	6.0
Persistent pain at IPG site	2	1.6	4.9
Post operative discomfort	4	3.1	7.1
Post operative 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

Table 39: Summary of all Adverse Events Within 180 Days of Initial Implant Or the Second Implant (N = 127 Patients)

A total of 327 adverse events in 97 (76%) subjects occurred during the study (Table 40).

Adverse events	Number of events
Total AEs	**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**
Post-operative Pain/Discomfort/Redness	17
Headache	8
Cognitive changes (transient)	7
Misplaced lead (4 revised and 2 non revised)	6
Infection	5
Intracranial Hemorrhage (2 symptomatic (1 persistent and 1 transient); 1 Non-symptomatic)	3
Paresis (symptomatic and transient)	2
Wound dehiscence	2
Pocket hematoma	2
Seizure (transient)	1
Stroke (symptomatic and persistent)	1

Adverse events	Number of events
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**

Table 40: Summary of all Adverse Events as Classified by the Data Safety Monitoring Board (N = 127 Patients)

All Serious Adverse Events

A total of 34 serious adverse events occurred in 29 patients during the study. No unanticipated device effects occurred during the study. Results are shown in Table 42. The events included 3 deaths, 8 infections, 3 intracranial hemorrhages, 2 paresis, 1 seizure and 1 stroke(Table 41).

Serious Adverse Events	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; 1pneumocephalus; 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* cardiac related and 1 unknown)	3
Hospitalization due to other medical conditions/events	16

*One additional subject had a cardiac arrest during pre-operative testing.

Table 41: Summary of Serious Adverse Events (N = 127 Patients)

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. Results are shown in Table 42.

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
Dysphasia	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
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
Post operative pain	1	0.8	3.7
Visual disturbances	1	0.8	3.7
Other	20	15.6	21.9
Total	55	NA	NA

Table 42: Summary of all Adverse Events Following the Second Implant (N = 39 Patients)

Device Revisions

The following table includes a summary of the device revisions through one. In addition to the revisions, 3 patients were explanted during the study.

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

Table 43: Device Revisions

Deaths

There were 2 deaths related to cardiac events. 1 death was due to unknown causes.

Beck Depression Inventory II

The Beck Depression Inventory 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 instrument 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. A comparison of the mean BDI-II scores from baseline to 12 months is provided below.

Baseline	
N	112
Mean ± Std	8.8 ± 7.6
Minimal Depression (scores 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%)
Day 365	
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 (scores 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.

Table 44: Baseline and Change From Baseline in the BDI - II

Mini Mental State Exam

A comparison of the mean MMSE scores from baseline to 12 months is provided below.

Baseline	
N	110
Mean ± Std	29.2 ± 1.2
Day 365	
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.

Table 45: Baseline and Change From Baseline to Day 365 in the MMSE

J. Essential Tremor Study Effectiveness Results

The analysis of effectiveness was based on the 127 evaluable patients at the 180 day time point. Key effectiveness outcomes are presented in tables 46 to 55. The primary effectiveness endpoint was based on the postural tremor score of the target limb between stimulation On and stimulation Off, at the Day 180 visit, as measured by the blind reviewer.

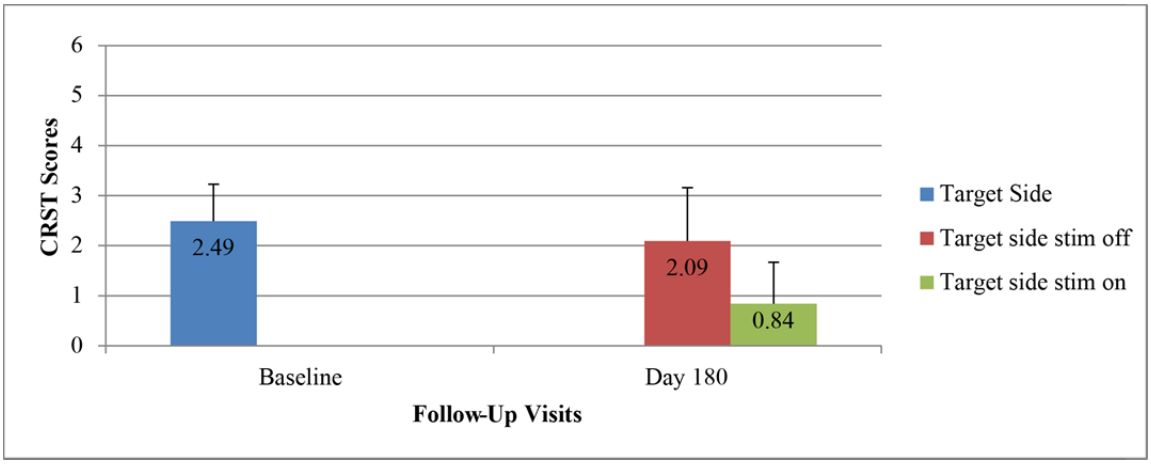
Among the 127 implanted patients, 118 had site physician assessments at 180 days. Among these 118 patients, 87 had blinded assessments with stimulation Off and 86 had blinded assessments with

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 Table 46 and Figure 6.

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.

Table 46: Mean Target Limb Severity Score (CRST) with Stimulation "Off" and Stimulation "On", As Assessed by the Blind Reviewer



Statistical difference was found between stimulation on vs. stimulation off at Day 180 (p<0.001).

Figure 6: Mean Target Limb Severity Score (CRST) with Stimulation "On" and "Off" as Assessed by the Blind Reviewer

K. Secondary Endpoints

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

The Clinical Rating Scale for Tremor, is a rating tool to assess the severity of postural, isometric, kinetic and task specific tremor in the dominant and non-dominant sides of the head, trunk and limbs of patients with ET. The CRST utilizes a 0 to 4 point scale where 0 indicates non-

symptomatic (normal) and 4 indicates the most severe rating of the patient's tremor symptoms. The following Figure 7 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.

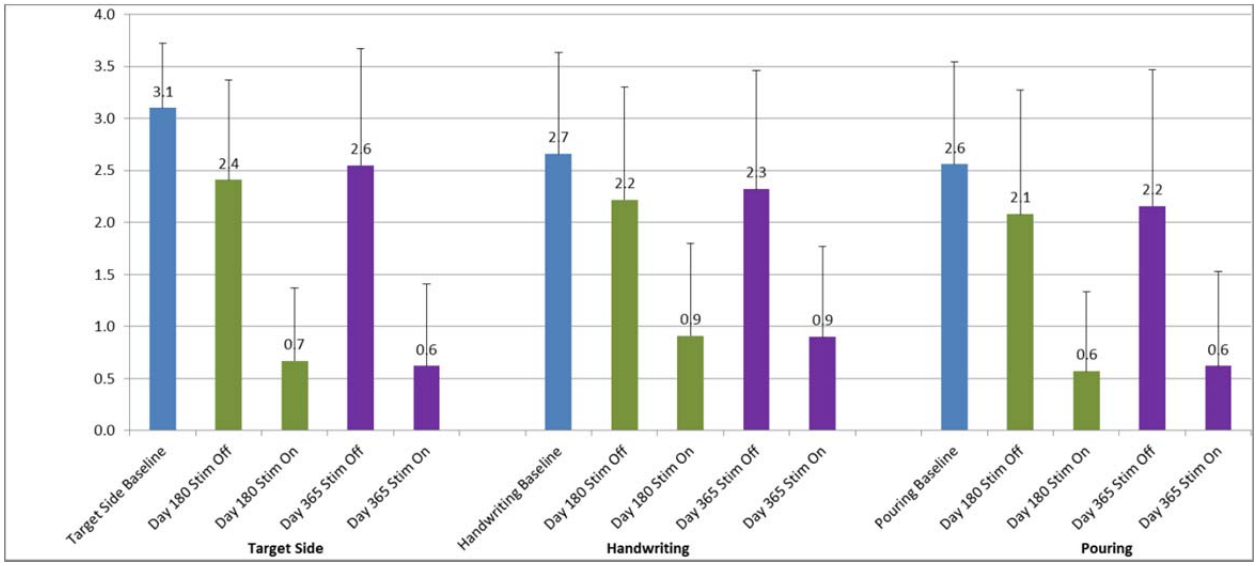


Figure 7: Mean Target Limb Severity, Handwriting and Pouring Scores (assessed by the CRST) at Baseline Compared to Day 365 with Stimulation "On" and "Off", as Assessed by the site Physician

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. Results are shown in Table 47.

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

Note: A decrease in score represents an improvement.

Table 47: Mean Target Limb Severity Score (CRST) with Stimulation "Off", Stimulation "On", and Change from "Off" to "On" as Assessed by the Site Physician

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 being on and off, 58.5% of patients respondedat Day 180 and 64.3% responded at Day 365. . The difference in these two responser analysis accounts for the carryover effects of stimulation and the time it takes for stimulaiton to be optimized. Results are shown in Table 48. All results demonstrate the positive improvement stimulation has on a patient's upper limb which allows for more use and control of the limb.

Day 180	
Between Stimulation Off and Stimulation On	
n/N (%)	69/118 (58.5%)
95% confidence Interval	49.0%, 67.5%
Between Baseline and On Stimulation	
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 On Stimulation	
n/N (%)	97/112 (86.6%)
95% confidence Interval	78.9%, 92.3%

[1] A reduction of 2 or more points

Table 48: CRST Target Limb Responder[1] Analysis Between Stimulation "Off" and Stimulation "On" and Between Baseline and "On" Stimulation as Assessed by the Site Physician

Day 180	
Between Baseline and Off Stimulation	
n/N (%)	0/118 (0%)
Between Baseline and On Stimulation	
n/N (%)	98/118 (83.1%)
Day 365	
Between Baseline and Off Stimulation	
n/N (%)	0/112 (0%)
Between Baseline and On Stimulation	
n/N (%)	97/112 (86.6%)

Table 49: Number of subject who had a 2 point reduction in CRST Target Limb as Assessed by the Site Physician

The following table provides the percent of patients whose treatment with DBS 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.

Successful Treatment with DBS as defined per protocol	
n/N (%)	98/118 (83.1%)
95% confidence Interval	75.0%, 89.3%

Table 50: Successful treatment with DBS

Bilateral Stimulation

For those patients that had bilateral stimulation, the site physician evaluated the patient's non-target side after 180 days of bilateral stimulation. At baseline, the mean non-target 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 non-target 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 8 shows these results, which demonstrate the positive improvement of bilateral stimulation.

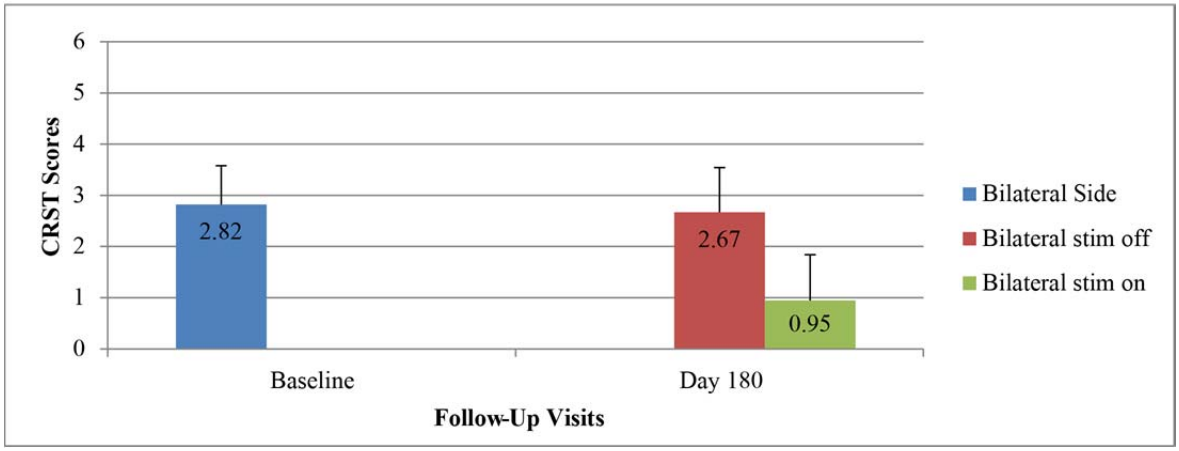


Figure 8: Mean Nontarget Limb Severity Score (CRST) at Baseline compared to Day 180 with Bilateral Stimulation "On" and "Off", as Assessed by the Site Physician

For those patients that had bilateral stimulation, the site physician also evaluated the patient's non-target side for tremor severity after 180 days with only the second side system on. At baseline, the mean non-target limb severity score for non-target side stimulation was 2.84. This mean decreased to -1.73 at Day 180. Additionally, the non-target 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 site physician. The mean difference between stimulation on and stimulation off is -1.62 . Figure 9 shows these results, which demonstrate the positive improvement that was achieved when the second side is implanted and stimulated.

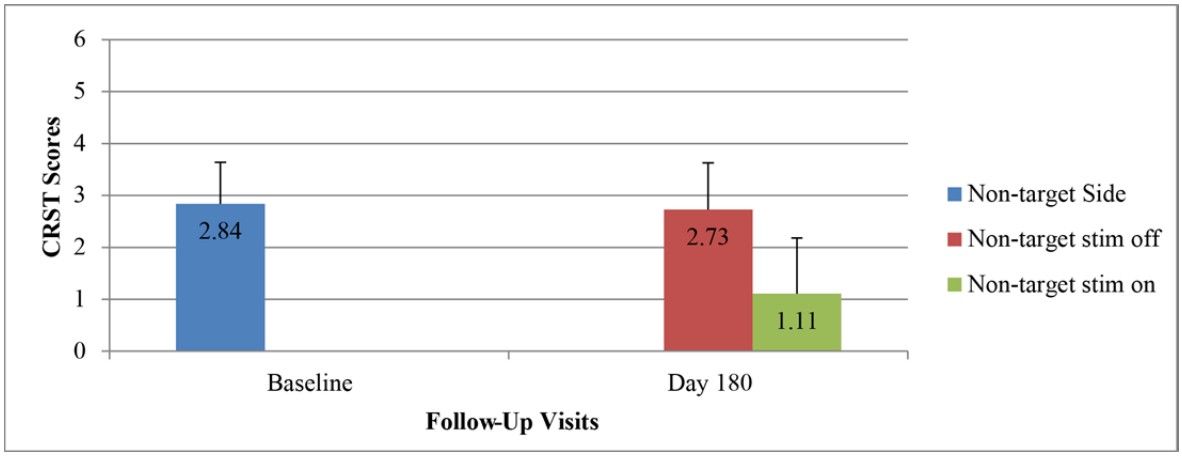


Figure 9: Mean non-target limb severity score (CRST) at baseline compared to Day 180 with single side stimulation on and off, as assessed by the site physician (non-target side stimulation)

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%)

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

Table 51: Investigator Assessment of Patients with Bilateral implants

Overall Motor Score as Measured by CRST

The motor score adds together all responses to the tremor assessment for questions 1-9 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. Results are shown in Table 52.

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.

Table 52: Mean Total Motor Score (CRST) With Stimulation Off, Stimulation On, and Change From Off to On As Assessed by the Site Physician

Activities of Daily Living (ADL) as Measured by CRST

The activity of daily living score adds together all responses to questions 15-21 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 site physician. The mean difference of -9.1 at Day 180, and a mean difference of -10.0 at Day 365. All results demonstrate the positive improvement stimulation has on a patient's activities of daily living. Results are shown in Figure 10.

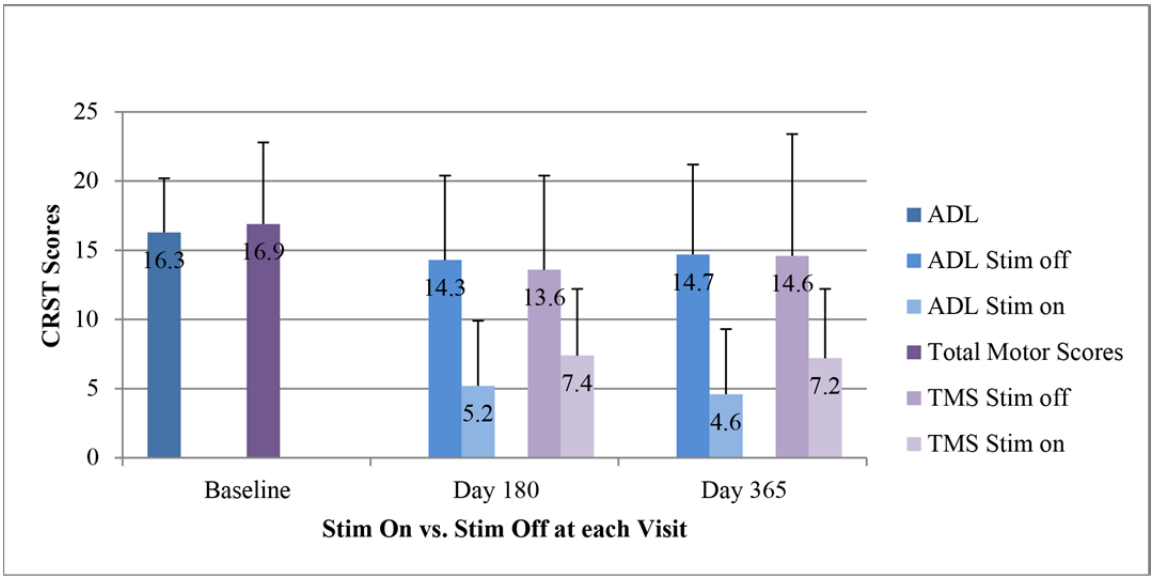


Figure ~~410~~: Activities of Daily Living (ADL) and Total Motor Scores (TMS) with stimulation off and on stimulation at Day 180 and Day 365 as assessed by the site physician by the CRST

Individual Component Scores of the CRST

The following table includes the individual components 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
Face	180	0.24	0.14	0.06	-0.17	-0.26	-0.08
Face	365	0.24	0.22	0.12	-0.12	-0.21	-0.02
Tongue Rest	90	0.20	0.11	0.04	-0.16	-0.25	-0.06
Tongue Rest	180	0.20	0.16	0.04	-0.14	-0.23	-0.04
Tongue Rest	365	0.20	0.12	0.05	-0.11	-0.20	-0.02
Tongue Post	90	0.67	0.39	0.24	-0.43	-0.57	-0.28
Tongue Post	180	0.67	0.42	0.19	-0.45	-0.60	-0.30
Tongue Post	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
Voice	180	1.15	1.03	0.47	-0.64	-0.79	-0.49
Voice	365	1.15	1.05	0.58	-0.50	-0.68	-0.33
Head Rest	90	0.42	0.27	0.11	-0.31	-0.43	-0.19
Head Rest	180	0.42	0.21	0.12	-0.30	-0.42	-0.18
Head Rest	365	0.42	0.35	0.12	-0.29	-0.42	-0.16

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

CRST Score	Day	Baseline Mean	Off Stim Mean	On Stim Mean	Change On-Baseline	Lower 95% CI	Upper 95% CI
Right Lower Act	90	0.32	0.23	0.14	-0.18	-0.31	-0.06
Right Lower Act	180	0.32	0.20	0.09	-0.24	-0.33	-0.15
Right Lower Act	365	0.32	0.35	0.11	-0.21	-0.31	-0.12
Left Lower Rest	90	0.09	0.06	0.07	-0.01	-0.07	0.05
Left Lower Rest	180	0.09	0.08	0.03	-0.07	-0.13	-0.01
Left Lower Rest	365	0.09	0.06	0.01	-0.09	-0.15	-0.03
Left Lower Post	90	0.25	0.19	0.16	-0.10	-0.19	-0.01
Left Lower Post	180	0.25	0.20	0.15	-0.10	-0.20	-0.01
Left Lower Post	365	0.25	0.32	0.18	-0.09	-0.21	0.03
Left Lower Act	90	0.26	0.16	0.12	-0.14	-0.24	-0.04
Left Lower Act	180	0.26	0.23	0.15	-0.12	-0.22	-0.02
Left Lower Act	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
Drawing A Right	180	2.34	1.93	0.81	-1.50	-1.69	-1.31
Drawing A Right	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
Drawing A Left	180	2.40	2.26	1.92	-0.47	-0.67	-0.28
Drawing A Left	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
Drawing B Right	180	2.58	2.18	0.97	-1.58	-1.79	-1.38
Drawing B Right	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
Drawing B Left	180	2.65	2.49	2.15	-0.49	-0.68	-0.30
Drawing B Left	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
Drawing C Right	180	2.26	1.97	0.88	-1.35	-1.56	-1.13
Drawing C Right	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
Drawing C Left	180	2.41	2.35	2.02	-0.39	-0.58	-0.19
Drawing C Left	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
Pouring Right	180	2.46	2.04	0.66	-1.81	-2.02	-1.59
Pouring Right	365	2.46	2.06	0.68	-1.78	-1.99	-1.57

CRST Score	Day	Baseline Mean	Off Stim Mean	On Stim Mean	Change On-Baseline	Lower 95% CI	Upper 95% CI
Pouring Left	90	2.28	2.17	1.80	-0.49	-0.71	-0.27
Pouring Left	180	2.28	2.17	1.72	-0.56	-0.77	-0.34
Pouring Left	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
Speaking	180	0.95	0.76	0.46	-0.47	-0.63	-0.32
Speaking	365	0.95	0.79	0.43	-0.51	-0.68	-0.34
Feeding	90	2.39	2.08	0.64	-1.75	-1.93	-1.58
Feeding	180	2.39	2.19	0.64	-1.75	-1.94	-1.57
Feeding	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
Liquids to Mouth	180	3.10	2.59	0.81	-2.29	-2.51	-2.07
Liquids to Mouth	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
Hygiene	180	2.33	2.02	0.57	-1.77	-1.98	-1.56
Hygiene	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
Dressing	180	2.15	1.80	0.68	-1.49	-1.70	-1.28
Dressing	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
Writing	180	2.84	2.61	0.97	-1.86	-2.06	-1.65
Writing	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
Working	180	2.50	2.35	1.05	-1.45	-1.66	-1.24
Working	365	2.50	2.39	0.91	-1.55	-1.78	-1.33

Table 53: Individual component scores of the CRST

Quality of Life in Essential Tremor (QUEST)

The QUEST is a self-administered questionnaire, which consists of 30 items scored in 5 specific domains of (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. Results of the QUEST are shown in Figure 11.

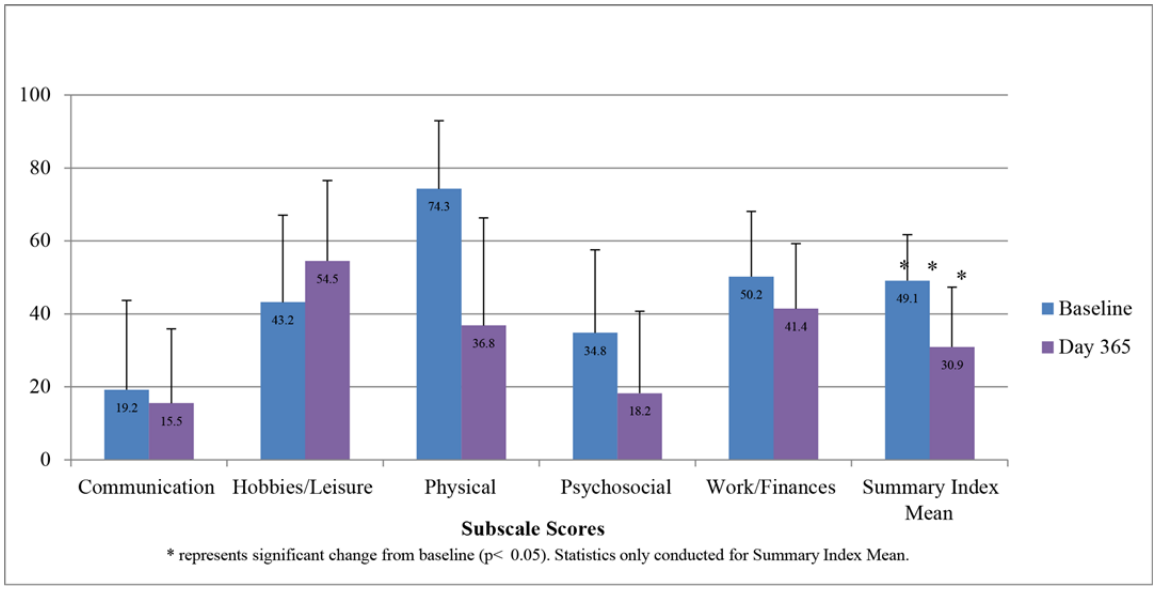


Figure 5~~11~~: QUEST questionnaire evaluation at Baseline and Day 365

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 eleven domains of health. The eleven domains are summarized into a physical and mental component score.

	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 Diff Baseline v. 365 Day	-0.02	2.1
95% CI	-2.5, 2.4	-0.6, 4.8

Note: An increase in score represents an improvement.

Table 54: Baseline and Change From Baseline in the SF36 Components and Individual Domains

A comparison of the caregiver and patient global assessments from baseline to days 180 and 365 are provided (Tables 55 to 56).

Baseline	
N	68
No disability: n (%)	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 55: Global Assessment by Caregiver

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%)
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%)

Table 56: Global Assessment by Patient

Subjects satisfaction with the device was assessed at day 180 and 365 (Table 57).

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%)

Table 57: Satisfaction with the DBS System's Functioning and Ability to Control Symptoms

XI. CONCLUSIONS DRAWN FROM CLINICAL STUDIES

a. Effectiveness Conclusions

Parkinson's Disease Study

Effectiveness for the Parkinson's disease indication was based on one hundred thirty six patients implanted at 15 U.S. sites. Patients were randomized in a 3:1 ratio to the stimulation or control groups. There were 101 subjects in the stimulation group and 35 subjects in the control group. The primary effectiveness endpoint was met at 90 Days with a statistically significant (p=0.003) improvement in "on time" without dyskinesias or with non-bothersome 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% response rate and the Control Group demonstrated a 38.2% responder rate. In addition, stimulation improved Parkinson's symptoms, severity of Parkinson's symptoms and activities of daily living in the medications 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 symptoms were sustained through one year as measured by the UPDRS components of motor examination and complications in the medications off baseline compared to medication off stimulation on condition. Data suggests that compared to 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 month and 12 months of stimulation with 58.8% and 57.1% respectively indicating none 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 patient noted they were either satisfied or very satisfied with their therapy. In addition, 96% of patients indicated they would recommend this deep brain stimulation system to others at 12 months.

The results of the clinical study demonstrate a clinically meaningful improvement in "on" time with Brio Neurostimulation System in patients with advanced Parkinson's disease.

Essential Tremor Study

Effectiveness for the essential tremor indication was based on 127 patients implanted at 12 U.S. sites. The primary effectiveness endpoint was based on the postural tremor score of the target limb between stimulation On and stimulation Off, at the Day 180 visit, as measured by the blind reviewer. The primary endpoint was successful, with the stimulation On performing significantly better in their postural or kinetic tremor reduction than stimulation Off at Day 180. In addition, the secondary endpoint of non-target and bilateral side CRST scores showed tremor reduction at Day 180 compared to baseline.

The secondary analyses supported the primary effectiveness endpoint. The CRST which assessed the patients' total motor, handwriting and pouring score demonstrated that stimulation improved all outcomes. In addition, the QUEST and the SF-36 showed improvement.

The results of the clinical study demonstrate a clinically meaningful reduction in tremor with the Brio Neurostimulation System in essential tremor patients with unilateral or bilateral disabling medication-refractory upper extremity tremor.

b. Safety Conclusions

Parkinson's Disease Study

The risks of the device for Parkinson's disease were based on a comparison of the adverse events during the randomized phase and longterm 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 (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 cause of these deaths were unrelated to the device and include sepsis secondary from a UTI, cancer and multiple infections which started with osteomyelitis of the big toe. There were no unanticipated adverse device effects.

Essential Tremor

The risks of the device for essential tremor were based on the adverse events collected in the clinical study. 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. 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 was 38.9%, which is less than 10 percentage points more than the comparator rate of 38.1%.

A total of 34 serious adverse events occurred in 29 patients during the study. These included 8 infections, 3 intracranial hemorrhages, 2 paresis, 1 seizure, 1 stroke and 3 deaths. Two of the 2 deaths were related to cardiac events and the cause of the other death was unknown.

A total of 327 adverse events in 127 (100%) subjects occurred during the study. The most common adverse events were headach, dysarthria, and jolting or shocking sensations. No unanticipated adverse events occurred during the study.

c. Benefit-Risk Conclusions

Parkinson's Disease

The probable benefits of the device are based on the clinical study. Effectiveness was demonstrated by an improvement in "on" time. At 90 days, 72.3% of the subjects receiving stimulation as compared to 38.2% of control subjects had an increase of 2.0 hours or more in "on time" compared to baseline. It would be expected that subjects with advanced Parkinson's disease would experience a similar benefit.

The adverse events that were reported were consistent with the safety profile of a legally marketed DBS system.

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 can not be precisely interpreted. Disappointment about being randomly assigned to the delayed-stimulation group might have also 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. There was only one patient that did not complete the one year study; thus missing data from this study was minimized and did not impact the results.

Essential Tremor

The probable benefits of the device are based on the clinical study. Effectiveness was demonstrated by a reduction in the tremor score. At one year, 86.6% of the patients achieved at least a 2-point reduction in the postural or kinetic tremor scores. It would be expected that subjects with essential tremor who have unilateral or bilateral disabling medication-refractory upper extremity tremor would experience a similar benefit.

The adverse events that were reported were consistent with the safety profile of a legally marketed DBS system.

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 DBS as an adjunct to medications to control their tremor. However, over time, adjunctive medications may be used which may also 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.

d. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use for the treatment of advanced Parkinson's disease and disabling upper extremity tremor due to essential tremor. The results of the clinical studies support a reasonable assurance of the safety and efficacy of the Brio Neurostimulation System, when used in a manner consistent with its labeling and intended use. The evidence supporting the safety and effectiveness of the Brio Neurostimulation System is based on a randomized double blind sham controlled study for Parkinson's disease and an open label study with a blinded assessment for essential tremor. The results from comprehensive pre-clinical testing show that the Brio DBS System performs as intended. The analyses also support a clinical benefit to risk determination that is favorable for the Parkinson's Disease and essential tremor indications.

XII. CONCLUSIONS DRAWN FROM NONCLINICAL STUDIES

The nonclinical laboratory testing performed on the DBS Leads, DBS Extensions, IPG, Charger, Patient Programmer 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. Further, the nonclinical laboratory studies conducted by SJM, when considered with the clinical experience, provides assurance that the Brio Neurostimulation System is safe and effective when used to treat Parkinson's disease and essential tremor.

XIII. FINANCIAL DISCLOSURE

a. Parkinson's Disease Study

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigaotrs of which none were full-time or part-time employees of the sponsor and one had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

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

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

b. Essential Tremor Study

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

XIV. PANEL RECOMMENDATIONS:

CDRH determined that an advisory panel was not necessary.

XV. CDRH DECISION:

CDRH issued an approval order on June 12, 2015.

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

XVI. APPROVAL SPECIFICATIONS

1. Directions for use: See device labeling.
2. Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings,Precautions, and Adverse Events in the device labeling.
3. Post-approval Requirements and Restrictions: See approval order.