# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Stimulator, Electrical, Implanted, for Parkinsonian Tremor

Device Trade Name: Vercise™ Deep Brain Stimulation (DBS) System

Device Procode: NHL

Applicant's Name and Address: Boston Scientific Corporation
25155 Rye Canyon Loop
Valencia, CA 91355

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150031

Date of FDA Notice of Approval: 12/08/2017

## II. INDICATIONS FOR USE

The Vercise Deep Brain Stimulation (DBS) System is indicated for use in bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled with medication.

## III. CONTRAINDICATIONS

The Boston Scientific Vercise™ DBS System, or any of its components, is contraindicated for:

- **Diathermy.** Shortwave, microwave, and/or therapeutic ultrasound diathermy. The energy generated by diathermy can be transferred to the Vercise DBS System, causing tissue damage at the contact site resulting in severe patient injury or death.

- **Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS)** The safety of these therapies in patients implanted with the Vercise DBS System has not been established. It is possible that the energy generated by these therapies can be transferred to the Vercise DBS System, causing tissue damage that may result in severe patient injury or death.

- **Magnetic Resonance Imaging (MRI).** Patients implanted with the Vercise DBS System should not be subjected to MRI. MRI exposure may result in a) dislodgement of implanted components, b) heating of the contacts or other system components, causing permanent tissue lesioning, c) damage to the Stimulator's

electronics, current induction through the DBS Leads and Vercise DBS System causing unpredictable levels of stimulation, d) distortion of the diagnostic image, e) Personal injury or even death.

- **Patient Incapability.** Patients who are unable to properly operate the Remote Control and Charging System should not be implanted with the Vercise DBS System.

- **Poor Surgical Candidates.** The Vercise DBS System is not recommended for patients who are poor surgical candidates.

- **Unsuccessful Test Stimulation.** The Vercise DBS System should not be used in patients who experience unsuccessful test stimulation.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions are provided in the Vercise DBS System labeling.

## V. DEVICE DESCRIPTION

The Vercise DBS System includes a Stimulator with DBS Leads for stimulation of selected targets (i.e., the subthalamic nucleus) in the brain. DBS Extensions are used to connect the DBS Leads to the Stimulator implanted near the clavicle.

The Vercise DBS System utilizes current steering across eight contacts per DBS Lead, which is intended to provide precise positioning of stimulation. The Stimulator is controlled by a handheld Remote Control, and can be programmed by a Clinician Programmer using the Bionic Navigator™ Software. Periodically, the rechargeable Stimulator battery must be replenished with a radiofrequency (RF) charging device provided in the Charging Kit.


**Figure 1. Vercise DBS System**

**Figure 2. Typical Implant Location**

## A. Implanted Components

- Implantable Pulse Generator (IPG, Model # DB-1110-C): 16-contact, multi-channel, implantable pulse generator with a rechargeable power source. Generates programmable electrical pulses that are conducted to targets in the brain via leads. The IPG can support up to two 8-contact leads. All contacts have independent current control. A charge density warning appears on the Clinician Programmer when stimulation settings are set to deliver $\geq 30\mu C/cm^2$/phase. Table 1 below provides a summary of the programmable stimulation parameters.

**Table 1: Vercise DBS System Stimulation Parameters**

| Parameters | Range |
|---|---|
| Waveform | Charge balanced asymmetric biphasic |
| Pulse Shape | Rectangular |
| Current or Voltage Regulated | Current |
| Amplitude Range | 0.1 - 12.7 mA per contact (up to 20.0 mA per Area) |
| Pulse Width Range | 10μs - 450μs |
| Frequency Range | 2 - 255Hz |
| Contact Connections (i.e., Channels) | 16 |
| Independent Areas of Stimulation (4 Programs with 4 Areas per Program) | 16 |
| Current Path Options | Unipolar, Bipolar, or Multipolar |

- Leads (Model # DB-2201-xx, xx = 30 or 45, i.e., length of 30cm or 45cm): The DBS leads deliver electrical pulses generated by the IPG to targets in the brain. The DBS Lead model DB-2201 has 8 cylindrical ring contacts at the distal end and is available in lengths of 30 cm and 45 cm. The lead specifications are provided in Table 2 below.

**Table 2: DBS Lead Specifications**

| Feature | Description |
|---|---|
| Number of Contacts | 8 |
| Contact Length | 1.5 mm |
| Contact Surface Area | 6.0 $mm^2$ |
| Contact Spacing (Center-to-Center) | 2.0 mm |
| Contact Span | 15.5 mm |
| Distal Contact to Tip Length | <1.3 mm |
| Diameter | 1.3 mm |
| Overall Length | 30 cm, 45 cm |
| Outer Jacket Tubing (Insulation) | Polyurethane |
| Contact Material | Platinum/Iridium |
| Impedance (Ω) | ≤ 90 (measured from each connector to corresponding electrode contact) |

- Lead Extension (Model # NM-3138-55): The DBS Extension consists of a connector at the distal end and 8 cylindrical contacts at the proximal end. The DBS Lead may be inserted and secured into the connector, which also contains 8 contacts that align with the contacts on the DBS Lead to form electrical connections. The proximal end is inserted into the IPG.

- Implantable Accessories:
  - Burr Hole Cover: The Burr Hole Cover is used to permanently secure the DBS lead and to cover the burr hole created in the skull during the surgical implantation of the DBS lead.
  - DBS Lead Boot: The DBS Lead Boot protects the proximal end of the DBS Lead prior to the Stimulator implant surgery.
  - Suture Sleeve: The Suture Sleeve may be used to anchor the DBS Lead or DBS Extension to the fascia.
  - M8 Adaptor: The M8 Adaptor is provided to connect Medtronic lead models (3387 and 3389) to the Boston Scientific Vercise IPG. The M8 Adaptor is

compatible with the following Medtronic lead extensions models: 3708640, 3708660, 3708695, 3708540, 3708560, 3708595.

**B. External Components**

- ETS (Model # DB-5110-C): The External Trial Stimulator (ETS) is a component that may be used for intraoperative testing of stimulation. It provides the identical stimulation capabilities as the IPG.

- Remote Control (Model # DB-5212-C): The Remote Control is a hand-held, battery operated unit that uses telemetry to communicate with the IPG and ETS. It allows the patient to control the stimulation therapy prescribed by the clinician (e.g., turn DBS system on and off).

- Charger (Model # NM-5312): The Charger uses radiofrequency (RF) energy to inductively charge the implanted IPG battery when the Charger is placed externally over the IPG implant site.

- Base Station (Model # NM-5305): The Base Station connects to a wall-mounted power supply and is utilized to recharge the Charger.

- Clinician Programmer (Model # DB-7161, NM-7161, DB-7161R, NM-7161R): The Clinician Programmer is used by the clinician to program the IPG and ETS, and thus prescribe stimulation therapy for the patient.

- Non-implantable or External Accessories:
  - Tunneling Tool: used to create a path for the DBS Lead and DBS Extension in the subcutaneous tissue.
  - Lead stop: may be attached to the lead to prevent the lead from being advanced beyond a certain depth into the neural tissue during its initial placement.
  - Lead Stylet: inserted in the lead to keep the lead stiff during placement.
  - Charging Collar: used to place the Charger externally over the IPG during charging.
  - Charger Spacer: a piece of material placed behind the Charger in the pocket of the Charging Collar.
  - Adhesive Kit: for attaching the Charger to the patient's body during charging. Alternative to Charging Collar.
  - O.R. Cable and Extension: connects the Lead Extension to the ETS during intraoperative testing.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

At present there is no cure for PD; treatment is focused on management of symptoms. A patient should fully discuss the below alternatives with his/her physician to select the method that best meets expectations and lifestyle.

**Non-Surgical Treatment Options**

Medical therapy for motor symptoms has been primarily focused on restoring dopamine levels through the administration of levodopa, dopamine agonists, or monoamine oxidase B inhibitors. Current standards for patient care recommend levodopa as first line of therapy for the symptomatic control during the early, uncomplicated stages of PD. Unfortunately, chronic treatment with levodopa, and other anti-parkinsonian agents frequently leads to significant side effects, especially dyskinesias and motor fluctuations.

**Surgical Treatment Options**
For subjects who have reduced response or complications due to to medical therapy, pallidotomy (destruction of a portion of the globus pallidus) and thalamotomy (destruction of a region of the thalamus) are available surgical treatment options. In the 1990s, high-frequency deep brain stimulation (DBS) was introduced as an adjunct to therapy towards reducing the motor complications of subjects with PD. Other DBS devices are also currently marketed in the United States, these include: Medtronic Activa®PC, Activa®RC, Activa®SC, and the St. Jude Medical Infinity Neurostimulation Systems.

## VII. MARKETING HISTORY

The Vercise DBS System has been commercially distributed in the European Union since its CE Mark approval in January 2012. It has also been commercially distributed in Canada, Australia, Japan, South America, Eastern Europe, Russia, Hong Kong, India and South Africa.

The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following is a list of known risks with the use of Deep Brain Stimulation for the treatment of Parkinson's disease. There may be risks that are unknown. Note that some of these events may be resolved or reduced by current steering, changing stimulation parameters, or by changing the position of the lead during surgery.

**Risks Associated with Surgical Procedure and Post-operative Period:**

- Allergic reaction to anesthesia or antibiotics including anaphylaxis
- Blood clot formation in the extremities (e.g., in the veins of the legs)
- Blood clot or air forming in or traveling through the blood stream, which can block blood flow to parts of the lungs or other tissue that could be life-threatening.
- Brain contusion (bruising)
- Brain or cerebspinal fluid infection or inflammation
- Cerebral spinal fluid (CSF) leaking outside the skull or collecting inside the skull abnormally.
- Confusion or problems with attention, thinking, or memory (acute or chronic)
- Death
- Fibrosis (thickened skin and scarring) around the lead extension (including tightening, tethering, and bowstringing)

- Hemiparesis (muscular weakness or partial paralysis on one side of the body)
- Hemiballism (uncontrollable involuntary movements of a limb or limbs on one or both sides of the body)
- Intracranial hemorrhage (which can lead to stroke, paralysis, or death)
- Intraparenchymal cyst
- Infection
- Injury to structures next to the implant, such as blood vessels, nerves, the chest wall, and the brain
- Injury to the nerves in the armpit (brachial plexus) leading to pain or weakness of the arm or hand
- Neurosurgery/anesthesia risks, including unsuccessful implant or pneumonia
- Pain at the surgical site(s), headache or discomfort
- Seizures
- Speech or language difficulties
- Subcutaneous hemorrhage or seroma (blood or fluid colletion under the skin, including the skin over the skull).
- Stroke resulting in temporary or permanent problems
- Swelling or bruising of the muscles or skin in the area of the lead or of the IPG implant

**Possible Side-Effects of Stimulation:**

- Confusion or problems with attention, thinking, or memory
- Gait difficulty (trouble walking) and falls
- Pain, headache or discomfort
- Pneumonia from difficulty with swallowing or from inhaling fluid
- Psychiatric disturbances such as anxiety, depression, lessened interest or emotion, hypersexuality, aggression, mania or hypomania, pyschosis, emotional sensitivity, sleep problems, suicide, or suicidal thoughts or attempts
- Seizures
- Sensory changes
- Speech or language problems
- Swallowing difficulty
- Systemic effects such as rapid heart beat, sweating, fever, dizziness, changes in kidney function, difficulty passing urine, sexual effects, nausea, difficulty having bowel movements, bloating
- Weakness, muscle spasms, shaking, restlessness, or problems with movement
- Undesirable sensations (e.g., tingling)
- Visual problems, eyelid or eye movement difficulties or other eye-related symptoms
- Weight changes

**Device-Related Risks:**

- Allergic or immune system response to implanted materials

- Failure or malfunction of any part of the device, including but not limited to: Battery leakage, battery failure, lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches, whether or not these problems require device removal and/or replacement
- Implant site complications such as pain, poor healing, redness, warmth, swelling or wound reopening
- Implanted device components (stimulator, lead, or extension) may move from original implanted location or wear through the skin, which may lead to the need for additional surgery
- Infection
- Interference from external electromagnetic sources
- Loss of adequate stimulation
- Pain, headache or discomfort
- Skin irritation or burns at the stimulator site
- Stiffness in muscles or joints
- Worsening of disease symptoms, potentially caused by loss of stimulation, medication changes, surgery, or illness. In rare cases worsening can become a life-threatening crisis associated with varied symptoms such as mental status changes, fever, and muscle rigidity
- Swelling, including fluid collecting around the device

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

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

Pre-clinical design verification testing provided evidence that the design outputs met the design input requirements. All conducted tests successfully met the acceptance criteria for the requirements. All tests results leveraged from the Precision SCS system were done so with an acceptable leveraging rationale.

**Vercise Implantable Pulse Generator (IPG)**
The hardware design verification testing was leveraged from the Precision SCS IPG which has the same hardware as the Vercise IPG.

**Table 3: IPG Verification Testing**

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| IPG Electronics | Verify the requirements for:<br>• Pulse Generation<br>• Analog IC Power Supply and Reference Circuits | • The IPG stimulation output parameters shall be within the specified tolerances.<br>• Internal IPG circuits shall function within their specified limits. |
| | • RF Telemetry Interface<br>• Battery Protection Circuitry | • The IPG RF receiver shall function as specified<br>• The battery protection circuits shall function as specified. |

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| Environmental and Mechanical Stresses | Verify the integrity and function of the IPG after exposure to environmental and mechanical stress conditions such as:<br>• High and low storage temperature<br>• Temperature changes<br>• Mechanical forces<br>• Random Vibration<br>• Drop<br>• High and low atmospheric pressures | The IPG shall pass device level functional tests and visual inspection after exposure to environmental and mechanical stresses. |
| | Verify the integrity of the header after mechanical stresses and suture pull. | Header shall not show delamination or cracking. |
| Hermeticity | Verify that the internal moisture content of the hermetically sealed IPG case is within acceptable limits. | The internal water vapor content shall be within specifications. |
| Immunity to Medical Procedures/Therapies | Verify that the IPG is functional after exposure to the following medical procedures/therapies:<br>• Diagnostic Ultrasound<br>• Electrocautery<br>• External Defibrillation<br>• X-Ray | The IPG shall pass device level functional tests and visual inspection after exposure. |
| IPG-Lead Interface | • Verify that the Lead to IPG connection meets the requirements for insertion, withdrawal and retention forces.<br>• Verify contact resistance.<br>• Verify electrical isolation | • The insertion, extraction and retention forces for the Lead-IPG Connector interface shall meet the specifications. Connector components shall maintain integrity after multiple insertion and withdrawal cycles.<br>• The resistance for each contact shall meet the specifications.<br>• The impedance between any two terminations shall be within the specifications. |
| IPG Battery | • Evaluate battery life.<br>• Verify cell performance and integrity. | • The evaluation of battery longevity under typical use conditions shall support the labeled battery life.<br>• After exposure to mechanical and environmental stresses, the battery cells must meet the requirements for hermeticity as well as electrical and mechanical integrity.<br>• The battery cells must meet the requirements for self-discharge and storage loss.<br>• After multiple discharge cycles, battery cells must meet visual, mechanical and hermeticity criteria.<br>• The battery cells shall maintain mechanical integrity during and after application of exposure to short circuits and abnormal discharging. |
| Charging | Verify that the IPG can be charged at the specified charging distances. | • The IPG charging shall meet the requirements when the Charger is at a specified distance from the IPG.<br>• The IPG must signal the Charger to stop the charge process within specified time period. |

## DBS Leads, Extensions and Accessories

**Table 4: DBS Leads, Extensions, and Accessories Verification Testing**

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| Physical and Mechanical Characteristics | Verify the physical and mechanical characteristics of :<br>• Lead<br>• Lead Extension<br>• Stylet<br>• Lead Boot<br>• Lead Stop<br>• Burr-Hole Cover | • Lead dimensions, surface finish, Lead straightness shall meet the specifications.<br>• The distal Lead shall experience minimal movement when the proximal Lead is folded at a specified angle.<br>• The Lead shall withstand the specified end-to-end pull force without loss of mechanical or electrical integrity.<br>• The force required to deflect the Lead tip shall meet the requirements.<br>• When exiting the cannula, deflection of the Lead tip shall be within specification.<br>• The Stylet dimensions and deflection force shall meet the specifications.<br>• The Lead Boot shall meet the requirements for fit, smooth profile, seal and retention force when connected to the lead.<br>• The Lead Stop shall meet the dimensional and geometrical requirements and be able to resist translational forces.<br>• The Burr-Hole Cover shall meet the requirements for dimensions, geometric specifications, lead clip placement and assembly.<br>• The Extension shall withstand tunneling and pull forces.<br>• The Lead and Extension shall maintain mechanical and electrical integrity after exposure to flex fatigue. |
| Electrical Tests | Verify that the Lead and Extension meets the requirements for electrical isolation and continuity of conductor paths. | • Current leakage shall be within specifications in dry and soaked states.<br>• The electrical DC resistance of the Lead and Extension shall meet the specifications. |
| Interface Tests | Verify the compatibility and interface between Lead, Extension and other Lead accessories. | • The retention force for the connection between Lead, Extension and other Lead accessories shall meet the specifications.<br>• Components shall maintain mechanical and electrical integrity following multiple connection and disconnection cycles between Lead and Lead accessories. |

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| | | • Lead shall maintain integrity after multiple clamp and unclamp cycles with the Burr-Hole Cover. The Lead is securely held in place by the Burr-Hole Cover.<br>• The locking force for the connection between Extension and IPG connector shall meet the specifications. |
| Storage Conditions | Verify integrity of DBS Leads and Sterile Kit components after exposure to temperature conditions likely to be encountered during shipping and storage. | • Components of DBS System Sterile Kits shall be functional after temperature cycling and after storage in high and low temperatures. |

**Vercise Remote Control**

The hardware design verification testing was leveraged from the Precision SCS Remote Control which has the same hardware as the Vercise Remote Control.

**Table 5: Remote Control Verification Testing**

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| Environmental and Mechanical Stress | Verify the integrity and function of the Remote Control after exposure to environmental and mechanical stress conditions such as:<br>• High and low storage temperature<br>• Temperature changes<br>• Mechanical shock<br>• Random Vibration<br>• Drop<br>• Humidity<br>• Button presses representing years of use | The Remote Control shall pass device level functional tests and visual inspection after exposure to environmental and mechanical stresses. |
| Remote Control Functions | Verify Remote Control functions. | • Remote Control shall respond to each key press as well as typically used combinations with appropriate action and appropriate display on the LCD screen.<br>• Infra-red communication success rate shall meet the specifications.<br>• RF communication with stimulators shall meet the specifications at the labeled distance.<br>• Remote Control shall display the proper battery level status.<br>• The Remote Control shall successfully execute the Power-On-Self test. |

**Charging System**

The hardware design verification testing was leveraged from the Precision Charger which is the same device as the Vercise Charger.

**Table 6: Charging System Verification Testing**

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| Environmental and Mechanical Stress | Verify the integrity and function of the Charger and Base Station after exposure to environmental and mechanical stress conditions such as:<br>• High and low storage temperature<br>• Temperature changes<br>• Mechanical forces<br>• Random Vibration<br>• Drop<br>• Humidity | The Charger and Base Station shall pass device level functional tests and visual inspection after exposure to environmental and mechanical stresses. |
| Charger Electronics | Verify functionality of the Charger electronics. | • Protection of charging terminals against over-voltage and over-current conditions shall operate as specified.<br>• The quiescent current, coil voltage and frequency, power dissipation and IPG charge current shall meet the specifications.<br>• The Charger electronics shall function as specified with regards to:<br>− indication of battery status level<br>− charging of the Charger battery<br>− indication of alignment with the IPG<br>− detection of end-of-charge signal when IPG is fully charged<br>− battery protection circuits. |
| Heating During Charging | Verify the requirements for heat generated during charging. | • The surface temperature of the Charger shall not exceed the acceptable limit while charging.<br>• The IPG case heating due to heat dissipation during charging shall be within acceptable limits. |
| Base Station | Test for continuity, spring contact fatigue and connector fatigue. | • The resistance between the DC power jack and spring contact shall meet the specifications.<br>• Spring contacts shall remain elastic after repeated deflections.<br>• Power supply plug shall fit and not be loose after repeated insertion/extraction cycles. |

## Vercise External Trial Stimulator (ETS)

The hardware design verification testing was leveraged from the Precision ETS which has the same hardware as the Vercise ETS.

**Table 7: ETS Verification Testing**

| Test | Purpose | Acceptance Criteria |
|---|---|---|
| ETS Electronics | Verify the requirements for:<br>• Pulse generation<br>• On/off switch and LED Indicator<br>• Operation within the operating temperature range, voltage range and load range<br>• Impedance measurements | • The ETS stimulation output parameters shall be within the specified tolerances across ranges of temperature, voltage and load.<br>• LED indicator should function as expected after repeated activation of the on/off switch.<br>• The impedance measurements shall meet the specifications. |
| Environmental and Mechanical Stress | Verify the integrity and function of the ETS after exposure to environmental and mechanical stress conditions such as:<br>• High and low storage temperature<br>• Temperature changes<br>• Mechanical shock<br>• Random Vibration<br>• Drop<br>• High and low atmospheric pressures<br>• Humidity | The ETS shall pass device level functional tests and visual inspection after exposure to environmental and mechanical stresses. |
| ETS - O.R. Cable Interface | • Verify that the O.R. Cable to ETS connection meets the requirements for insertion, withdrawal and retention forces. | After repeated insertion/withdrawal cycles, the output from every pin of the connector shall meet the specifications and the connector shall maintain mechanical and electrical integrity. |

**Software**

Software testing established that the system meets the software requirements and user needs for the intended uses.

**Electromagnetic Compatibility (EMC) and Wireless Technology**

EMC testing was performed in accordance with the relevant clauses of the following standards and met specified acceptance criteria:

- IEC 60601-1-2: 2014, "*Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests*" (appropriate essential performance criteria were used)
- ANSI/AAMI/ISO 14708-3:2008(R2011): *Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators"*, Part 27

Testing to address compatibility with Radio-frequency Identification (RFID) and Electronic Article Surveillance systems was also provided.

The wireless technology of the system includes RF telemetry between the Remote Control and the Stimulators and wireless inductive charging of the IPG. These connections were verified to meet the range, security, data integrity and overall system functionality requirements through design verification testing.

**Biocompatibility**

Biocompatibility of all tissue-contacting components of the Vercise™ Deep Brain Stimulation (DBS) 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 Vercise DBS Leads are considered permanent (> 30 days) implants in contact with neural tissue/bone, cerebrospinal fluid (CSF), and blood (indirect contact through CSF). The Vercise IPG, Lead Extensions, Suture sleeves, and Burr-Hole Cover are considered permanent (> 30 days) implants in contact with tissue/bone. The Lead Boot is considered an implant device with prolonged (24 hours – 30 days) tissue/bone contact. and implanted accessories meet the biocompatibility requirements for tissue/bone contacting permanent implants per EN ISO 10993-1:2009 COR2010. The Charging Collar is considered an intact skin-contacting device with limited (≤ 24 hours) contact.

Biocompatibility of the Vercise DBS Leads was demonstrated by cytotoxicity and neuroimplantation testing on the final, sterilized Vercise DBS Leads, leveraging testing previously conducted on the Linear 8 Contact Lead (Model # SC-2138 and SC-2208) approved in P030017, and leveraging biocompatibility data on U.S. marketed devices with direct blood contact. An ISO MEM elution cytotoxicity test was conducted on the Vercise DBS Lead with passing results. A neuroimplantation study was conducted in a swine model to assess the safety of the Vercise DBS Leads at approximately 30 and 180 days post-implantation. Implantation of the Vercise DBS Leads was not associated with any unexpected adverse effects. Both cytotoxicity and implantation studies on the Vercise DBS Leads were conducted in compliance with Good Laboratory Practices (GLP) regulations (21 CFR Part 58). The sensitization, intracutaneous reactivity, systemic toxicity (acute, subchronic, and chronic toxicity), material-mediated pyrogenicity, genotoxicity, and carcinogenicity endpoints for the Vercise DBS Leads were assessed by leveraging biocompatibility information on the Linear 8 Contact Lead (P030017). This was appropriate because the Vercise DBS Leads and Linear 8 Contact Lead are identical in terms of the tissue-contacting materials and are manufactured and sterilized by the same processes. Hemolysis (indirect contact) endpoint was assessed by leveraging hemocompatibility data on the U.S. marketed devices (approved in P010012/S274 and P050046/S012) with identical tissue-contacting materials as the Vercise DBS Leads.

Biocompatibility of the Vercise IPG was demonstrated by leveraging testing previously conducted on the Precision SCS System IPG Model SC-1110 (P030017). Leveraging this testing information was appropriate because the Vercise IPG is identical to the Precision SCS System IPG in terms of the tissue-contacting materials, manufacturing including sterilization processes, and the nature and duration of tissue contact.

The Vercise Lead Extensions are the same lead extensions used in the Precision SCS System (P030017).

Biocompatibility of the Vercise Suture Sleeves was demonstrated by appropriately leveraging testing previously conducted on Linear 8 Contact Lead (Model # SC-2138 and SC-2208) approved in P030017. The Vercise Suture Sleeves are made of the

identical silicone material that is present in the Linear 8 Contact Lead and both devices have permanent (> 30 days) contact with tissue/bone. In addition, an ISO MEM elution cytotoxicity test was conducted on the finished, sterilized 4.0 cm Vercise Suture Sleeve with passing results.

The Burr Hole Cover consists of a Base, Retaining Clip, Cap and two Screws. Biocompatibility of the Base, Retaining Clip, and the Cap was demonstrated by testing conducted on these components in their finished, sterilized forms and by leveraging data in the device master file and in the US marketed devices with identical material. The MEM elution cytotoxicity, guinea pig maximization sensitization, intracutaneous reactivity, intramuscular implantation (13 weeks), acute systemic toxicity, rabbit pyrogenicity, and genotoxicity (Ames, in vitro chromosomal aberration, and mouse micronucleus) tests were conducted on the Base, Retaining Clip, and Cap. All biocompatibility tests were conducted in compliance with GLP regulations (21 CFR Part 58). All pre-specified test acceptance criteria were met for all tests and all tests passed. The data in the device master file and the US marketed devices were leveraged for the assessment of subchronic/chronic toxicity and carcinogenicity endpoints. Biocompatibility of the Screws was demonstrated by appropriately leveraging biocompatibility data on Precision SCS System IPG Model SC-1110 (P030017) with identical material and nature and duration of tissue contact. In addition, the final, sterilized Burr Hole Cover was used in the swine neuroimplantation study (30 and 180 days) and no device material related adverse findings were noted in the study.

Biocompatibility of the Vercise Lead Boot was demonstrated by leveraging testing previously conducted on the Precision SCS System 55cm 8 Contact Lead Extension (Model SC-3138-55) approved under P030017. Leveraging this testing information was appropriate since the Vercise Lead Boot is identical to the Precision SCS System 55cm 8 Contact Lead Extension (Model SC-3138-55) in terms of the tissue-contacting materials, manufacturing and sterilization processes. In addition, an ISO MEM elution cytotoxicity assay was conducted on the finished, sterilized Vercise Lead Boot with passing results.

Biocompatibility testing was conducted on the finished DBS Charging collar in accordance with GLP regulations (21 CFR Part 58). The agarose overlay cytotoxicity assay, primary skin irritation, and repeated patch dermal sensitization tests were conducted on the DBS Charging Collar, All pre-specified test acceptance criteria were met for all tests and all tests passed.

**Sterilization**

The Vercise IPG, DBS Lead, Extension, OR Cable, Burr Hole Cover and other implanted accessories are sterilized using a validated EO sterilization cycle to achieve a minimal sterility assurance level of $10^{-6}$. Validation of the EO sterilization process for these devices was done in accordance with EN ISO 11135:2014 *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*. EO residual levels found on these devices following EO sterilization process are shown to

be below the maximum allowable limits of EO and Ethylene chlorhydrin (ECH) residual levels specified in EN ISO 10993-7:2008(Cor) 2009 *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.*

The bacterial endotoxin levels on these device, determined using Limulus Amebocyte Lysate (LAL) testing in accordance with the USP Chapter <161> *Transfusion and Infusion Assemblies and Similar Medical Devices*, and ANSI/AAMI ST72:2011 *Bacterial endotoxins - Test methods, routine monitoring and alternatives to batch testing*, comply with the bacterial endotoxin limits specified in the and FDA's Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (June 2012).

**Packaging and Shelf Life**
Packaging performance and stability testing results demonstrated that the packaging system for the sterile components of the BSN Vercise DBS System can withstand the environmental and mechanical stresses likely to be encountered during transportation and storage and maintain its sterile barrier up to two years of the established shelf-life.

### B. Animal Studies

A study was performed to evaluate the safety of the Vercise DBS System in a swine model at approximately 30 and 180 days post-implantation.

The safety of the leads and electrical stimulation at different stimulation settings was evaluated. Implantation of the DBS leads, and activation of the electrodes in those leads, did not appear to be associated with unexpected adverse effects. In summary, the morphological reactions associated with the placement, presence, and activation of the lead are similar to previously approved implantable DBS technologies.

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

Two studies, the INTREPID Study, and the VANTAGE Study, were the basis for the PMA approval decision.

The INTREPID Study data was considered for both safety and effectiveness. Safety was evaluated based on all available data on 292 consented subjects while the effectivess was evaluated using the cohort of 160 randomized subjects per the pre-specified interim analysis. Enrollment for the INTREPID Study is still ongoing.

The VANTAGE Study data were considered for safety only. This included 40 consented patients.

**INTREPID STUDY**
The applicant has undertaken the INTREPID clinical study in the U.S. under IDE #G120075 to establish a reasonable assurance of safety and effectiveness of Deep Brain Stimulation (DBS) with Vercise System as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson's disease (PD) that are

not adequately controlled with medication.A summary of the clinical study is presented below.

## A. Study Design

INTREPID is a multi-center, prospective, double blind, randomized (3:1) controlled study. The study was designed to evaluate the safety and effectiveness of the Vercise™ System for bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled with medication..

Patients were treated starting in May 2013. The data used in consideration of this PMA reflected data collected through December 31, 2016, and included 292 patients from 23 investigational sites. Safety was evaluated based on all patients enrolled in the study within this timeframe (May 2013-December 2016) while effectiveness was analyzed using the 160 subjects who had been randomized, per the pre-specified interim analysis.

Subjects who passed screening criteria were implanted bilaterally with the Vercise DBS System in the subthalamic nucleus (STN) for the treatment of their Parkinson's disease.

The initial epoch of the study was a period of 12 weeks during which subjects remained blinded to their treatment assignment, and during which a blinded assessor (who was unaware of the subject assignment) completed all study assessments (i.e., double blind study design). The treating neurologist was responsible for subjects' programming and adjustment of their anti-parkinsonian medications. Subjects were randomized in a 3:1 ratio to either receive Active or Control settings. Subjects in the Active group received therapeutic settings titrated by the treating neurologist to best clinical effect.. Subjects in the Control group received sham stimulation where the stimulation was not set to therapeutic levels. At the Week 12 post-randomization visit, all subjects began an open-label period, with a follow-up period up to 5 years. The study design is shown in Figure 3.

Subjects completed a 3-day PD diary [1] to document their PD symptoms prior to each study visit. During specified in-office study visits, subjects completed study assessments in their *stim on/meds off* and *stim on/meds on* condition. A neuropsychological battery of tests was also completed during study screening, Week 12 and Week 52 visits, to evaluate the cognitive and behavioral aspects of the subject prior-to and after receiving their DBS implant.

To obtain a comprehensive overview of subjects' responses to treatment in the study, additional assessments were administered including the Unified Parkinson's Disease Rating Scale [2] (UPDRS), 39-item Parkinson's Disease Questionnaire [3] (PDQ-39), Modified Schwab and England [2] (SE), Treatment Satisfaction, Short Form Survey [4] (SF-36v2), and Global Impression of Change [5] (assessed by subject and assessor).

During the study, subjects were evaluated without medication (*meds off* condition) and one-hour following intake of their anti-parkinsonian medications (*meds on* condition). The *meds off* and *meds on* condition assessments were completed during screening, and at Baseline, Weeks 12, 26, and 52 visits post-randomization. These were also to be completed at Year 2, 3, 4 and 5 Visits post-randomization.

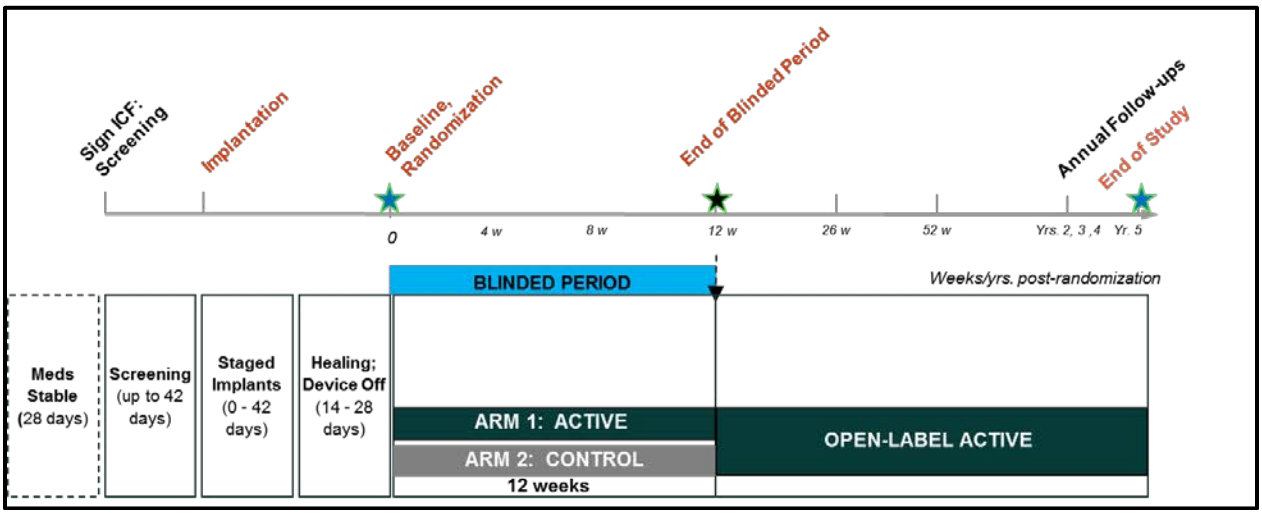


**Figure 3: INTREPID Study Schematic**

Safety event rates were monitored for the entire duration of the study by an independent Data and Safety monitoring board (DSMB) comprised of medical and statistical expert reviewers.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the INTREPID Study was limited to patients who met the following key inclusion criteria:

   - Age at the time of enrollment: 22 - 75 years
   - Duration of idiopathic PD: ≥ 5 years of motor symptoms with persistent disabling PD symptoms or drug side effects despite optimal medical therapy;
   - Severity of modified Hoehn and Yahr (H&Y) [6] stage ≥ 2 (*meds off* condition)
   - Greater than or equal to 6 hours of poor motor function (OFF time plus ON time with troublesome dyskinesias) per day as assessed by PD diary [1]
   - UPDRS-III [2] score of ≥ 30 in the *meds off* condition and improvement by ≥ 33% following intake of anti-parkinsonian medications
   - Dementia Rating Scale [7] (DRS-2) score ≥ 130
   - Beck Depression Inventory II [8] (BDI-II) score < 17 in the *meds on* condition
   - Willing and able to comply with all visits and study related procedures (e.g., using the remote control, charging system and completing the PD Diary [1])

- Able to understand the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed.

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

- Any intracranial abnormality or medical condition that would contraindicate DBS surgery
- Have untreated clinically significant depression per Diagnostics and Statistical Manual of Mental Disorders [9] (DSM-IV) criteria as determined by BDI-II [8] score $\geq 17$.
- History of suicide attempt or current active suicidal ideation as determined by a positive response to Items 2 -5 of suicide ideation sub-scale of the Columbia Suicide Severity Rating Scale [10] (C-SSRS).
- Any current drug or alcohol abuse, per DSM-IV [9] criteria
- Any history of recurrent or unprovoked seizures or hemorrhagic stroke
- Any prior movement disorder treatments that involved intracranial surgery or device implantation.
- Any other active implanted devices including neurostimulators (e.g., cochlear implant, pacemaker) and /or drug delivery pumps, whether turned on or off. Passive implants (e.g., knee prostheses) allowed provided that they do not interfere with the functioning of the Vercise™ System.
- Any significant medical condition that is likely to interfere with study procedures or likely to confound evaluation of study endpoints
- Any terminal illness with life expectancy of < 1 year
- A female who is breastfeeding or of child-bearing potential with a positive urine pregnancy test or not using adequate contraception
- Any impairment that would limit subject's ability to record PD Diary entries or perform wound care, unless a caregiver is available to assist.

2. Follow-up Schedule

The follow-up schedule is as noted in Figure 3. The following assessments were conducted to derive the study endpoints:

- Anti-parkinsonian Medications (levodopa equivalents)
- Clinical Dyskinesia Rating Scale (CDRS)
- Clinical Global Impression of Change (CGI-C)
- Clinical Global Impression of Change – Subject (CGI-C: Sub)
- EQ-5D 5 Level (EQ-5D-5L)
- Hand-Arm Movement between two points
- Parkinson's Disease Diary (PD diary)
- Parkinson's Disease Questionnaire (PDQ-39)
- Resource Utilization Inventory (RUI)

- Schwab and England Scale (SE)
- SF-36v2 Health Survey (SF-36 v2)
- Stand-Walk-Sit Test
- Treatment Satisfaction Questionnaire
- Unified Parkinson's Disease Rating Scale (UPDRS-I, II, III, IV).

Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, the endpoint included the rates of occurrence of the following adverse device effects (ADEs) at 52 weeks post-randomization:

- Cerebrovascular accident (CVA) and subdural hematomas
- Death
- Seizure
- Suicide or suicide attempt
- Pre-specified motor/sensory symptoms
  - Dystonia;
  - Eye Deviation, Conjugate;
  - Eyelid Apraxia;
  - Muscle Spasm;
  - Postural/Gait Disturbances;
  - Speech Disorders;
  - Swallowing Disorders;
  - Undesired Sensations, Non-target Stimulation Area;
  - Visual Disturbances.
- Pre-specified psychiatric symptoms
  - Anxiety;
  - Apathy without Mood Disorder;
  - Depression;
  - Emotional Reactivity;
  - Hallucinations;
  - Impulsive Behavior;
  - Mania;
  - Psychosis.

The primary effectiveness endpoint for the study was the difference in the mean change from baseline to 12 weeks post-randomization between the Active and Control groups in the mean number of waking hours per day with good symptom control and no troublesome dyskinesia, as measured on the PD Diary [1], with no increase in anti-parkinsonian medications. The study met success criteria for the primary endpoint based on the pre-specified interim analysis.

The following secondary endpoints were analyzed at 12 weeks post-randomization between the Active and Control groups as compared with Baseline:

- Motor function as assessed by UPDRS III [2] scores in *stim on/meds off* condition and in *stim on/meds on* condition
- Activities of Daily Living (UPDRS II) [2] from UPDRS in *stim on/meds on* condition
- Quality of life as assessed by PDQ-39 [3], SF-36v2 [4] and SE [2]
- Treatment Satisfaction
- Global impression of change [5] as assessed by subjects and clinicians.

4. Pre-Specified Statistical Analysis Plan

   The study was designed such that there would be at least 160 randomized subjects, with a maximum of up to 310, at up to 30 US sites. These sample sizes would be based on the outcomes of four pre-specified interim analyses throughout the study. The four interim analyses would be performed as follows:

   - For futility after 60 randomized subjects reached the 12 week post-randomization follow-up visit, and
   - For effectiveness and futility after 160, 200, and 240 randomized subjects reached the 12 week post-randomization follow-up visit

   The adaptive design used the Lan-DeMets group sequential method with the O'Brien-Flemming spending function and Pocock spending function.

   A two group t-test with a one-sided 0.025 significance level (adjusted for the interim analyses) was used to assess the primary endpoint. The Intent-To-Treat (ITT) analysis set was used for the primary analysis. Missing data at 12 week post-randomization were imputed appropriately. The 95% confidence interval (CI) of the treatment effect was reported.

   Secondary endpoints were successively analyzed according to a parallel gatekeeping procedure (Benjamini and Hochberg) with five endpoint families using the aforementioned order.

## B. Accountability of PMA Cohort

At the time of database lock, a total of 292 subjects provided consent to participate in the study at 23 participating sites in the U.S. One hundred and seventy seven subjects received the Vercise DBS System. The cohort of 160 randomized subjects were identified as the pre-specified interim analysis group. Figure 4 depicts a flowchart shows the disposition of subjects in the study.

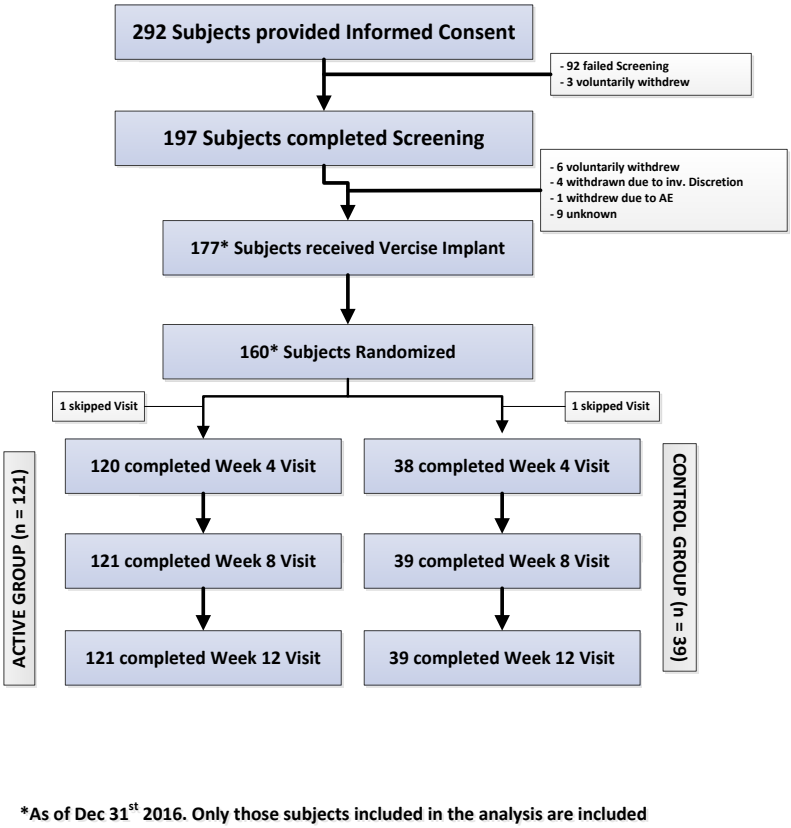


**Figure 4: Disposition of INTREPID Subjects**

## C. Study Population Demographics and Baseline Parameters

One hundred and sixteen of 160 subjects (72.5%) were male, The mean age of subjects in the study at the time of consent was 59.9 ± 7.95 years. 43.1% (69/160) of subjects were younger than 60 years of age and 10.6% (17/160) of subjects were over the age of 70.

Subjects' medical history revealed that two subjects had a prior intracranial surgery - one had a temporal lobe biopsy and the other had surgical repair of a Chiari malformation. Four subjects had a history of major depressive disorder and two had a diagnosis of dopamine dysregulation syndrome. In the last four weeks prior to screening, 30% (48/160) reported anxiety and 17.5% (28/160) reported restless legs syndrome.

Subjects were diagnosed with bilateral idiopathic Parkinson's disease with disease duration of 10.1 ± 3.61 years and mean severity of Hoehn and Yahr (H&Y) [6] score of 2.8 ± 0.73. Subjects' mean UDPRS III [2] Scores in *meds off* condition was 43.4 ± 9.6. Following intake of anti-parkinsonian medications, mean UPDRS III [2] scores improved by 57.5% (18.5 ± 8.26) in *meds on* condition.

Subjects completed a 3-day diary [1] in which they reported their PD symptoms in 30 minute increments. Subjects reported poor motor function with regard to the time spent ON with troublesome dyskinesias and OFF. These are summarized in Table 8 below. Subjects also reported a poor quality of life per quality of life and activities of daily living scores obtained via the PDQ-39 [3], Schwab and England [2], H&Y [6] and EQ-5D 5L [11].

**Table 8: INTREPID Study Clinical Characteristics**

| | All Randomized Subjects |
|---|---|
| | Mean (SD) N |
| Parkinson's disease Duration | 10.1 (3.61) 160 |
| | |
| Parkinson's Disease Diary (hours/day) | |
| Asleep | 7.20 (1.47) 158 |
| OFF Time | 6.92 (2.99) 158 |
| ON without dyskinesia | 4.65 (2.67) 150 |
| ON with non-troublesome dyskinesia | 3.65 (1.90) 120 |
| ON with troublesome dyskinesia | 4.35 (2.63) 105 |
| | |
| UPDRS III Scores | |
| UPDRS-III score (*meds off* condition) | 43.4 (9.60) 153 |
| UPDRS-III score (*meds on* condition) | 18.5 (8.26) 157 |

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of the INTREPID study safety data was based on a total of 292 consented (enrolled) subjects. Of these 292 subjects, 177 subjects received the Vercise System. Safety data for all the consented (enrolled) subjects (n = 292) is presented in this section (Table 2). Additionally, the safety data on the interim analysis cohort (n = 160) up to Week 12 post randomization (end of blinded period) is presented in Table 3. Please note that the VANTAGE Study (see below) also includes supplemental safety data on 40 patients implanted with the Vercise system.

The primary safety endpoint of the study included the rates of occurrence of pre-specified adverse device effects (ADEs) at 52 weeks post-randomization. Additional safety parameters evaluated in the study included the rates of occurrence of all serious adverse events (SAEs) and all adverse device effects (ADEs), including serious adverse device effects (SADEs) and unanticipated adverse device effects (UADEs) at 5 years post-randomization (available upon study completion).

Safety events were monitored for the entire duration of the study by an independent Data and Safety monitoring board (DSMB) comprised of medical and statistical expert reviewers.

**All Adverse Events**

A total of 788 adverse events in 143 subjects were reported in the study as of December 31, 2016. Of 788 events, 74 events were considered as Serious Adverse Events (SAE) and 714 events were considered non-serious adverse events. There were no unanticipated adverse events.

Data on all 788 adverse events was reported to FDA. Table 9 below presents only those AEs that are related to hardware, stimulation or procedure. Of 788 events, a total of 65 events were reported as related to hardware, 157 related to stimulation and 128 related to procedure.

**Table 9: All Adverse Events related to hardware, stimulation or procedure**

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Event | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Abnormal behavior | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Adverse drug reaction | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Affect lability | 0 (0.0%) | 2 (0.7%) | 1 (0.3%) |
| Aggression | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Agitation | 1 (0.3%) | 3 (1.0%) | 0 (0.0%) |
| Agitation postoperative | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Amnesia | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Anxiety | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Apathy | 1 (0.3%) | 2 (0.7%) | 1 (0.3%) |
| Aphasia | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Apraxia | 0 (0.0%) | 4 (1.4%) | 0 (0.0%) |
| Arthralgia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Asthenia | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Balance disorder | 1 (0.3%) | 12 (3.4%) | 1 (0.3%) |
| Blepharospasm | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Burning sensation | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| Cerebral hemorrhage | 1 (0.3%) | 0 (0.0%) | 3 (1.0%) |
| Cervicobrachial syndrome | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Chest discomfort | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Cognitive disorder | 3 (1.0%) | 2 (0.7%) | 3 (1.0%) |
| Complex partial seizures | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Confusion postoperative | 2 (0.7%) | 0 (0.0%) | 3 (1.0%) |
| Confusional state | 0 (0.0%) | 0 (0.0%) | 6 (2.1%) |
| Convulsion | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Depressed mood | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Depression | 2 (0.7%) | 2 (0.7%) | 4 (1.4%) |
| Device related infection | 4 (1.4%) | 0 (0.0%) | 4 (1.4%) |
| Diplopia | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Dizziness | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Dysarthria | 0 (0.0%) | 7 (1.7%) | 1 (0.3%) |
| Dysgeusia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Event | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Dyskinesia | 0 (0.0%) | 33 (10.3%) | 1 (0.3%) |
| Dysphagia | 0 (0.0%) | 6 (1.7%) | 1 (0.3%) |
| Dysphonia | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Dyspnoea | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Dystonia | 0 (0.0%) | 4 (1.4%) | 0 (0.0%) |
| Ecchymosis | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Electrocardiogram change | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Emotional disorder | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Encephalitic infection | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Epicondylitis | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Fall | 0 (0.0%) | 9 (2.7%) | 4 (0.3%) |
| Fatigue | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Freezing phenomenon | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Gait disturbance | 0 (0.0%) | 4 (1.4%) | 1 (0.3%) |
| Hematoma | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Hallucination, auditory | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Hallucination, visual | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Headache | 1 (0.3%) | 1 (0.3%) | 4 (1.0%) |
| Hiccups | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Hypersensitivity | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Hypoaesthesia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Hypomania | 0 (0.0%) | 3 (1.0%) | 0 (0.0%) |
| Hypotension | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Hypoventilation | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Impaired healing | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Implant site cellulitis | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Implant site erythema | 2 (0.7%) | 0 (0.0%) | 1 (0.3%) |
| Implant site hemorrhage | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Implant site hypersensitivity | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| Implant site infection | 4 (1.4%) | 0 (0.0%) | 3 (1.0%) |
| Implant site edema | 15 (4.8%) | 0 (0.0%) | 13 (4.1%) |
| Implant site pain | 3 (1.0%) | 0 (0.0%) | 1 (0.3%) |
| Implant site paresthesia | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Implant site reaction | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Impulsive behavior | 0 (0.0%) | 4 (1.4%) | 2 (0.7%) |
| Insomnia | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Intracranial hypotension | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Irritability | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Mania | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Medical device pain | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Memory impairment | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Mental status changes | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Musculoskeletal pain | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Musculoskeletal stiffness | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Myocardial infarction | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Nausea | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Neck pain | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| Oesophageal obstruction | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Oropharyngeal discomfort | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Pain in extremity | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Paresthesia | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Event | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Paranoia | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Parkinson's disease | 1 (0.3%) | 2 (0.7%) | 1 (0.3%) |
| Parosmia | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Photophobia | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Photosensitivity reaction | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Pneumocephalus | 3 (0.7%) | 0 (0.0%) | 5 (1.4%) |
| Postoperative fever | 0 (0.0%) | 0 (0.0%) | 2 (0.7%) |
| Procedural vomiting | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Psychotic disorder | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Pyrexia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Respiratory disorder | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Road traffic accident | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Salivary hypersecretion | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Sleep disorder | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Somnolence | 0 (0.0%) | 0 (0.0%) | 2 (0.7%) |
| Speech disorder | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Staphylococcal skin infection | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Stitch abscess | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Subdural hemorrhage | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Suicidal ideation | 0 (0.0%) | 2 (0.7%) | 0 (0.0%) |
| Suicide attempt | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Supraventricular tachycardia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Suture related complication | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) |
| Thrombophlebitis superficial | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Tremor | 2 (0.7%) | 5 (1.0%) | 3 (1.0%) |
| Urinary tract infection | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Venous injury | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Vomiting | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Weight decreased | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Weight increased | 0 (0.0%) | 5 (1.7%) | 0 (0.0%) |
| Wound dehiscence | 2 (0.7%) | 0 (0.0%) | 3 (1.0%) |
| Wound hemorrhage | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Wound infection | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| **TOTALS** | **65 (20.70%)** | **157 (48.80%)** | **128 (39.10%)** |

Incidence = Number of subjects with events divided by all consented subjects (n = 292)

**Adverse Events up to 12 Weeks Post Randomization**

In the cohort of 160 randomized subjects, a total of 362 events in 111 subjects were reported from time of consent to 12 weeks post randomization.

Of 362 adverse events, 283 events occurred in 86 subjects in the Active group and 79 events occurred in 25 subjects in the Control group. All 362 adverse events were reported to FDA. Table 10 below summarizes only those events related to procedure, stimulation, or hardware, based on their treatment assignment.

**Table 10: Adverse Events related to hardware, stimulation or procedure up to 12 weeks post randomization based on treatment assignment**

| | Related to Hardware | | Related to Stimulation | | Related to Procedure | |
|---|---|---|---|---|---|---|
| | Number of Events (Incidence) | | Number of Events (Incidence) | | Number of Events (Incidence) | |
| Event | Active | Control | Active | Control | Active | Control |
| Abnormal behavior | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Adverse drug reaction | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Aggression | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Agitation | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Agitation postoperative | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Amnesia | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Anxiety | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Aphasia | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Apraxia | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Arthralgia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Asthenia | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Balance disorder | 1 (0.8%) | 0 (0.0%) | 6 (5.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Blepharospasm | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Burning sensation | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cerebral hemorrhage | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Chest discomfort | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cognitive disorder | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Confusion postoperative | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (2.5%) | 0 (0.0%) |
| Confusional state | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (4.1%) | 1 (2.6%) |
| Convulsion | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Depressed mood | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) |
| Depression | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 1 (2.6%) |
| Device related infection | 3 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (2.5%) | 0 (0.0%) |
| Diplopia | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dysarthria | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Dyskinesia | 0 (0.0%) | 0 (0.0%) | 22 (16.5%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) |
| Dysphagia | 0 (0.0%) | 0 (0.0%) | 4 (3.3%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Dysphonia | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dyspnoea | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dystonia | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Electrocardiogram change | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Fall | 0 (0.0%) | 0 (0.0%) | 3 (2.5%) | 0 (0.0%) | 4 (0.8%) | 0 (0.0%) |
| Freezing phenomenon | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Gait disturbance | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Hematoma | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Hallucination, auditory | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Hallucination, visual | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Headache | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 2 (2.6%) |
| Hiccups | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Hypersensitivity | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Hypoaesthesia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Hypomania | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypotension | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Hypoventilation | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Impaired healing | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Implant site erythema | 1 (0.8%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Implant site infection | 2 (1.7%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 1 (2.6%) |

| | Related to Hardware | | Related to Stimulation | | Related to Procedure | |
|---|---|---|---|---|---|---|
| | Number of Events (Incidence) | | Number of Events (Incidence) | | Number of Events (Incidence) | |
| Event | Active | Control | Active | Control | Active | Control |
| Implant site edema | 8 (5.8%) | 2 (5.1%) | 0 (0.0%) | 0 (0.0%) | 5 (3.3%) | 3 (7.7%) |
| Implant site pain | 1 (0.8%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Implant site paresthesia | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Implant site reaction | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Impulsive behavior | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Insomnia | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Intracranial hypotension | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Mania | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Memory impairment | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Mental status changes | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (5.1%) |
| Myocardial infarction | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Nausea | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Neck pain | 1 (0.8%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Oropharyngeal discomfort | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Paranoia | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Parkinson's disease | 0 (0.0%) | 1 (2.6%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pneumocephalus | 3 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (3.3%) | 0 (0.0%) |
| Postoperative fever | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Procedural vomiting | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Pyrexia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Somnolence | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 1 (2.6%) |
| Staphylococcal skin infection | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Stitch abscess | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Supraventricular tachycardia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Tremor | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 1 (2.6%) |
| Urinary tract infection | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Venous injury | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Vomiting | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Weight increased | 0 (0.0%) | 0 (0.0%) | 3 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Wound dehiscence | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 1 (2.6%) |
| Wound haemorrhage | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| **TOTALS** | **29 (22.20%)** | **11 (28.50%)** | **67 (53.60%)** | **2 (5.20%)** | **76 (58.20%)** | **22 (54.40%)** |

Incidence = Number of subjects with events divided by number of subjects in each group (Active = 121 subjects, Control = 39 subjects)

**Serious Adverse Events**

Among all consented (enrolled) subjects (n=292), a total of 74 Serious Adverse Events (SAE) were reported in 46 subjects. All 74 serious adverse events were reported to FDA. Only the serious adverse events related to hardware, stimulation or procedure are summarized in Table 11 below. Of 74 Serious Adverse Events, 19 were related to hardware, 2 related to stimulation, and 31 related to procedure.

Infection has been the most commonly reported serious adverse event associated with device-hardware/procedure (8 events, representing 2.7% of subjects). There were three events (each) of device-hardware/procedure-related serious adverse events of peri-operative intracranial hemorrhage (representing 1% of subjects) and seizure (representing 1% of subjects). There were no device-hardware /procedure-

related ischemic strokes. Stimulation-related serious adverse events include one event of mania and one event of a failed suicide attempt.

**Table 11: Serious Adverse Events related to hardware, stimulation or procedure**

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Event | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Aphasia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Cerebral hemorrhage | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Complex partial seizures | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Confusion postoperative | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Confusional state | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Convulsion | 1 (0.3%) | 0 (0.0%) | 2 (0.7%) |
| Device related infection | 4 (1.4%) | 0 (0.0%) | 4 (1.4%) |
| Encephalitic infection | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Hypoventilation | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Implant site hemorrhage | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Implant site infection | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Implant site edema | 5 (1.7%) | 0 (0.0%) | 5 (1.7%) |
| Intracranial hypotension | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Mania | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) |
| Myocardial infarction | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Pneumocephalus | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Pyrexia | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Staphylococcal skin infection | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Subdural hemorrhage | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Suicide attempt | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |
| Wound dehiscence | 1 (0.3%) | 0 (0.0%) | 1 (0.3%) |
| Wound hemorrhage | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Wound infection | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| **TOTALS** | **19 (6.10%)** | **2 (0.60%)** | **31 (9.90%)** |

Incidence = Number of subjects with events divided by all consented subjects (n = 292)

In the cohort of 160 randomized subjects, a total of 26 serious adverse events in 20 subjects were reported. Of those, 21 serious adverse events in 16 subjects were in the active group and 5 serious adverse events in 4 subjects were in the control group was reported.

Table 12 summarizes only the serious adverse events related to hardware, stimulation or procedure up to Week 12 post randomization based on treatment assignment.

**Table 12: Serious Adverse Events related to hardware, stimulation or procedure up to 12 weeks post randomization based on treatment assignment**

| | Related to Hardware | | Related to Stimulation | | Related to Procedure | |
|---|---|---|---|---|---|---|
| | Number of Events (Incidence) | | Number of Events (Incidence) | | Number of Events (Incidence) | |
| Event | Active | Control | Active | Control | Active | Control |
| Aphasia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Confusion postoperative | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |

| | Related to Hardware | | Related to Stimulation | | Related to Procedure | |
|---|---|---|---|---|---|---|
| | Number of Events (Incidence) | | Number of Events (Incidence) | | Number of Events (Incidence) | |
| Event | Active | Control | Active | Control | Active | Control |
| Confusional state | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Convulsion | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Device related infection | 3 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (2.5%) | 0 (0.0%) |
| Hypoventilation | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Implant site edema | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Implant site infection | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Intracranial hypotension | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Myocardial infarction | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Pneumocephalus | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Pyrexia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| Staphylococcal skin infection | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.6%) |
| Wound hemorrhage | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) |
| **TOTALS** | **5 (4.10%)** | **4 (10.40%)** | **0 (0.00%)** | **0 (0.00%)** | **13 (10.60%)** | **4 (10.40%)** |

Incidence = Number of subjects with events divided by number of subjects in each group (Active = 121 subjects, Control = 39 subjects)

**Deaths**

Two deaths were reported. One subject died as a result of accidental physical trauma which was determined to be unrelated to the study device and/or implant procedure. The other cause of death is unknown; additional information is not available, and the relationship of the death to the device or stimulation is not known

2. Effectiveness Results

The study efficacy results are based on the cohort of 160 randomized subjects who completed their Week 12 post randomization. Please note that though the total number of randomized subjects is 160, the total number of subjects available for analysis is 156 (118 active and and 38 control). This is because four subjects (3 in treatment group and 1 in the control group) did not have baseline scores.

Based on the results of the pre-specified interim analysis, the study successfully met its primary endpoint with statistically significant improvement ($p < 0.001$) in mean change in waking hours per day with good symptom control and no troublesome dyskinesia, with no increase in antiparkinsonian medications (i.e., Levodopa Equivalent Dosage (LED)), from baseline to 12 weeks post-randomization in the Active ($3.74 \pm 4.79$ hours) compared to the Control group ($0.72 \pm 3.56$ hours) as shown in Table 13.

**Table 13: Mean change in waking hours per day with good symptom control and no troublesome dyskinesia, with no increase in antiparkinsonian medications (LED), from baseline to 12 weeks post-randomization**

| | Active Group | Control Group |
|---|---|---|
| | Mean (SD) N [ 95% CI ] | Mean (SD) N [ 95% CI ] |
| Baseline | 7.78 (3.65) 118 [7.1 - 8.4] | 8.08 (2.92) 38 [7.1 - 9.0] |

| | Active Group | Control Group |
|---|---|---|
| 12 weeks post-randomization | 12.37 (3.56) 118<br>[11.7 - 13.0] | 8.96 (3.94) 38<br>[7.7 - 10.3] |
| Change from baseline to 12 weeks post-randomization | 3.74 (4.79) 118<br>[2.9 - 4.6] | 0.72 (3.56) 38<br>[-0.5 - 1.9] |
| Difference in change from baseline to 12 weeks post-randomization between Active and Control groups | 3.03 (4.52)<br>[1.4 - 4.7] | |
| p-value | <0.001 | |

Post-hoc analysis was performed to report the improvement in mean change in waking hours per day with good symptom control and no troublesome dyskinesias from Baseline to 12 weeks post-randomization, without requirement in the anti-parkinsonian medication (as included in the primary endpoint). An improvement of 4.6 ± 4.81 hours in the Active group compared to 0.88 ± 3.57 hours in the Control group was noted.

**Secondary Endpoints**

For the following secondary endpoints the sample size is reported as a single "n" out of the 160 (active and control) pre-specified interim analysis cohort. These analyses are reported using the available data only; this is acceptable because the missing data rate for this study is sufficiently low (~5%).

***UPDRS III***

UPDRS III is the motor sub-section of the Unified Parkinson's disease Rating Scale (UPDRS) [2] and is used to evaluate overall motor disability.

This questionnaire was administered in the *meds off* and *meds on* condition.

*Meds off* condition

This section summarizes the results in the *meds off* condition. Subjects withheld their anti-parkinsonian medications for at least 12 hours (or overnight) prior to study visit.

A 12.0 ± 11.4 (n = 115) point improvement in the UPDRS III scores in the *stim on/meds off* condition was reported in the Active group compared to a 1.19 ± 8.96 (n = 37) in the Control group as illustrated in Figure 5 below. A difference of 10.83 ± 10.88 ($p < 0.001$)[1] points between both the groups was found.

[1] Not adjusted for multiplicity

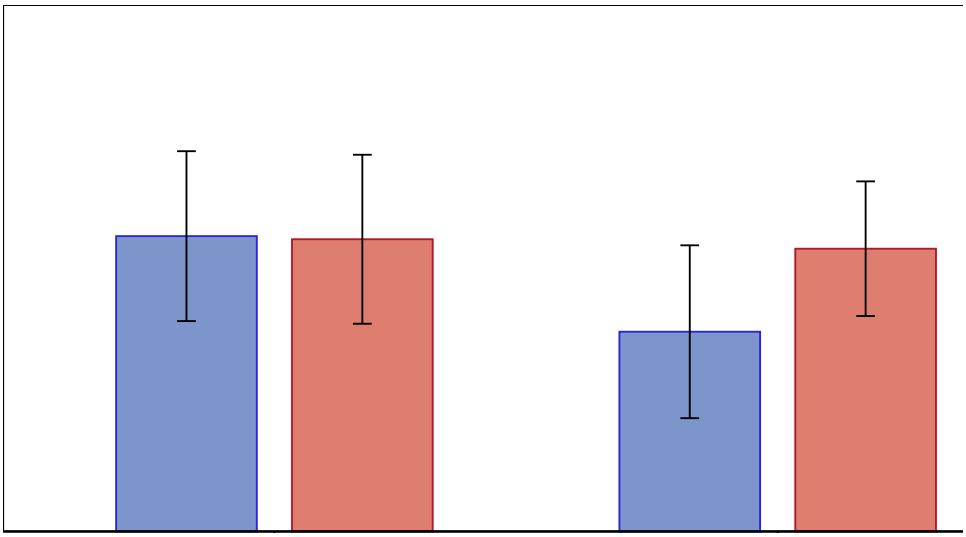

**Figure 5: Difference between the Active and Control groups in the mean change in UPDRS-III Score from baseline meds off to 12 weeks post-randomization stim on/meds off.**

At 12 weeks post-randomization, subjects in the Active group demonstrated over twice the improvement for clinical. Subjects in the Control group showed almost no change.

<u>*Meds on* Condition</u>

In the *meds on* condition, subjects took their usual anti-parkinsonian medications and assessments were performed at 1 hour (± 10 minutes) post-dosing. (Note that it is possible that subjects may not have reached their Best *meds on* condition but instead be at a partial meds on condition at 1 hour post-dosing.) All *meds on* assessments were completed without any additional intervention (i.e. additional medication given or longer wait to get to Best *meds on* condition).

A larger improvement in UPDRS III scores in *stim on/meds on* condition at Week 12 post-randomization was noted in the Active group (5.06 ± 8.72, n = 114) compared to the Control group (2.84 ± 11.20, n = 37) as shown in Figure 4. However, this difference between the two groups was not statistically significant.

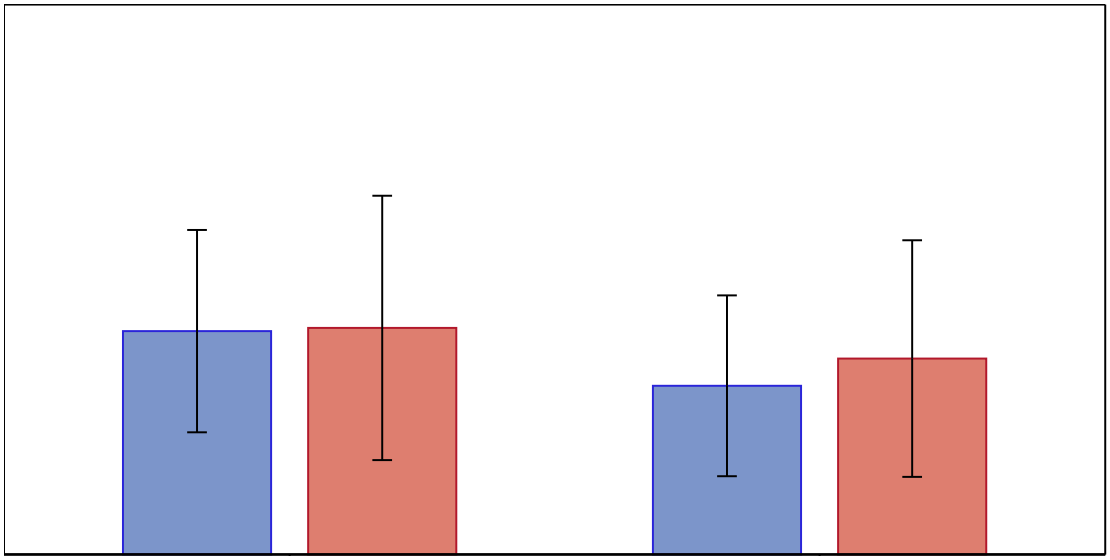

**Figure 6: Difference between the Active and Control groups in the mean change in UPDRS-III scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.**

***PDQ-39***

The impact of treatment on subjects' quality of life was evaluated using the PDQ-39 [3], a 39-item questionnaire designed to measure the specific impact of Parkinson's disease on quality of life. The questionnaire measures the impact on health-related quality of life along 8 dimensions including mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort to contribute to a PDQ-39 summary index (higher scores indicate worsening of quality of life).

This questionnaire was administered in the *meds on* condition.

A 7.79 ± 12.55 (n = 115) point improvement (22%) in the Active group and a 2.56 ± 13.81 (n = 37) worsening (23%) in Control group was noted in the PDQ-39 summary index score as illustrated in Figure 7 below.

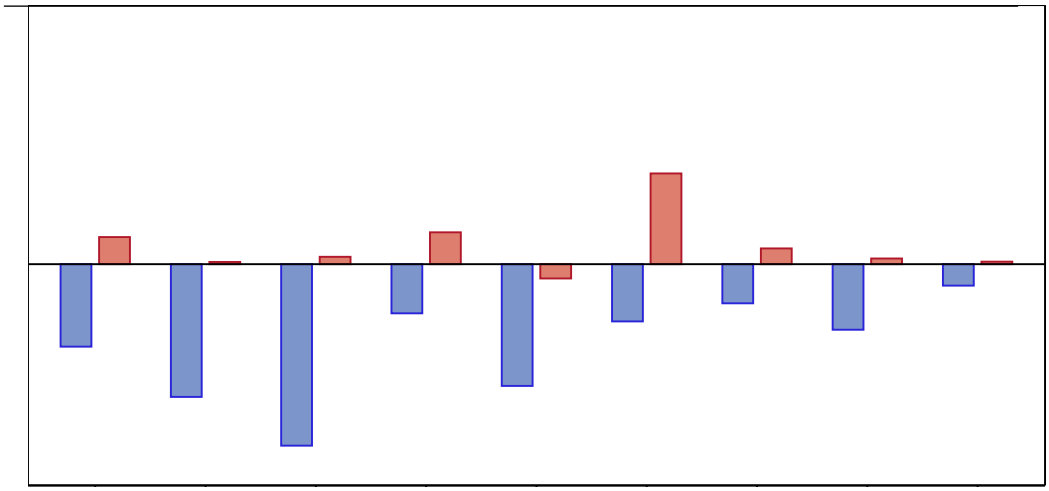

**Figure 7: Difference between the Active and Control groups in mean change in PDQ-39 score from baseline to 12 weeks post-randomization. P value from two sample test (Not adjusted for multiplicity).**

As illustrated in Figure 5 several sub-domains of the PDQ Questionnaire - mobility, ADL, stigma and cognition showed improvement in the Active group at Week 12 post-randomization.

***Modified Schwab and England (SE)***

Modified Schwab and England [2] (SE) is a single-item scale to quantify a PD patients' ability to perform activities of daily living. Scores range from 0% (completely bed-ridden) to 100% (completely independent) with higher scores indicating better function.

This questionnaire was administered in the *meds on* condition.

As shown in Figure 8, a 5.70 ± 14.26 (n = 114) point improvement in SE scores in the Active group as compared to a 1.89 ± 7.76 (n = 37) point worsening in SE scores in the Control group was reported.

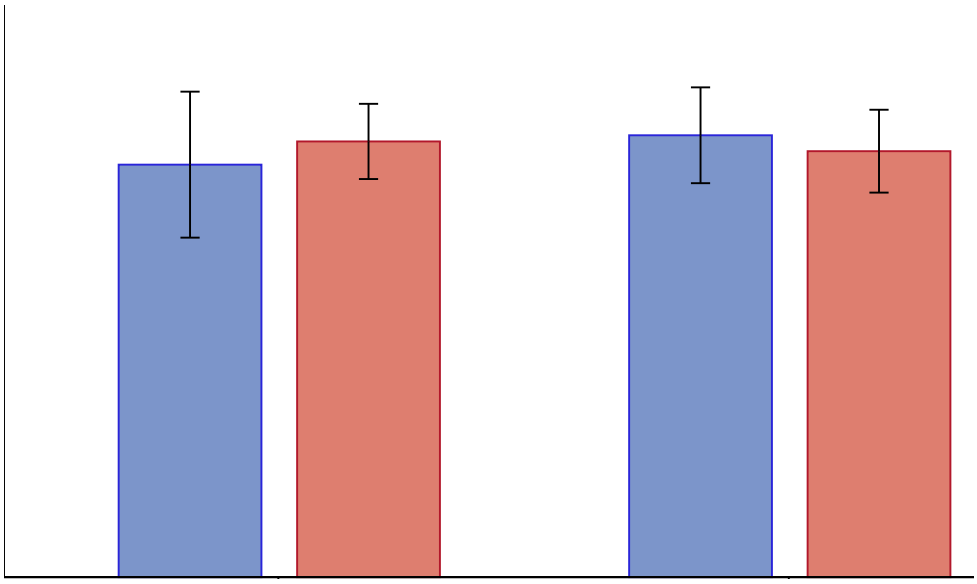

**Figure 8: Difference between the Active and Control groups in the mean change in SE scores from baseline to 12 weeks post-randomization.**

This difference in quality of life as measured by SE scores between Active and Control groups was statistically significant ($p < 0.01$)[2].

***Clinical Global Impression of Change (CGI-C) as assessed by physician***

Physicians (blinded assessor) were asked to report their impression of change in subjects' symptoms in a manner similar to what was done by subjects' themselves at Week 12 post-randomization. The responses are illustrated in Figure 9 below.

[2] Not adjusted for multiplicity

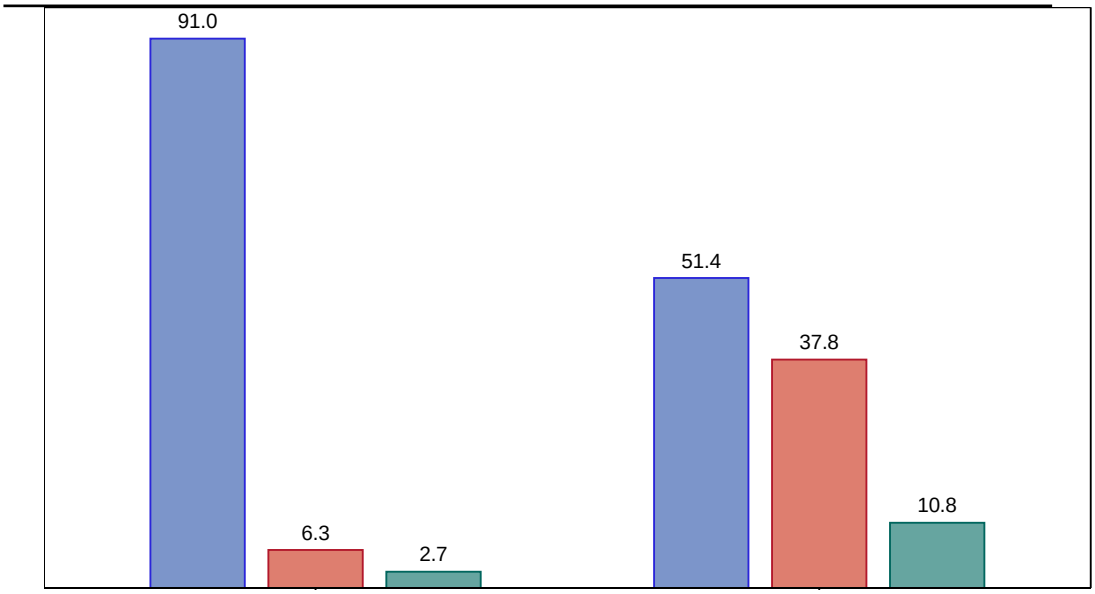


**Figure 9: Difference between the Active and Control groups in the mean CGI-C, as assessed by the physician, at Week 12 post-randomization.**

At Week 12 post-randomization, in the opinion of the blinded assessor (clinician), 91.0 % of subjects in the Active group improved following DBS. A significant percentage of these subjects were in the "very much improved" and "much improved" category.

For those subjects in the Control group, the assessor reported 37.8% of subjects had no change in their PD symptoms. It was also interesting to note that they reported 51.4% of subjects showed improvement at 12 weeks as well.

A statistically significant ($p < 0.0001$)[3] difference between the Active and Control groups was observed.

***Clinical Global Impression of change as assessed by subjects***

Subjects were asked to report their impression of change in their symptoms at Week 12 post-randomization as compared with Baseline using a questionnaire with a seven-point scale ( ranging from "marked worsening" to "very much improved"). This questionnaire was administered in the *meds on* condition.

The results are illustrated in Figure 10 below.

[3] Not adjusted for multiplicity

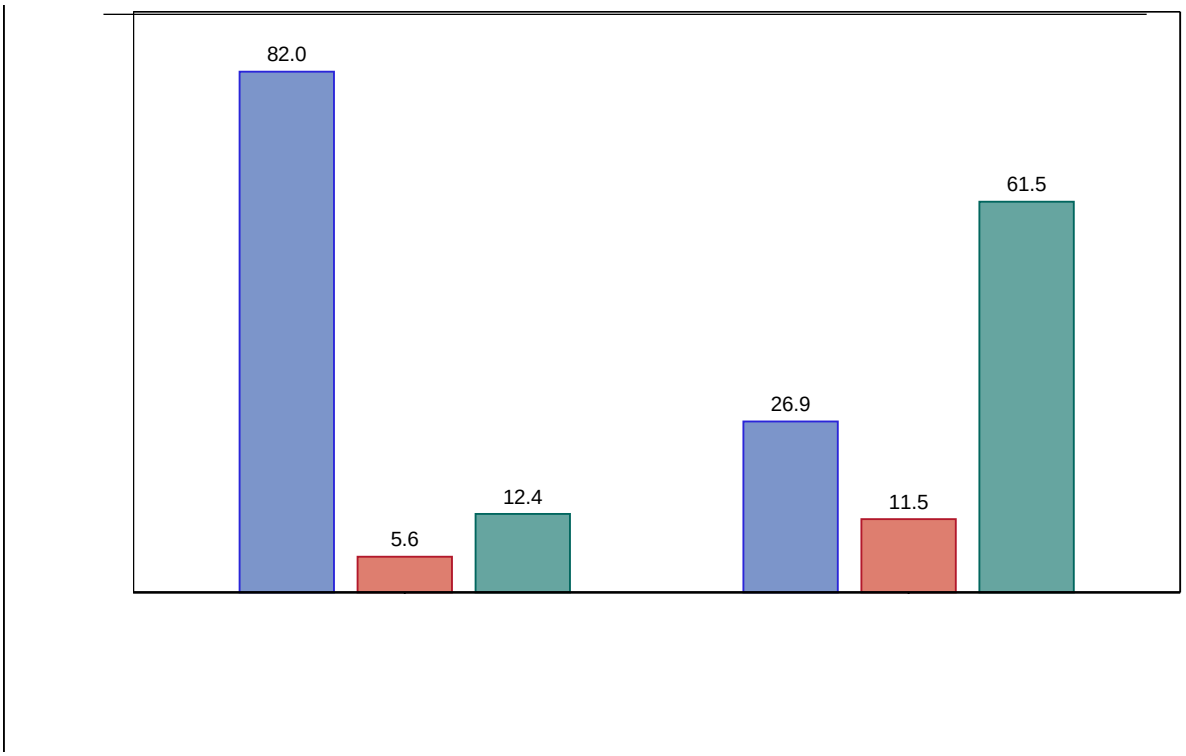


**Figure 10: Difference between the Active and Control groups in the mean CGI-C, as assessed by the subject, at Week 12 post-randomization. P value from Fisher's Exact test.**

At Week 12 post-randomization, 82.0% of Active subjects reported an improvement in their PD symptoms compared to 26.9% in the Control group. In the Control group, while 26.9% reported improved, a majority (61.5%) reported worsened disease state at 12 weeks.

A statistically significant ($p < 0.0001$)[4] difference between the Active and Control groups was reported.

***Treatment Satisfaction score***

Subjects' satisfaction with treatment was assessed where they rated their overall satisfaction with the device and their willingness to recommend the therapy. They were also asked if they would be willing to repeat the treatment process again.

The responses of subjects in the Active and Control groups are summarized in the Table 14 below.

**Table 14: Treatment Satisfaction Score at 12 weeks post-randomization**

| | Active Group | Control Group |
|---|---|---|
| Overall Satisfaction | %(n/N) | %(n/N) |
| Extremely Dissatisfied | 3.4% (4 / 116) | 11.1% (4 / 36) |
| Very Dissatisfied | 3.4% (4 / 116) | 13.9% (5 / 36) |

[4] Not adjusted for multiplicity

| | Active Group | Control Group |
|---|---|---|
| Dissatisfied | 1.7% (2 / 116) | 16.7% (6 / 36) |
| Somewhat Satisfied | 5.2% (6 / 116) | 13.9% (5 / 36) |
| Satisfied | 16.4% (19 / 116) | 16.7% (6 / 36) |
| Very Satisfied | 28.4% (33 / 116) | 22.2% (8 / 36) |
| Extremely Satisfied | 41.4% (48 / 116) | 5.6% (2 / 36) |
| Willingness to go through treatment process again | | |
| Yes | 90.5% (105 / 116) | 80.6% (29 / 36) |
| No | 9.5% (11 / 116) | 19.4% (7 / 36) |
| Would recommend therapy to a friend with Parkinson's disease | | |
| Yes | 91.4% (106 / 116) | 83.3% (30 / 36) |
| No | 8.6% (10 / 116) | 16.7% (6 / 36) |

91.4% of subjects in the Active group and 58.4% in the Control group reported being overall satisfied (varying degrees) with their treatment.

Over 90% of subjects in the Active group were willing to go through the treatment process again and would also recommend the therapy to a friend with Parkinson's disease. A similar trend was observed in the Control group as well.

A statistically significant ($p < 0.0001$)[5] difference in treatment satisfaction score for both the groups was reported.

***UPDRS II (Activities of Daily Living)***

UPDRS II is a sub-section of the UPDRS Scale [2] and focuses on subjects' activities of daily living such as speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing, etc. UPDRS II was administered in the *meds off* and *meds on* condition during the study.

This section describes the results in the *meds on* condition. Details on how the *meds on* condition was achieved are summarized earlier in this section. A $1.74 \pm 5.90$ ($n = 115$) in the Active group versus a $0.06 \pm 5.25$ ($n = 36$) point improvement in the Control group in UPDRS II scores in the *stim on/meds on* condition was reported at Week 12 post-randomization as shown in Figure 11 below.

[5] Not adjusted for multiplicity

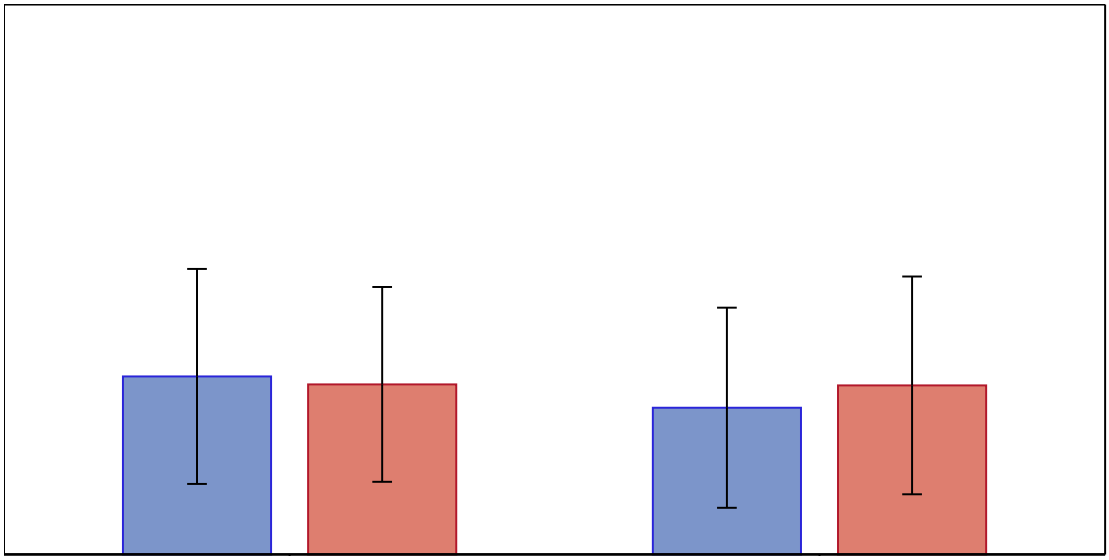

**Figure 11: Difference between the Active and Control groups in the mean change in UPDRS-II scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.**

The change in UPDRS II scores in *meds on* condition was not statistically significant.

***SF-36 v2 (Quality of Life)***

SF-36v2 [4] is a quality of life scale that measures subjects' functional health and well-being from their own point of view. It is comprised of several questions spanning eight health domains which contribute to the scoring of two component summary measures: physical health and mental health.

Subjects in the Active group noted an improvement of 3.35 ± 7.90 points compared to a slight worsening (-0.23 ± 6.79) in the Control group in the physical health domain. In the mental health domain, both groups showed small improvements as shown in Table 15 below. The difference between the two groups is not statistically significant.

**Table 15: Mean change in the SF-36v2 score from baseline to 12 weeks post-randomization for Active and Control groups**

| | SF-36v2 Physical (PCS) Mean (SD) N [ 95% CI ] | | SF-36v2 Mental (MCS) Mean (SD) N [ 95% CI ] | |
|---|---|---|---|---|
| | Active Group | Control Group | Active Group | Control Group |
| Baseline | 39.77 (7.64) 114) [38.3 - 41.2] | 39.55 (6.52) 36) [37.3 - 41.8] | 49.97 (8.23) 113 [48.4 - 51.5] | 50.33 (8.44) 36 [47.5 - 53.2] |
| 12 weeks post-randomization | 43.12 (7.95) 114 [41.6 - 44.6] | 39.32 (8.37) 36 [36.5 - 42.1] | 51.18 (9.04) 113 [49.5 - 52.9] | 52.01 (9.82) 36 [48.7 - 55.3] |

| | SF-36v2 Physical (PCS) Mean (SD) N [ 95% CI ] | | SF-36v2 Mental (MCS) Mean (SD) N [ 95% CI ] | |
|---|---|---|---|---|
| | Active Group | Control Group | Active Group | Control Group |
| Change from baseline to 12 weeks post-randomization | 3.35 (7.90) 114 [1.9 - 4.8] | -0.23 (6.79) 36 [-2.5 - 2.1] | 1.21 (9.53) 113 [-0.6 - 3.0] | 1.68 (8.16) 36 [-1.1 - 4.4] |
| Difference in change between Active and Control groups | 3.58 (7.65) [0.7 - 6.5] | | -0.47 (9.22) [-4.0 - 3.0] | |
| p-value | 0.0591 | | | |
| PCS = Physical Component Summary score.<br>MCS = Mental Component Summary score.<br>p-value is from a two-sided two-group paired Hotelling's T-square test using the 2x1 vector of PCS and MCS differences in change between Active and Control groups. Not adjusted for multiplicity. | | | | |

3. Subgroup Analyses
   None

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

## E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included investigators of which none were full-time or part-time employees of the sponsor and only 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: one 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. The information provided does not raise any questions about the reliability of the data.

# XI. SUMMARY OF SUPPLEMENTAL CLINICAL SAFETY INFORMATION

VANTAGE Study was a multi-center, prospective, open-label, single-arm study of the safety and efficacy of the Vercise DBS System for bilateral stimulation of the subthalamic nucleus (STN) in the treatment of moderate to severe idiopathic Parkinson's Disease (PD).

Six (6) sites participated in this study from Austria, France, Germany, Italy, Spain and the U.K. Enrollment was completed between November 2010 and December 2012. The study population included male and female patients, ages 21 to 75, diagnosed with idiopathic PD as determined by clinical presence of at least 2 of the 3 cardinal features (resting tremor, rigidity, and bradykinesia) and good levodopa response. Subjects were required to have a PD symptom severity level based on the following criteria:

- Modified Hoehn and Yahr [6] stage ≥ 2
- Unified Parkinson's Disease Rating Scale [2] (UPDRS) motor exam of ≥ 30 in the "Meds Off" condition
- Motor complications that cannot be controlled with pharmacologic therapy.

During the first 52 weeks post-implant, there were 2 pre-implant visits and 3 evaluation follow-up visits at 12, 26, and 52 weeks post-implant. Following DBS implant, clinicians monitored anti-parkinsonian medication dosages.

To obtain a comprehensive picture of patients improvement in the study, data collected at study visits (baseline and follow-up) included a 3-day motor diary recorded at home prior to the visit, the Unified Parkinson's Disease Rating Scale [2] (UPDRS), Parkinson's Disease Questionnaire [3], Short Form Health Survey [4], and Global Impression of Change [5]. At each visit, patients were evaluated without medication (Meds Off) and with medication (Meds ON). At follow-up visits post-implant, patients were evaluated with the DBS device turned on (Stim On).

A total of 40 patients were implanted in the study with the Vercise DBS system. The majority of study patients were male (27/40; 67.5%). The mean age of study patients was 60.2 years (±7.82) and the mean duration of PD symptoms was 11.7 years (±4.57).
Of the 40 patients implanted with the Vercise DBS System, 39 completed the 52 weeks of follow-up. 1 patient (2.5%) terminated prior to the 26 Week Visit due to death following pneumonia, not related to the study device or procedure.

## A. Safety Results

### All Adverse Events

During the 52 weeks post-implant period, a total of 125 adverse events (AEs) were reported in 37 implanted patients. Out of 125 adverse events, 107 were non-serious and 18 were serious adverse events. All adverse event relationships were assessed and reported by the investigators. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All adverse events reported by study site personnel as related to hardware, stimulation or procedure is summarized in Table 16 below. Of the 125 events, 6 events were considered related to hardware, 17 events were related to stimulation and 12 events were related to procedure.

**Table 16: All Adverse Events related to Hardware, Stimulation or Procedure**

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Preferred Term | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Anxiety | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Apathy | 0 (0.0%) | 3 (7.5%) | 2 (5.0%) |
| Confusional state | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Device migration | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Diplopia | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Dysarthria | 0 (0.0%) | 1 (2.5%) | 1 (2.5%) |
| Dystonia | 0 (0.0%) | 2 (2.5%) | 0 (0.0%) |
| Fall | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Gait disturbance | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Hallucination, auditory | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Hypoaesthesia | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Implant site haematoma | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Implant site infection | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Incision site infection | 1 (2.5%) | 0 (0.0%) | 1 (2.5%) |
| Laboratory test abnormal | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Localised infection | 1 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Movement disorder | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| Neck pain | 1 (2.5% | 0 (0.0%) | 0 (0.0%) |
| Parkinson's disease | 1 (2.5%) | 1 (2.5%) | 0 (0.0%) |
| Postoperative wound infection | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Respiratory depression | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Speech disorder | 0 (0.0%) | 2 (5.0%) | 1 (2.5%) |
| Staphylococcal infection | 1 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Tremor | 1 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Weight increased | 0 (0.0%) | 1 (2.5%) | 0 (0.0%) |
| **TOTALS** | **6 (12.50%)** | **17 (40.00%)** | **12 (30.00%)** |

Incidence = Number of subjects with events divided by all implanted subjects (n = 40)

**Serious Adverse Events**

A total of 18 Serious Adverse Events (SAE) were reported in 10 subjects. All serious adverse events related to hardware, stimulation or procedure is summarized in Table 17 below. Of 18 Serious Adverse Events, 2 were related to hardware and 3 were related to procedure. There were no serious adverse events related to stimulation.

**Table 17: Serious Adverse Events related to hardware, stimulation or procedure**

| | Related to Hardware | Related to Stimulation | Related to Procedure |
|---|---|---|---|
| Preferred term | Number of Events (Incidence) | Number of Events (Incidence) | Number of Events (Incidence) |
| Device migration | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Implant site infection | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Localised infection | 1 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Respiratory depression | 0 (0.0%) | 0 (0.0%) | 1 (2.5%) |
| Staphylococcal infection | 1 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| **TOTALS** | **2 (5.0%)** | **0 (0.0%)** | **3 (7.5%)** |

Incidence = Number of subjects with events divided by all implanted subjects (n = 40)

Two serious adverse events of infection reported as related to the study device occurred in 1 patient. These events included an initial infection of the patient's scalp treated with antibiotics and recurrent scalp infection (due to staphylococcus), which was also treated with antibiotics. Both infections have resolved without residual effects. In addition, there were 3 SAEs which were considered related to the study-procedure. The procedure related events include one event of implant site infection in the vicinity of the Implantable Pulse Generator (IPG) pocket (treated with antibiotics and surgical revision of the pocket area); one event of IPG migration (treated with surgical repositioning of the IPG); and one event of respiratory depression occurring during the implant procedure as a result of poor body positioning (treated with repositioning of the patient). All 3 procedure-related SAEs resolved without residual effects.

Of the 16 serious adverse events which were not device or hardware - related, 14 have resolved with/without residual effects; 2 are presently not resolved. These include individual reports of lumbago and neoplasm. One SAE of pneumonia resulted in death.

The safety profile in VANTAGE Study was similar to those seen in the INTREPID Study and other recent studies of DBS. The most frequent device and/or procedure-related adverse events included infection, device migration and respiratory depression. All serious adverse events (SAEs) related to either a device or procedure resolved without residual effects. There were no unanticipated adverse events and the overall incidence of device and procedure-related SAEs is comparable to published reports. The VANTAGE Study data further supports the results from the INTREPID Study in demonstrating the safety of the Vercise DBS System.

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

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

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The INTREPID Study was designed to evaluate the safety and effectiveness of bilateral DBS of the subthalamic nucleus (STN) with the Vercise System as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled with medication.

Of the 292 subjects that provided consent to participate in the study, 177 subjects were implanted bilaterally in the sub-thalamic nucleus (STN). The effectiveness data is based

on the cohort of 160 randomized subjects as identified in the pre-specified interim analysis. Subjects were randomized in a 3:1 ratio to either receive active or control settings for 12 weeks (blinded period). All assessments were completed by blinded personnel.

The study successfully met the primary endpoint ($p < 0.001$) with a mean difference of 3.03 ± 4.2 hours in the mean change from baseline to 12 weeks post-randomization between the Active and Control groups in the mean number of waking hours per day with good symptom control and no troublesome dyskinesia as measured on the PD diary, with no increase in antiparkinsonian medications. Post-hoc analysis showed that this improvement was further improved when the analysis was limited to changes in ON time only (i.e. no requirement on medication as described in the primary endpoint). An improvement of 4.6 ± 4.81 hours in the Active group compared to 0.88 ± 3.57 hours in the Control group was noted. Okun et al. [14] reported a mean improvement of 4.27 hours in the active group compared to 1.77 hours in the control group. With INTREPID as a double-blinded study, this further confirms the contribution of the Vercise DBS System and overall positive effects of DBS in PD.

The study passed several of its secondary endpoints including UPDRS III scores in the stim on/meds off condition, PDQ-39, Modified Schwab and England, Global Impression of Change as assessed by clinician and Treatment Satisfaction, thus supporting the primary endpoint. All the assessments for the study secondary endpoints were completed by blinded personnel who were not aware of treatment assignment. A mean 30% improvement (12.02 ± 11.42 points) was noted in UDPRS III scores (stim on/meds off) in the Active group compared to 2% (1.19 ± 8.96) in the Control group. The improvement noted in the Active group is also clinically meaningful as it meets the threshold of at least 5 points or 20% change in UPDRS III scores [12].

Study endpoints related to UPDRS II in *stim on/meds on* condition, UPDRS III in the *stim on/meds on* condition and SF-36 did not meet pre-specified criteria. However, the improvement in UPDRS III scores noted in the Active group did meet the requirement of clinical significance [12]. Both UPDRS II and UPDRS III do not tend to show large improvement in the *meds on* condition as reported in the literature ([13], [14]). Additionally, the study assessments were not completed in accordance to the CAPSIT protocol [15] as typically outlined in the literature (i.e., INTREPID *meds on* assessments were completed at one hour post dosing, not at BEST ON condition).

An overall improvement (statistically significant) in quality of life as reported by improvement in PDQ-39 and modified Schwab and England scales was noted. Based on Global Impression of Change as compared to study start, 82% of subjects self-reported varying degrees of improvement as compared to Baseline which was corroborated by assessors' response of 91%, who similarly reported varying degrees of improvement in their subjects. Furthermore, 91% of subjects in the Active group reported being overall satisfied with their treatment.

## B. Safety Conclusions

The risks of the device are based on safety data collected in two clinical studies – INTREPID and VANTAGE. The INTREPID safety data was based on a total of 292 consented (enrolled) subjects. Of these 292 subjects, 177 subjects received the Vercise System. The VANTAGE Study provided supplemental safety data on 40 patients implanted with the Vercise System.

In the INTREPID Study, a total of 788 adverse events in 143 subjects were reported at the time of the data snapshot. Of these, 74 events were reported as serious adverse events. Infection has been the most commonly reported serious adverse event associated with device-hardware/procedure (8 events, representing 2.7% of subjects). There were three events (each) of device-hardware/procedure-related serious adverse events of peri-operative intracranial hemorrhage (representing 1% of subjects) and seizure (representing 1% of subjects). These events are comparable to published reports ([13], [14], [16]).

The safety profile in VANTAGE Study was similar to those seen in the INTREPID Study and other recent studies of DBS. The most frequent device and/or procedure-related adverse events included infection, device migration and respiratory depression.

The nature and incidence rate of the reported adverse events in both the studies were anticipated.

## C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in INTREPID Study. The effectiveness was demonstrated by an improvement in subjects' ON time (good symptom control and no troublesome dyskinesias) at 12 weeks post randomization. A mean improvement of 3.74 ± 4.79 hours (n = 118) in the Active group compared to 0.72 ± 3.56 hours (Control group, n = 38) in their ON time without increase in antiparkinsonian medications was reported.

The adverse event profile and safety profile were similar to those seen in other recent studies of DBS.

### Considerations

Typically, following DBS of the sub-thalamic nucleus for PD, patients are able to reduce their antiparkinsonian medications – one of the benefits of choosing STN as a target. However, in some cases, an increase in medications may be required to manage the synergistic effect of stimulation and medication. The study primary endpoint was a composite endpoint consisting of change in ON time and medication usage. In its analysis, a strict ruling for those subjects with an increase in medications was implemented. For all those subjects who had an increase in antiparkinsonian medications, their change in ON time from Baseline was marked as "zero" for the purpose of analysis. This is not commonly implememented in such analysis.

The study collected data in the meds on condition at one hour post dosing was unique to the study. Typically, assessments in the meds on condition are completed at subjects' BEST ON condition as recommended by the CAPSIT protocol [15].

Hence, a comparison of data in the study to the literature must be made with caution considering some of the unique factors and scientific rigors in the INTREPID Study.

**Patient Perspectives**

This submission did not include specific information on patient perspectives for this device other than, treatment satistfaction data, which was collcted as a Secondary Endpoint. Please see Table 14 above.

### 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 in the treatment of moderate to advanced Parkinson's disease. The results of the safety data from the above mentioned clinical studies provide reasonable assurance of the safety of the Vercise DBS System, when used in accordance to indications of use. The evidence supporting the safety and effectiveness of Vercise DBS System is based on an interim analysis of a prospective, multi-center, double-blinded randomized controlled trial designed to evaluate the clinical benefit of the Vercise DBS System for bilateral stimulation of the subthalamic nucleus in the treatment of Parkinson's disease. The results from comprehensive pre-clinical testing confirmed that the Vercise System performs as intended. The studies and testing outcomes demonstrate that the benefits outweigh associated risks.

## XIV. CDRH DECISION

CDRH issued an approval order on 12/08/2017.

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

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES


[1] R. Hauser, F. Deckers and P. Lehert, "Parkinson's Disease Home Diary: Futher Validation and Implications for Clinical Trials," *Mov Disord,* vol. 19, no. 12, pp. 1409-1413, 2004.

[2] S. Fahn, R. Elton and Members of the UPDRS Development Committee, "Unified Parkinson's Disease Rating Scale," in *Recent Developments in Parkinson's Disease,* S. Fahn, D. Marsden, D. Calen and M. Goldstein, Eds., Florham Park, NJ: MacMillan Healthcare Information, 1987, pp. 153 - 163.

[3] V. Peto, C. Jenkinson, R. Fitzpatrick and R. Greenhall, "The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease," *Qual Life Res.,* vol. 4, no. 3, pp. 241-248, Jun 1995.

[4] J. Ware, M. Kosinski and S. Keller, SF-36 Physical and Mental Health Summary Scales: A User's manual, Boston: The Health Insitute, New England Medical Center, 1994.

[5] G. W, *ECDEU Assessment Manual for Psychopharmacology Revised,* Rockville, MD: National Institute of Mental Health, 1976.

[6] C. Goetz, W. Poewe, O. Rascol, C. Sampaio, G. Stebbins, C. Counsell, N. Giladi, R. Holloway, C. Moore, G. Wenning, M. Yahr and L. Seidl, "Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations The Movement Disorder Society Task Force on rating scales for Parkinson's disease," *Movement Disorders,* vol. 19, no. 9, pp. 1020-1028, 2004.

[7] P. Jurica, C. Leiten and S. Mattis, *Dementia Rating Scale-2,* Lutz, FL: Psychological Assessments Resources, 2001.

[8] A. Beck, K. Gregory and R. Steer, *Beck Depression Inventory-II (BDI-II),* San Antonio, TX: The Psychological Corporation , 1996.

[9] A. P. Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

[10] K. Posner, G. Brown, B. Stanley, D. Brent, K. Yershova, M. Oguendo, G. Currier, G. Melvin, L. Greenhill, S. Shen and J. Mann, "The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults," *Am J Psychiatry,* vol. 168, no. 12, pp. 1266-1277, 2011.

[11] M. Herdman, C. Gudex, L. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel and X. Badia, "Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)," *Quality of Life Research* , vol. 20, pp. 1727 - 1736, 2011.

[12] A. Schrag, C. Sampaio, N. Counsell and W. Poewe, "Minimal Clinically Important Change on the Unified Parkinson's Disease Rating Scale," *Mov. Disorders,* vol. 21, no. 8, pp. 1200-1207, 2006.

[13] G. Deuschl, C. Schade-Brittinger, P. Krack, J. Volkmann, H. Schafer, K. Botzel, C. Daniels, A. Deutschlander, U. Dillmann, W. Eisner, D. Gruber, W. Hamel, J. Herzog, R. Hilker, S. Klebe, M. Kloss, J. Koy, M. Krause, A. Kupsch, D. Lorenz, S. Lorenzl, H. Mehdorn, J. Moringlane, W. Oertel, M. Pinsker, H. Reichmann, A. Reuss, G. Schneider, A. Schnitzler, U. Steude, V. Sturm, L. Timmermann, V. Tronnier, T. Trottenberg, L. Wojtecki, E. Wolf, W. Poewe and J. Voges, "A randomized trial of deep-brain stimulation for Parkinson's Disease," *N Engl J Med,* vol. 355, no. 9, pp. 896-908, Aug 31 2006.

[14] M. Okun, B. Gallo, G. Mandybur, J. Jagid, K. Foote, F. Revilla, R. Alterman, J. Jankovic, R. Simpson, F. Junn, L. Verhagen, J. Arle, B. Ford, R. Goodman, R. Stewart, S. Horn, G. Baltuch, B. Kopell, F. Marshall, D. Peichel, R. Pahwa, K. Lyons, A. Troster, J. Vitek, M. Tagliati and SJM DBS Study Group, "Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial," *Lancet Neurol,* vol. 11, no. 2, pp. 140-149, Feb 2012.

[15] G. Defer, H. Widner, R. Marie, P. Remy and M. Levivier, "Core assessment program for surgical interventional therapies in Parkinson's Disease (CAPSIT-PD)," *Mov Disord,* vol. 14, no. 4, pp. 572-584, Jul 1999.

[16] F. Weaver, K. Follett, M. Stern, K. Hur, C. Harris, W. J. Marks, J. Rothlind , O. Sagher, D. Reda, C. Moy, R. Pahwa, K. Burchiel, P. Hogarth, E. Lai, J. Duda, K. Holloway, A. Samii, S. Horn, J. Bronstein, G. Stoner, J. Heemskerk and G. Huang, "Bilateral deep brain stimulation vs best medical therapy for subjects with advanced Parkinson disease: a randomized controlled trial," *JAMA,* vol. 301, no. 1, pp. 63-73, Jan 7 2009.