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Vercise™ Deep Brain Stimulation Systems for Parkinson's Disease

Clinical Summary

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How to Use This Document

This document provides clinical summary information for the Vercise™, Vercise™ PC, Vercise Gevia™, and Vercise Genus™ Deep Brain Stimulation (DBS) Systems.

Read all information carefully before using the DBS System. For other device-specific information not included in this manual, refer to the appropriate DFU for your Boston Scientific DBS System as listed in your *DBS Reference Guide*.

Guarantees

Boston Scientific Corporation reserves the right to modify, without prior notice, information relating to its products in order to improve their reliability or operating capacity.

Trademarks

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All other trademarks are the property of their respective owners.

Technical Support

There are no user serviceable parts. If you have a specific question or issue, please contact your sales representative or call (833) DBS-INFO or (833) 327-4636.

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Definition of Terms

Clinical Rating Scales

Global Impression of Change (1): The global impression of change (GIC) is a generic, single-item scale for quantifying one's overall impression of the patient's improvement following therapy. GIC can be patient-reported, clinician-reported or caregiver-reported.

Modified Schwab and England (2): The modified Schwab and England (SE) assessment is a disease-specific single-item scale for quantifying a PD (Parkinson's disease) patient's ability to perform activities of daily living.

Parkinson's Disease Diary (3) (PD diary): A patient-reported motor diary measuring the patient's state in 30 minute interval for 3 consecutive days at home. The patient reports his or her state in one of five categories:

"On without dyskinesia":	Good motor function resulting from therapeutic effects of anti-parkinsonian medication and stimulation but without the drug-induced side effect movements known as dyskinesia.
"On with non-troublesome dyskinesia":	Good motor function from the therapy but with involuntary movements of dyskinesia that are not disturbing to the patient.
"On with troublesome dyskinesia":	Good motor function and relief from PD symptoms but with involuntary movements of dyskinesia that are disturbing to the patient.
"Off":	When medication effect has worn off and the medication is no longer providing clinical benefits including improvement of mobility, lessening of slowness, and improved stiffness.
"Asleep":	Asleep.

39-Item Parkinson's Disease Questionnaire (4): The 39-item Parkinson's Disease Questionnaire (PDQ-39) is a disease-specific patient-reported assessment for measuring the specific impact of PD on a patient's quality of life in the following domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort.

Unified Parkinson's Disease Rating Scale (2) (UPDRS): A standard scale for assessing the current state and progression of Parkinson's Disease (PD). This assessment contains 4 sections: (I) Mentation, Behavior, and Mood, (II) Activities of Daily Living (ADL), (III) Motor Examination, and (IV) Complications of Therapy.

36-Item Short Form Survey (5) (SF-36) v2: A quality of life scale that measures functional health and well-being from patients' own point of view. It is comprised of 36 questions spanning eight health domains that contribute to the scoring of two component summary measures: physical health and mental health.

Symptoms and Side Effects

Bradykinesia: Slowness of movement.

Dysarthria: Poorly articulated or slurred speech.

Dyskinesia: Abnormal involuntary movements, typically non-painful writhing that can be caused by dopaminergic drug therapy.

Dystonia: Abnormal, often painful involuntary muscle contractions of opposing muscles that twist a body part into an uncomfortable, position or posture.

Rigidity: Stiffness or inflexibility of the neck, limbs or joints.

Tremor: Involuntary, regular, sinusoidal, shaking of a limb or the head.

Clinical Study Terms

Meds OFF: A condition/period of assessment where patients have withheld their anti-parkinsonian medications or when they are not medicated as the medications have worn off.

Meds ON: A condition/period of assessment when the patient has taken their anti-parkinsonian medications and the medication has taken effect.

Levodopa equivalent: The conversion in milligrams (mg) to levodopa equivalent dose for non-levodopa medications. For example, 100 mg of standard levodopa = 125 mg of controlled-release levodopa; 10 mg of bromocriptine; 1 mg of pergolide; 1 mg of pramipexole; 3 mg of ropinirole; 4mg/24h of rotigotine; 60-90 mg pirebedil.

Serious adverse event (SAE): Any adverse event that led to death or led to a serious deterioration in the health of the patient that either resulted in:

- a life-threatening illness or injury.
- a permanent impairment of a body structure or a body function.
- in-patient or prolonged hospitalization of existing hospitalization.
- medical/surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Introduction

The Vercise™ Deep Brain Stimulation (DBS) System includes a Stimulator with DBS Leads for stimulation of the subthalamic nucleus (STN) in the brain. DBS Extensions are used to connect the DBS Leads to the Stimulator implanted near the clavicle. The Vercise DBS System is able to provide precise, independent current steering across each of the eight contacts per DBS Lead.

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.

Indications for Use (Vercise): 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.

Indications for Use (Vercise PC, Vercise Gevia, and Vercise Genus): The Vercise PC, Vercise Gevia, and Vercise Genus Deep Brain Stimulation (DBS) Systems are indicated for use in the following:

- 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.
- Bilateral stimulation of the globus pallidus internus (GPi) as an adjunctive therapy in reducing some of the symptoms of advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled with medication.
- Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

This Clinical Summary document provides data from two studies: the INTREPID Study, and the VANTAGE Study. The INTREPID Study data has been collected per the pre-specified interim analysis of the ongoing U.S. Clinical Study sponsored by Boston Scientific (May 2013 through December 2016). Additional long-term data from INTREPID is anticipated upon study completion. Safety data from INTREPID includes all available data on 292 consented subjects while effectiveness data is presented for the cohort of 160 randomized subjects per the pre-specified interim analysis. Enrollment for the INTREPID Study is still ongoing. Supplemental safety data from the Boston Scientific VANTAGE Study that was conducted outside the U.S. (OUS) is also provided. This included 40 consented patients.

Appendix A provides a summary of the data supporting the clinical effectiveness of GPi stimulation for Parkinson's disease. The clinically established safety and effectiveness profile of the Medtronic Activa Parkinson's Control Therapy for bilateral GPi stimulation was leveraged based on the technical equivalence of the Boston Scientific systems to the Medtronic Activa Parkinson's Control Therapy system.

Appendix B provides a summary of the data supporting the clinical effectiveness of thalamic stimulation for the suppression of parkinsonian tremor and essential tremor. The clinically established safety and effectiveness profile of the Medtronic Activa Tremor Control System for unilateral thalamic stimulation was leveraged based on the technical equivalence of the Boston Scientific systems to the Medtronic Activa Tremor Control System.

INTREPID Clinical Study

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™ Deep Brain Stimulation (DBS) 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., a 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 of up to 5 years. The study design is shown in Figure 1 below.

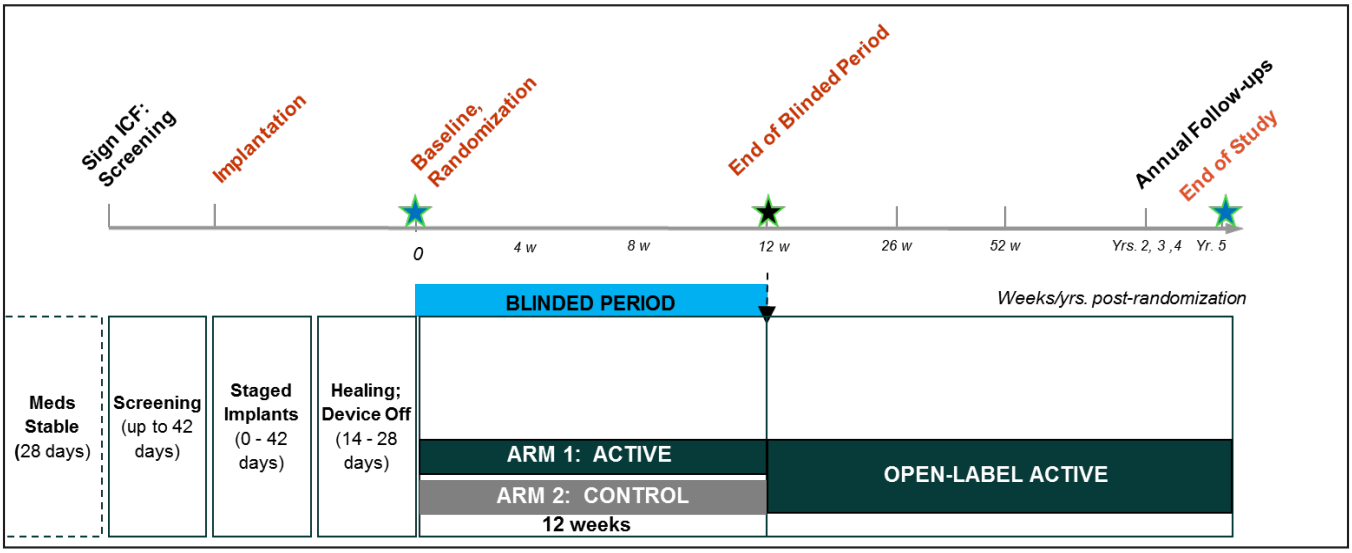

Figure 1. INTREPID Study Schematic

Subjects completed a 3-day Parkinson's Disease (3)(PD) diary 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' response 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 (4) (PDQ-39), Modified Schwab and England (2) (SE), Treatment Satisfaction, Short Form Survey (5) (SF-36 v2), and Global Impression of Change (assessed by subject and assessor) (1).

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.

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.

Study Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Age at the time of enrollment: 22 - 75 years
- Duration of idiopathic Parkinson's disease (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 (6) (H&Y) 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 Parkinson's Disease (3) (PD) diary
- Unified Parkinson's Disease Rating Scale – Section III (2) (UPDRS III) score of ≥ 30 in the *meds off* condition and improvement by ≥ 33% following intake of anti-parkinsonian medications
- Dementia Rating Scale – 2 (7) (DRS-2) score ≥ 130 and Beck Depression Inventory II (8) (BDI-II) score < 17 in the *meds on* condition
- Be 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 (3))
- Able to understand the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed.

Key Exclusion Criteria:

- Any intracranial abnormality or medical condition that would contraindicate Deep Brain Stimulation (DBS) surgery
- Have untreated clinically significant depression per DSM-IV (9) (Diagnostics and Statistical Manual of Mental Disorders) criteria as determined by Beck Depression Inventory II (8) (BDI-II) score ≥ 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) (Diagnostics and Statistical Manual of Mental Disorders) 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.
- Have 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 (3) entries or perform wound care, unless a caregiver is available to assist.

Clinical Endpoints

The primary safety 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 efficacy 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 Parkinson's Disease (PD) Diary (3), with no increase in antiparkinsonian 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 Unified Parkinson's Disease Rating Scale – Section III (2) (UPDRS III) scores in *stim on/meds off* condition and in *stim on/meds on* condition
- Activities of Daily Living (Unified Parkinson's Disease Rating Scale – Section II) (2) (UPDRS II) in *stim on/meds on* condition
- Quality of life as assessed by Parkinson's Disease Questionnaire (4) (PDQ-39), 36-Item Short Form Survey (5) (SF-36) v2 and Modified Schwab and England (2) (SE)
- Treatment Satisfaction
- Global impression of change (1) as assessed by subjects and clinicians.

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.

Patient Accountability

Enrollment

A total of 292 subjects provided consent to participate in the study at 23 participating sites in U.S. One hundred and seventy-seven subjects received the Vercise™ Deep Brain Stimulation (DBS) System. The cohort of 160 randomized subjects was identified as the pre-specified interim analysis group. The following flowchart (Figure 2) shows the disposition of subjects in the study.

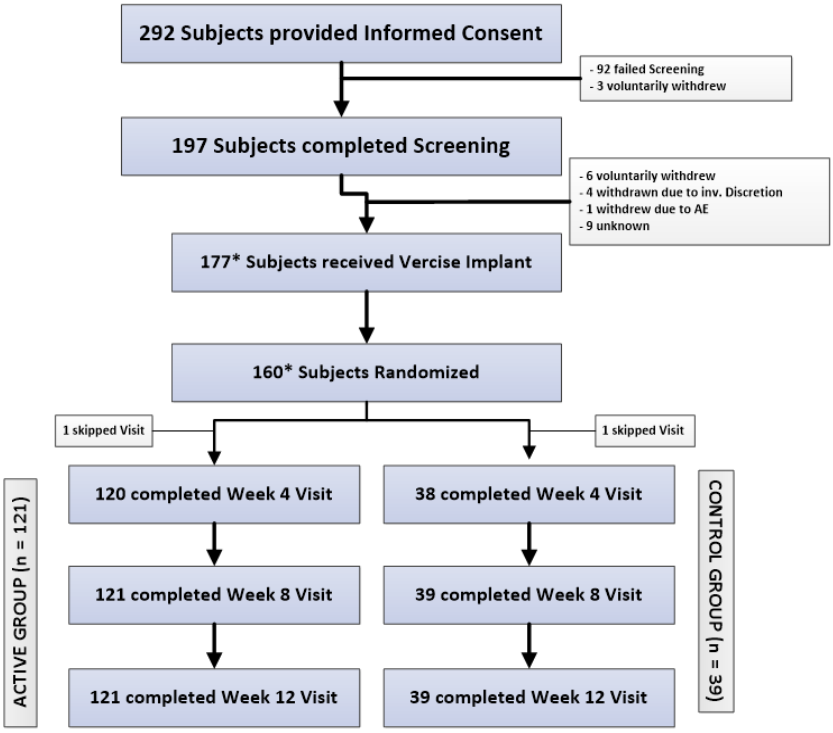

Figure 2. INTREPID Study Disposition

Study Population Demographics and Baseline Characteristics

One hundred sixteen of 160 subjects (72.5%) were male. The mean age of subjects 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 (3) (PD) with disease duration of 10.1 ± 3.61 years and mean severity of modified Hoehn and Yahr (6) (H&Y) score of 2.8 ± 0.73. Subjects' mean Unified Parkinson's Disease Rating Scale – Section III (2) (UDPRS III) 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 (3) 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 as summarized in Table 1 below. Subjects also demonstrated a poor quality of life as reported by scores in 39-Item Parkinson 's Disease Questionnaire (4) (PDQ-39), Modified Schwab and England (2) (SE), Modified Hoehn and Yahr (6) (H&Y) and EuroQol-5D-5L (11) (EQ-5D-5L) scores.

Table 1: 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

Safety Results

The analysis of the INTREPID 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 the 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 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.

All Adverse Events

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

All adverse events related to hardware, stimulation or procedure are summarized in Table 2 below. Of 788 events, a total of 65 events were reported as related to hardware, 157 related to stimulation and 128 related to procedure.

Table 2: All Adverse Events related to hardware, stimulation or procedure

	Related to Hardware	Related to Stimulation	Related to Procedure
Events	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%)

Table 2: All Adverse Events related to hardware, stimulation or procedure

	Related to Hardware	Related to Stimulation	Related to Procedure
Events	Number of Events (Incidence)	Number of Events (Incidence)	Number of Events (Incidence)
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%)
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%)

Table 2: All Adverse Events related to hardware, stimulation or procedure

	Related to Hardware	Related to Stimulation	Related to Procedure
Events	Number of Events (Incidence)	Number of Events (Incidence)	Number of Events (Incidence)
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%)
Paranoia	0 (0.0%)	2 (0.7%)	0 (0.0%)
Parkinson's disease	1 (0.3%)	2 (0.7%)	1 (0.3%)

Table 2: All Adverse Events related to hardware, stimulation or procedure

	Related to Hardware	Related to Stimulation	Related to Procedure
Events	Number of Events (Incidence)	Number of Events (Incidence)	Number of Events (Incidence)
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. Table 3 summarizes only those events related to procedure, stimulation, or hardware, based on their treatment assignment.

Table 3: 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%)

Table 3: 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)	
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%)
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%)

Table 3: 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)	
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%)**

Serious Adverse Events

Among all the consented (enrolled) subjects (n = 292), a total of 74 Serious Adverse Events (SAE) were reported in 46 subjects. All serious adverse events related to hardware, stimulation or procedure are summarized in Table 4 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). Stimulation-related serious adverse events include one event of mania and one event of a failed suicide attempt.

Table 4: 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 5 summarizes only those serious adverse events related to hardware, stimulation or procedure up to Week 12 post randomization based on treatment assignment.

Table 5: 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%)
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.

Efficacy Results

Primary Endpoint

The study efficacy results are based on a 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 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 a 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 ± 4.79 hours) compared to the Control group (0.72 ± 3.56 hours) as shown in Table 6.

Table 6: 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]
12 weeks post-randomization	12.37 (3.56) 118 [11.7 - 13.0]	8.96 (3.94) 38 [7.7 - 10.3]
Change from baseline to 12 weeks post-randomization	3.74 (4.79) 118 [2.9 - 4.6]	0.72 (3.56) 38 [-0.5 - 1.9]
Difference in change from baseline to 12 weeks post-randomization between Active and Control groups	3.03 (4.52) [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%).

Unified Parkinson's disease Rating Scale – Section III (UPDRS III)

UPDRS III is the motor sub-section of the Unified Parkinson's disease Rating Scale (2) (UPDRS) and is used to evaluate overall motor disability, including the classic symptoms of Parkinson's Disease (PD).

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 3 below. A difference of 10.83 ± 10.88 ($p < 0.001$)[1] points between both the group was found.

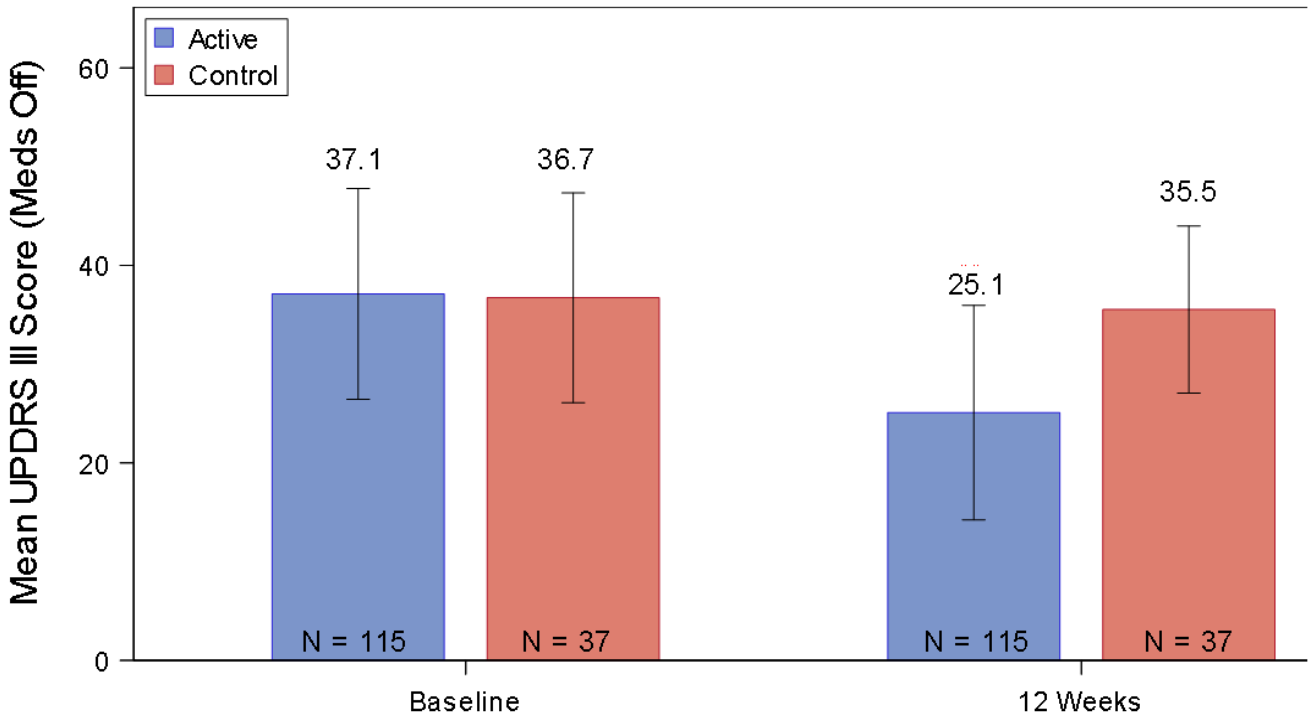

Figure 3. Difference between the Active and Control groups in the mean change in UPDRS-III Score from baseline *meds off* to 12 weeks post-randomization *stim on/meds off*.

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

1 Not adjusted for multiplicity

Meds on condition

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.

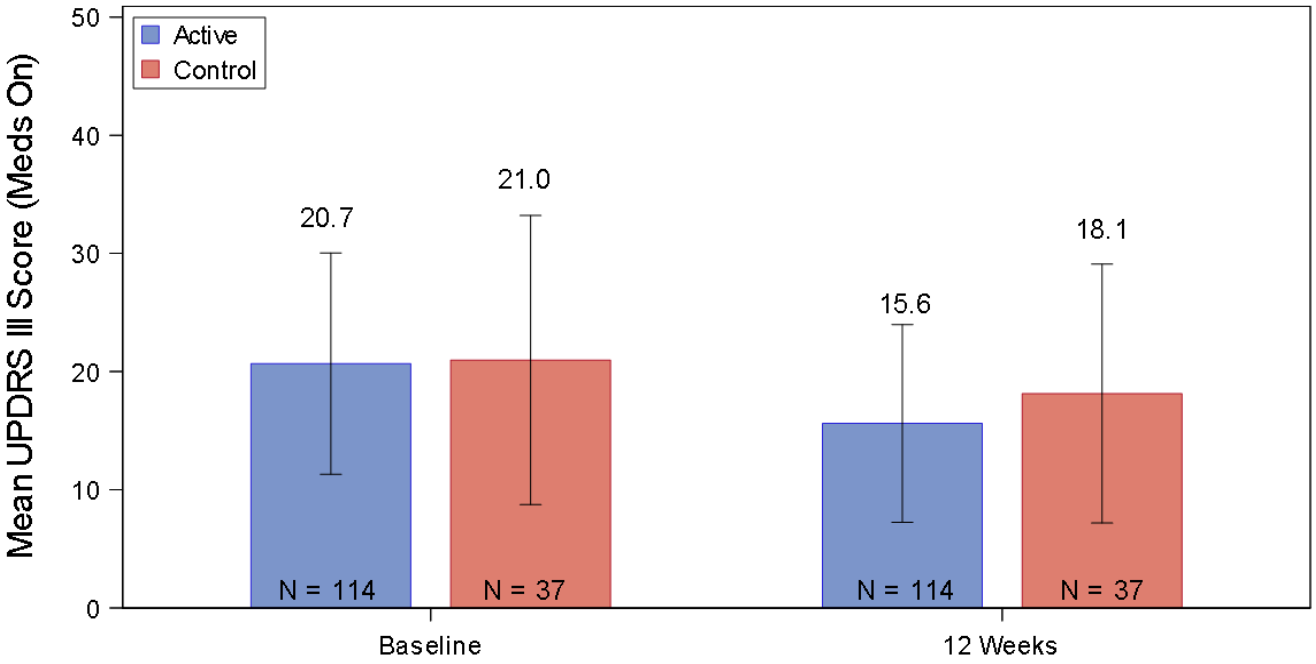

Figure 4. Difference between the Active and Control groups in the mean change in UPDRS-III scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.

39-Item Parkinson's Disease Questionnaire (PDQ-39)

The impact of treatment on subjects' quality of life was evaluated using 39-Item Parkinson's Disease Questionnaire (4) (PDQ-39), 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 (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 5 below.

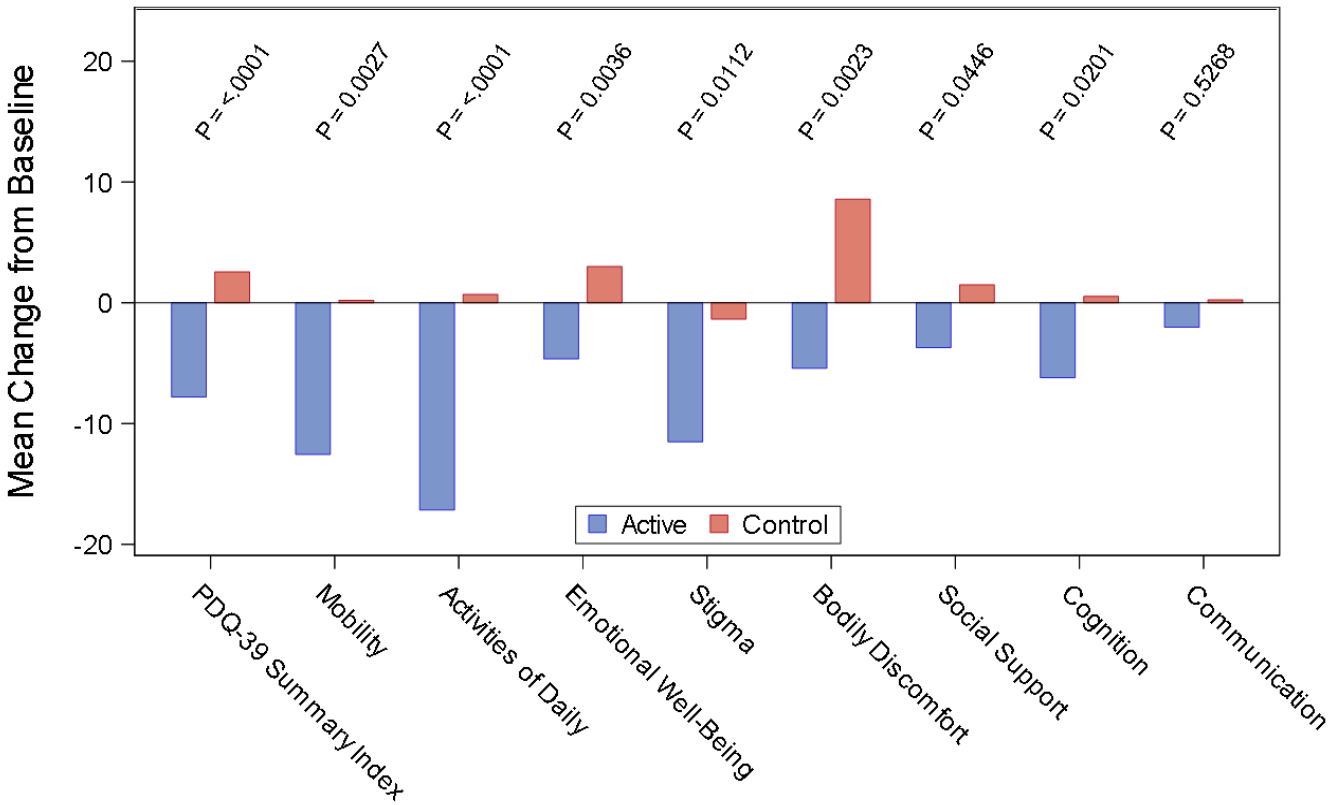

Figure 5. Difference between the Active and Control groups in mean change in PDQ-39 score from baseline to 12 weeks post-randomization. P value from two sample test (Not adjusted for multiplicity).

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 6, 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.

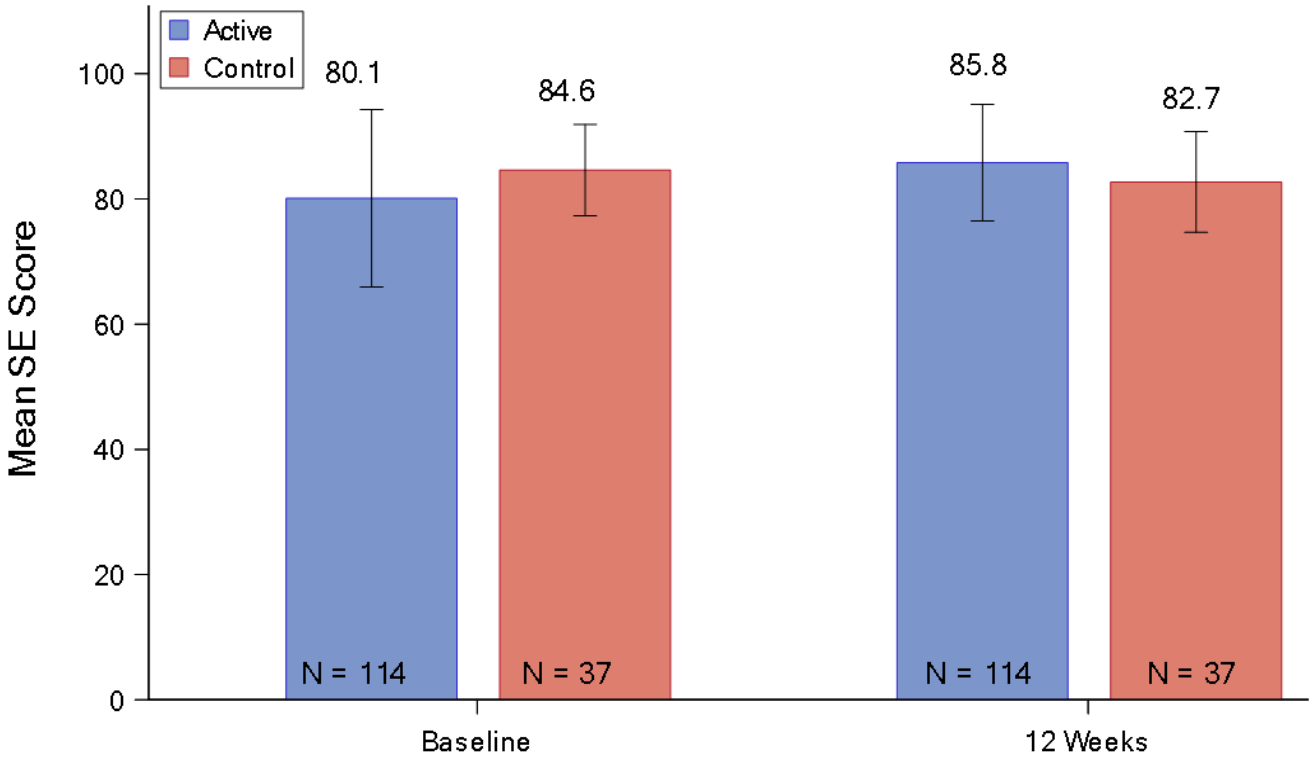

Figure 6. Difference between the Active and Control groups in the mean change in SE scores from baseline to 12 weeks post-randomization.

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

2 Not adjusted for multiplicity

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

Physicians (blinded assessor) were asked to report their impression of change (1) 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 7 below.

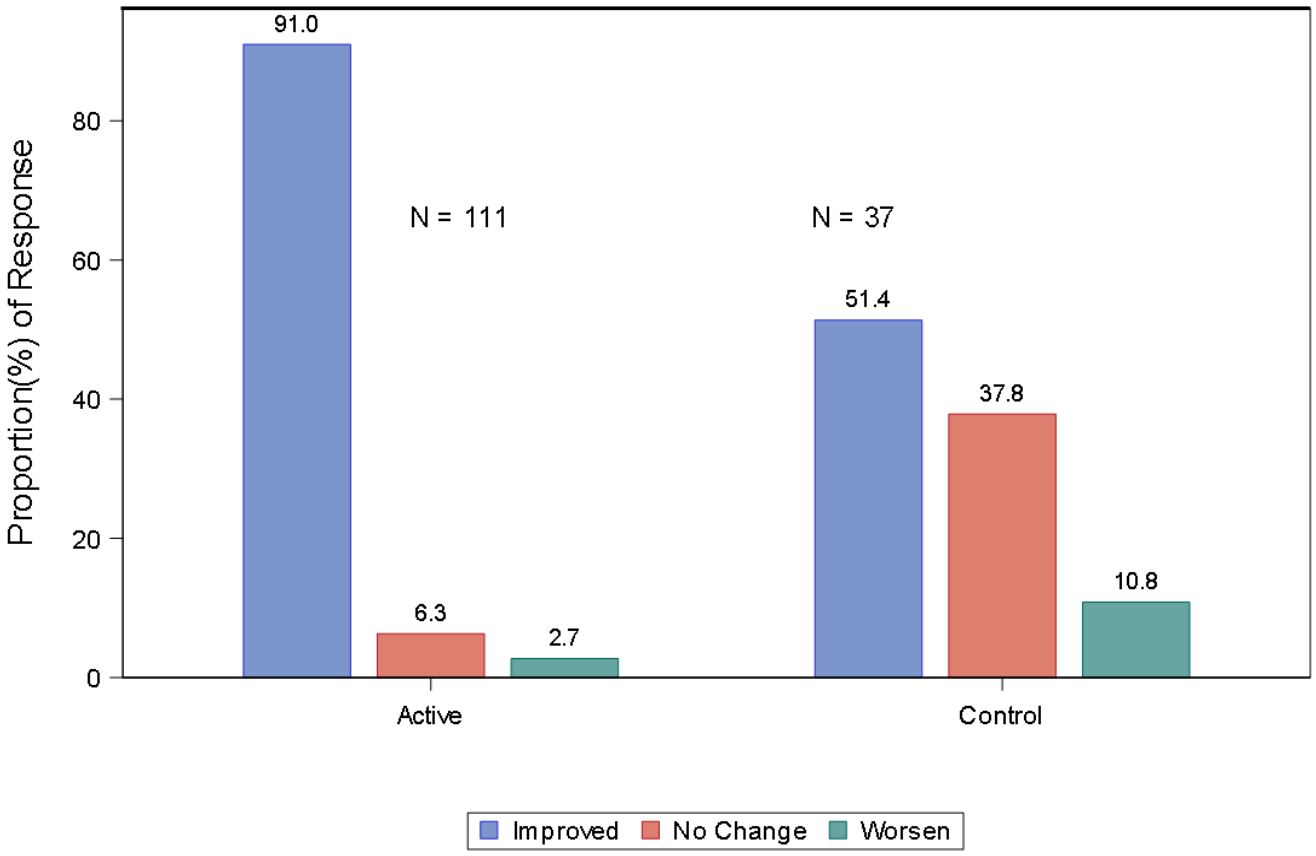

Figure 7. Difference between the Active and Control groups in the mean CGI-C, as assessed by the physician, at Week 12 post-randomization.

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.

3 Not adjusted for multiplicity

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 8 below.

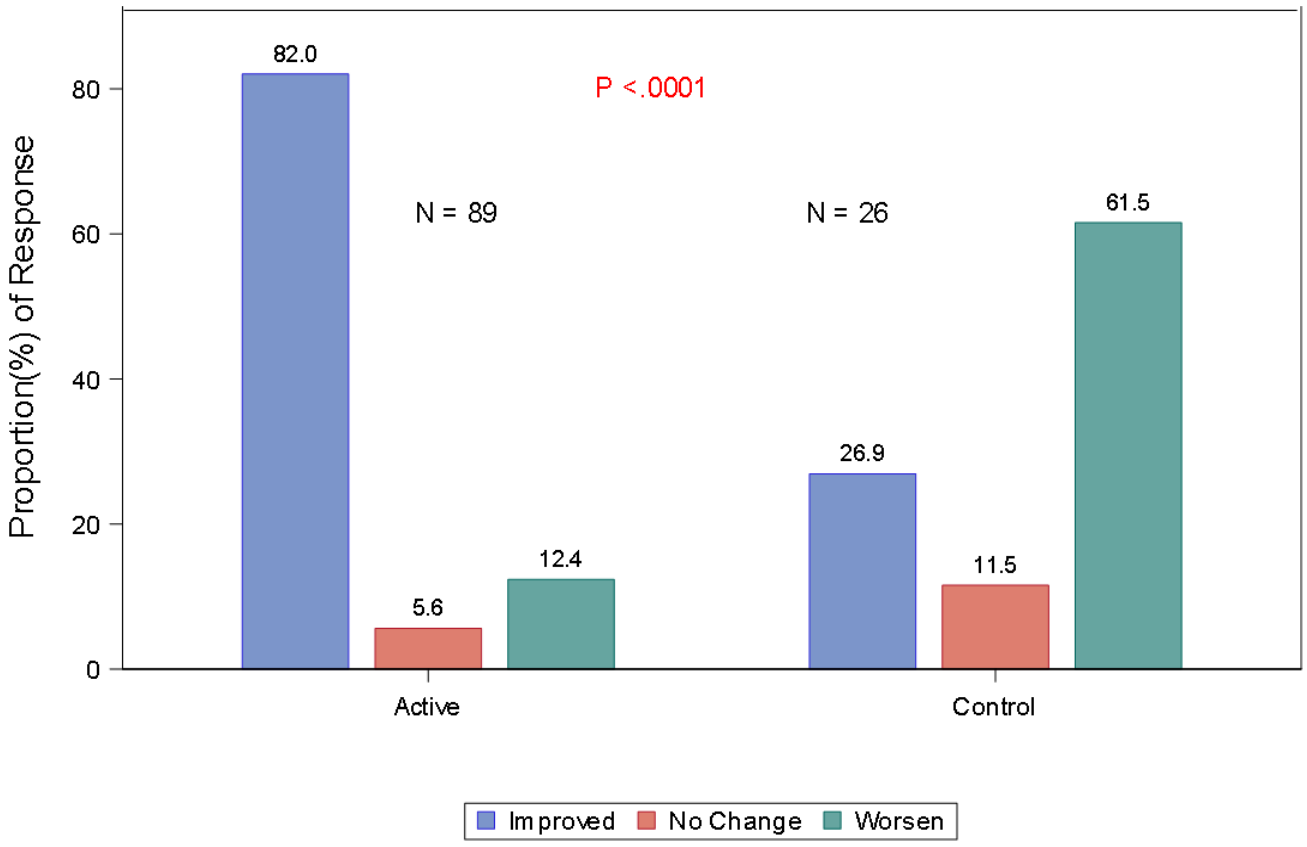

Figure 8. Difference between the Active and Control groups in the mean CGI-C, as assessed by the subject, at Week 12 post-randomization. P value from Fisher's Exact test.

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.

4 Not adjusted for multiplicity

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 Table 7 below.

Table 7: 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)
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.

5 Not adjusted for multiplicity

Unified Parkinson's Disease Rating Scale – Section II (UPDRS II) (Activities of Daily Living)

Unified Parkinson's Disease Rating Scale – Section II (2) (UPDRS II) is a sub-section of the UPDRS Scale 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 ± 5.90 (n = 115) in the Active group versus a 0.06 ± 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 9 below.

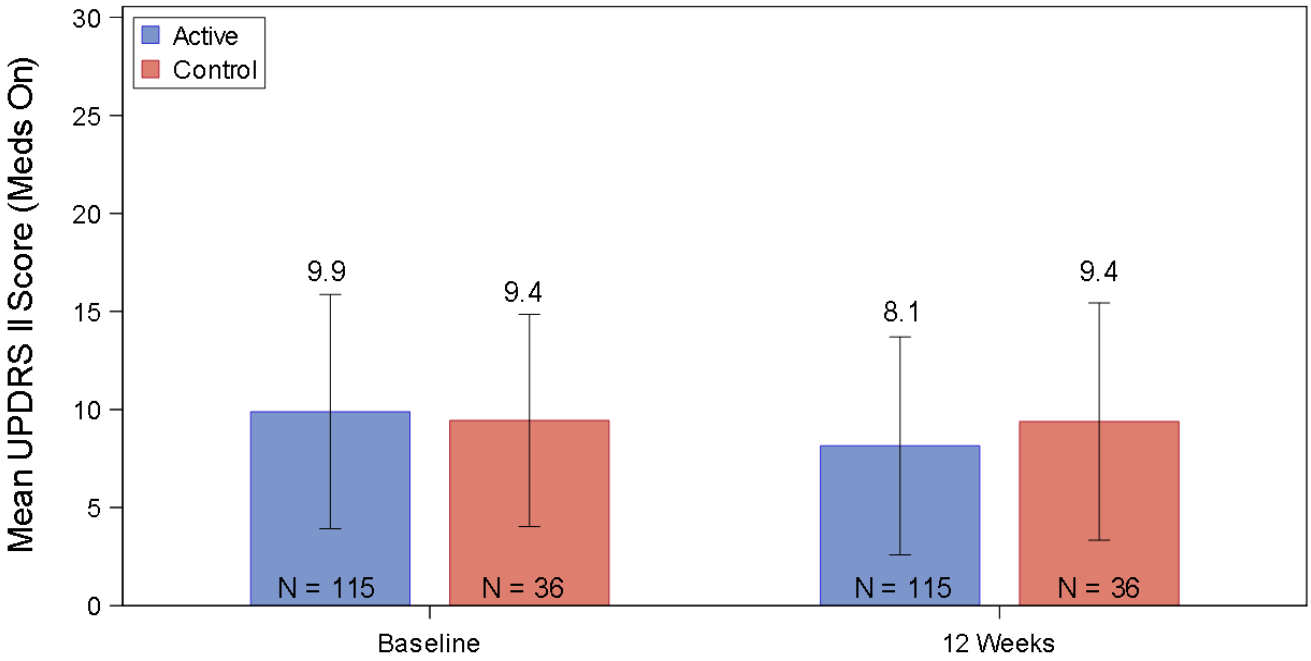

Figure 9. Difference between the Active and Control groups in the mean change in UPDRS-II scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.

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

36-Item Short Form Survey (SF-36 v2) (Quality of Life)

36-Item Short Form Survey (5) (SF-36v2) 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 8 below. The difference between the two groups is not statistically significant.

Table 8: 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]
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.

MCS = Mental Component Summary score.

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.

Conclusions from INTREPID Clinical Study

The INTREPID Study was designed to evaluate the safety and effectiveness of the Boston Scientific Vercise™ Deep Brain Stimulation (DBS) System for bilateral stimulation of the subthalamic nucleus (STN) in the treatment of patients with advanced, levodopa-responsive bilateral Parkinson's disease (PD), which is not adequately controlled with medication.

Of the 292 subjects who provided consent to participate in the study, 177 subjects were implanted bilaterally in the STN with the Vercise DBS System. This document provides the effectiveness data for 160 randomized subjects that completed their Week 12 post-randomization visit as of December 31, 2016 and safety data for 292 enrolled subjects.

The primary endpoint of the study was the difference in change from Baseline to Week 12 post-randomization visit between the Active and Control groups in subjects' ON time with no increase in antiparkinsonian medications. ON time included "ON time" as well as "ON time with non-troublesome dyskinesias" as measured on the Parkinson's Disease (PD) diary (3). This validated measure was utilized for the primary endpoint as the PD diary allowed for subjects' to assess their own health status without any bias from study investigators or their interpretation. The PD diary collects subjects' PD symptoms/health status in 30 minute increments during their awake hours – this allows for a deeper understanding of their disease state including fluctuations and impact to their daily routine. In addition to ON time, the primary endpoint also included a requirement that subjects must have no increase in their antiparkinsonian medications during the blinded period as calculated via levodopa equivalents. This was included to isolate the benefits of DBS for the treatment of PD. This additional criterion is stringent and further added to the scientific rigor of the INTREPID Study. Other randomized controlled trials including Okun 2012 (12), Weaver 2009 (13), Deuschl 2006 (14) did not have this additional criterion.

Though the study is still ongoing, per the scheduled 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 (LED), from baseline to 12 weeks post-randomization in the Active (3.74 ± 4.79 hours) compared to the Control group (0.72 ± 3.56 hours). Post-hoc analysis showed that this improvement increased when the analysis was performed with no requirement in 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.

In addition to their ON time (good symptom control and no troublesome dyskinesia), subjects in the Active group also noted a significant improvement in their OFF time when the medication is no longer effective and subjects' symptoms return.

The primary endpoint result was also supported by several secondary endpoints including improvement in Unified Parkinson's Disease Rating Scale – Section III (2) (UPDRS III) scores, quality of life such as 39-Item Parkinson's Disease Questionnaire (4) (PDQ-39), Modified Schwab and England (2) (SE) scores. The overall change in subjects' disease state during the study follow-up as compare to Baseline was evaluated by the subjects and physicians to provide different perspectives. In the Active group, 82.0% of subjects reported varying degrees of improvement as compared to Baseline, which was supported by physician response of 91.0%, who similarly reported varying degrees of improvement in their subjects.

91.4% of subjects in the Active group reported being overall satisfied with their treatment. A similar trend was observed when subjects were asked if they would recommend the therapy or be willing to repeat the treatment again. This is indicative of the overall impact that DBS with the Vercise System had on subjects' PD state and their overall quality of life.

There were no unanticipated adverse events and the overall incidence of device/procedure-related serious adverse events (SAEs) was comparable to published reports. The adverse event and safety profiles were similar to those seen in other recent studies of DBS Systems.

Results of this prospective, multi-center, double-blinded randomized controlled trial designed to evaluate the Vercise DBS System for bilateral stimulation of the subthalamic nucleus in the treatment of Parkinson's disease demonstrated that its benefits outweigh the associated risks. Furthermore, the safety and effectiveness of the Vercise System were established.

VANTAGE Clinical Study

Study Design

VANTAGE is 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), 39-Item Parkinson's Disease Questionnaire (4) (PDQ-39), 36-Item Short Form Survey (5) (SF-36 v2), and Global Impression of Change (1). 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).

Patient Accountability

A total of 40 patients were implanted in the study with the Vercise Deep Brain Stimulation (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 Parkinson's Disease (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.

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 9 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 9: 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 (12.5%)**	**17 (40.0%)**	**12 (30.0%)**

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 10 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 10: 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), 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.

Conclusion from VANTAGE Clinical Study

The safety profile in VANTAGE Study was similar to those seen in the INTREPID Study and other recent studies of Deep Brain Stimulation (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.

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

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

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

Technical Comparison

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

VTA modeling has been used to estimate the degree of neuronal activation and by extension the degree of stimulation efficacy [15]. The modeled Boston Scientific 8-contact Standard and Directional DBS leads were able to achieve a comparable VTA volume and shape when compared the Medtronic leads. In all the modeled scenarios the percent deviation of the VTAs of the Boston Scientific leads from the VTA of the Medtronic lead ranged between 4.34% (meaning greater coverage for Boston Scientific leads) and -3.26%. The results show that parameters of the Vercise PC and Vercise Gevia DBS Systems can be varied to achieve a VTA comparable to that achieved by the Medtronic Activa Parkinson's Control Therapy approved in P960009/S007; the range of deviation is acceptable. These results also demonstrate that a desired VTA can be achieved by adjusting stimulation parameters on any of the lead models (Boston Scientific 8-contact Standard and Directional DBS leads, Medtronic lead models 3387 and 3389).

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

The Vercise PC and Vercise Gevia DBS Systems demonstrated the capability to replicate at least the same output as the Medtronic Activa Parkinson's Control Therapy System indicating it can provide at least a comparable level of efficacy. Though the waveforms of Vercise PC/Gevia and Soletra differ in their method of charge balancing they both have the capability to inhibit and excite action potentials. The degree of neuronal activation with DBS is proportional to the amount

of charge delivered. The intensity of the charge delivered (charge density) also has implications for clinical safety. For parameters that differ between the devices, the Vercise PC and Vercise Gevia DBS Systems ensure safety by providing a charge density limit and preventing charge imbalance conditions.

The Boston Scientific INTREPID Parkinson's study of STN stimulation provides further assurance of the safety of the additional parameters provided by the Boston Scientifc DBS devices. The study was used to support the safety of DBS at therapeutic levels for Parkinson's disease. Although patients in the study were implanted in the STN, both STN and GPi are grey matter nuclei that can be stimulated to treat some of the symptoms of Parkinson's disease.

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

Effectiveness Conclusions

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

Safety Conclusions

Boston Scientific performed a multi-center, prospective, double-blind, randomized, controlled study (INTREPID Study) that was design to evaluate the safety and effectiveness of the Vercise DBS System for bilateral stimulation of the STN as an adjunctive therapy for improving dyskinesia and other symptoms in adults with advanced, levodopa-responsive bilateral Parkinson's disease which is not adequately controlled with medication. This study was used to support approval of the Vercise DBS System under P150031. Additional details of this study is provided in the SSED for P150031 that is available on the CDRH website. The Vercise PC and Vercise Gevia DBS Systems were approved under P150031/S001 based on a similarity of technological characteristics to the Vercise DBS System. Although the data were used to support the safety of DBS at the STN, findings have applicability to the safety of stimulation at the GPi of similarity of the technological characteristics. Location of the stimulation is different, but stimulation related adverse effects can be resolved at either of the grey matter locations by adjustments to stimulation parameters.

The INTREPID safety data was based on a total of 292 consented (enrolled) subjects. Of these 292 subjects, 177 subjects received 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. The nature and incidence rate of the reported adverse events in the study was anticipated.

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

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

Overall Conclusions

The data in this application and its applicability to the Vercise PC and Vercise Gevia DBS Systems for GPi stimulation support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With regard to reasonable assurance of the effectiveness of the Vercise PC and Vercise Gevia DBS Systems, Boston Scientific provided adequate evidence of the sufficient similarity of the Vercise PC and Vercise Gevia DBS Systems and the Medtronic Activa Parkinson's Control Therapy with regard to technological characteristics. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control Therapy is directly applicable towards establishing reasonable assurance of the effectiveness of the Vercise PC and Vercise Gevia DBS Systems.

With regard to reasonable assurance of the safety of the Vercise PC and Vercise Gevia DBS Systems, Boston Scientific also provided adequate evidence of the sufficient similarity to the Vercise DBS System approved under P150031. Although the data were used to support the safety of DBS at the STN, the findings have applicability to the safety of stimulation at the GPi because of the similarity of the technological characteristics, although the location of the stimulation is different. Boston Scientific also provided adequate evidence of the sufficient similarity of the Vercise PC and Vercise Gevia DBS Systems and the Medtronic Activa Parkinson's Control Therapy with regard to technological characteristics. Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Parkinson's Control is directly applicable towards establishing reasonable assurance of the safety of the Vercise PC and Vercise Gevia DBS Systems for GPi stimulation.

In conclusion, given the available information identified above and its applicability to the Vercise PC and Vercise Gevia DBS Systems, the data supports that the probable benefits for the Vercise PC and Vercise Gevia DBS Systems outweigh its probable risks for GPi stimulation.

Appendix B: Summary of Clinical Effectiveness of Thalamic Stimulation for the Suppression of Tremor

In lieu of providing a clinical data set for Vercise PC, Vercise Gevia and Vercise Genus DBS Systems, Boston Scientific provided a technological comparison (including a comparison of the technology, surgical procedures, and instructions for use) of Vercise PC/Gevia/Genus DBS Systems to the Medtronic Activa Tremor Control System which was approved under P960009 for unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) for the suppression of parkinsonian tremor and essential tremor in the upper extremity. The purpose of the technological comparison was to establish sufficient similarity of the Boston Scientific and Medtronic DBS devices such that FDA could apply Section 216 of the Food and Drug Modernization Act (FDAMA), i.e., the "six-year rule," to assess the effectiveness profile of Vercise PC, Vercise Gevia and Vercise Genus DBS Systems.

According to FDA's "Guidance on Section 216 of the Food and Drug Modernization Act of 1997" available at: https://www.fda.gov/media/71743/download"https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073709.pdf, FDA may choose to utilize the publicly available detailed Summary of Safety and Effectiveness Data (SSED) of a previously approved device to support approval of a PMA for a new device if the applicant provides "a detailed justification of how the information in the earlier SSED applies to the applicant's device" and if the applicant is able "to describe how the devices are similar enough to allow for the data from the earlier device to apply to the new device."

Technical Comparison

For the purposes of establishing sufficient similarity of Vercise PC/Gevia/Genus DBS Systems and the Medtronic Activa Tremor Control System, Boston Scientific provided a technical comparison of the devices. Deep brain stimulation (DBS) systems work by sending electrical stimulation from an implanted neurostimulator to leads in the brain where the current is dispersed through electrodes into the brain tissue in order to activate neurons in specific brain regions. The clinical response of stimulation varies depending on the brain target and the orientation of the DBS lead within the target. As part of DBS programming, the clinician can adjust the combination of parameters, including amplitude, pulse width, frequency and electrode configuration, to tailor the stimulation field to the needs of each patient. By comparing the Volume of Tissue Activation (VTA) of the Vercise PC/Gevia/Genus DBS Systems to the Medtronic Activa Tremor Control System, it was determined that the Vercise PC/Gevia/Genus DBS Systems stimulate, and thus activate, neurons with volume of brain tissue equivalent to that which was shown to be safe and effective for the Medtronic Activa Tremor Control System approved in P960009.

VTA modeling has been used to estimate the degree of neuronal activation and by extension the degree of stimulation efficacy [15]. The modeled Boston Scientific 8-contact Standard and Directional DBS leads were able to achieve a comparable VTA volume and shape when compared to the Medtronic leads. In all the modeled scenarios the percent deviation of the VTAs of the Boston Scientific leads from the VTA of the Medtronic lead ranged between 0.61% (meaning greater coverage for Boston Scientific leads) and -3.26%. The results show that parameters of the Vercise PC/Gevia/Genus DBS Systems can be varied to achieve a VTA comparable to that achieved by the Medtronic Activa Tremor Control System approved in P960009; the range of deviation is acceptable. These results also demonstrate that a desired VTA can be achieved by adjusting stimulation parameters on any of the lead models (Boston Scientific 8-contact Standard and Directional DBS leads, Medtronic lead model 3387).

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

The Vercise PC/Gevia/Genus DBS Systems demonstrated the capability to replicate at least the same output as the Medtronic Activa Tremor Control System indicating it can provide at least a comparable level of efficacy. Though the waveforms of Vercise PC/Gevia/Genus pulse generators and the Medtronic Model 7424 Itrell II pulse generators differ in their method of charge balancing, they both have the capability to inhibit and excite action potentials. The degree of neuronal activation with DBS is proportional to the amount of charge delivered. The intensity of the charge delivered (charge density) also has implications for clinical safety. For parameters that differ between the devices, the Vercise PC/Gevia/Genus DBS Systems ensure safety by providing a charge density limit and preventing charge imbalance conditions.

The Boston Scientific INTREPID Parkinson's study of STN stimulation provides further assurance of the safety of the additional parameters provided by the Boston Scientific DBS devices. The study was used to support the safety of DBS at therapeutic levels for Parkinson's disease. Although patients in the study were implanted in the STN, both STN and VIM are grey matter nuclei that can be stimulated to treat some of the symptoms of Parkinson's disease.

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

Effectiveness Conclusions

Boston Scientific provided adequate evidence of the sufficient similarity of the Vercise PC/Gevia/Genus DBS Systems to the Medtronic Activa Tremor Control with regard to its technological characteristics as described in Section IX(B). Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Tremor Control System approved under P960009 is directly applicable towards establishing reasonable assurance of the effectiveness of the Vercise PC/Gevia/Genus DBS Systems for thalamic stimulation for the suppression of parkinsonian tremor and essential tremor. As detailed in the SSED for the Medtronic Activa Tremor Control System, in the prospective US Tremor Study of the Medtronic Activa Tremor Control System, activities of daily living showed statistically significant improvement in both essential tremor and Parkinson's disease patients. For the prospective European Tremor Study, activities of daily living and other functional improvements were statistically significant in both essential tremor and Parkinson's disease patients.

Safety Conclusions

Boston Scientific provided adequate evidence of the sufficient similarity of the Vercise PC/Gevia/Genus DBS Systems with regard to its technological characteristics. Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Tremor Control System approved under P960009 is directly applicable towards establishing reasonable assurance of the safety of the Vercise PC, Vercise Gevia, and Vercise Genus DBS Systems for thalamic stimulation for the suppression of parkinsonian tremor and essential tremor.

As detailed in the SSED for the Medtronic Activa Tremor Control System, the frequency of adverse events reported in the US and European Tremor Trials did not differ markedly from the frequencies reported for DBS in the European Basic Study and DBS for Pain Study that were performed to generate a safety profile for the Activa System.

Boston Scientific also performed a multi-center, prospective, double-blind, randomized, controlled study (INTREPID Study) that was designed to evaluate the safety and effectiveness of the Vercise DBS System for bilateral stimulation of the STN as an adjunctive therapy for improving dyskinesia and other symptoms in adults with advanced, levodopa-responsive bilateral Parkinson's disease which is not adequately controlled with medication. This study was used to support approval of the Vercise DBS System under P150031. Additional details of this study is provided in the SSED for P150031 that is

available on the CDRH website. The Vercise PC, Vercise Gevia and Vercise Genus DBS Systems were approved under P150031/S001 and P150031/S034 based on a similarity of technological characteristics to the Vercise DBS System. Although the data were used to support the safety of DBS at the STN, findings have applicability to the safety of stimulation at the VIM because of similarity of the technological characteristics. Location of the stimulation is different, but stimulation related adverse effects can be resolved at either of the grey matter locations by adjustments to stimulation parameters.

Overall Conclusions

The data in this application and its applicability to the Vercise PC, Vercise Gevia and Vercise Genus DBS Systems for thalamic stimulation for the suppression of parkinsonian tremor and essential tremor support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With regard to reasonable assurance of the effectiveness of the Vercise PC/Gevia/Genus DBS Systems, Boston Scientific provided adequate evidence of the sufficient similarity of the Vercise PC/Gevia/Genus DBS Systems and the Medtronic Activa Tremor Control System with regard to technological characteristics. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Tremor Control System is directly applicable towards establishing reasonable assurance of the effectiveness of the Vercise PC, Vercise Gevia and Vercise Genus DBS Systems.

With regard to reasonable assurance of the safety of the Vercise PC/Gevia/Genus DBS Systems, Boston Scientific also provided adequate evidence of the sufficient similarity to the Vercise DBS System approved under P150031. Although the data were used to support the safety of DBS at the STN, the findings have applicability to the safety of stimulation at the VIM because of the similarity of the technological characteristics, although the location of the stimulation is different. Boston Scientific also provided adequate evidence of the sufficient similarity of the Vercise PC/Gevia/Genus DBS Systems and the Medtronic Activa Tremor Control System with regard to technological characteristics. Therefore, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the Medtronic Activa Tremor Control System is directly applicable towards establishing reasonable assurance of the safety of the Vercise PC/Gevia/Genus DBS Systems for thalamic stimulation for the suppression of parkinsonian tremor and essential tremor.

In conclusion, given the available information identified above and its applicability to the Vercise PC, Vercise Gevia and Vercise Genus DBS Systems, the data supports that the probable benefits for these DBS Systems outweigh its probable risks for thalamic stimulation for the suppression of parkinsonian tremor and essential tremor.

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