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Vercise™ Deep Brain Stimulation (DBS) System for Parkinson's disease (PD)

Clinical Summary

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Contents

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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; 60-90mg 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: 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.

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.

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 (ie, 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.

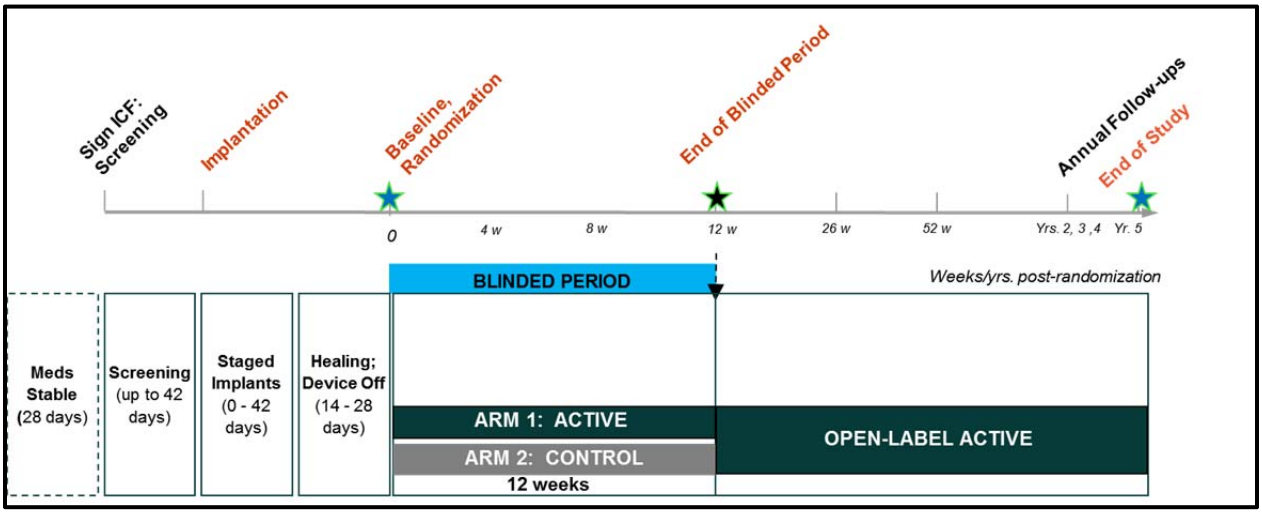


Figure 1: INTREPID Study Schematic

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.

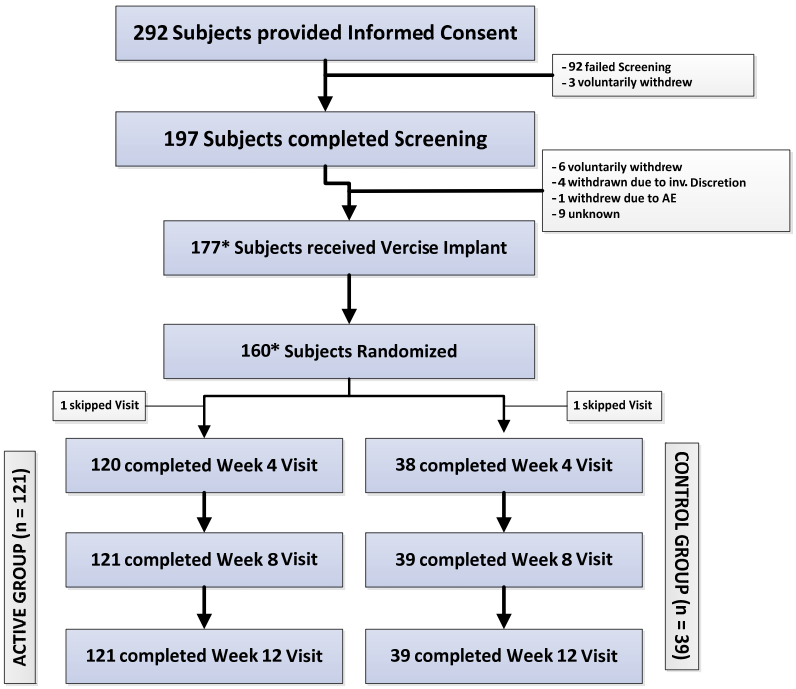
A two group t-test with a one-sided 0.025 significance level (adjusted for the interim analyses) was used to assess the primary endpoint. The Intent-To-Treat (ITT) analysis set was used for the primary analysis. Missing data at 12 week post-randomization were imputed appropriately. The 95% confidence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



*As of Dec 31st 2016. Only those subjects included in the analysis are included

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
Event	Number of Events (Incidence)	Number of Events (Incidence)	Number of Events (Incidence)
Abnormal behavior	0 (0.0%)	2 (0.7%)	0 (0.0%)
Adverse drug reaction	0 (0.0%)	0 (0.0%)	1 (0.3%)
Affect lability	0 (0.0%)	2 (0.7%)	1 (0.3%)
Aggression	0 (0.0%)	1 (0.3%)	0 (0.0%)
Agitation	1 (0.3%)	3 (1.0%)	0 (0.0%)
Agitation postoperative	0 (0.0%)	0 (0.0%)	1 (0.3%)
Amnesia	1 (0.3%)	0 (0.0%)	2 (0.7%)
Anxiety	0 (0.0%)	1 (0.3%)	1 (0.3%)
Apathy	1 (0.3%)	2 (0.7%)	1 (0.3%)
Aphasia	0 (0.0%)	1 (0.3%)	1 (0.3%)
Apraxia	0 (0.0%)	4 (1.4%)	0 (0.0%)
Arthralgia	0 (0.0%)	0 (0.0%)	1 (0.3%)
Asthenia	0 (0.0%)	1 (0.3%)	0 (0.0%)
Balance disorder	1 (0.3%)	12 (3.4%)	1 (0.3%)
Blepharospasm	0 (0.0%)	1 (0.3%)	1 (0.3%)
Burning sensation	1 (0.3%)	0 (0.0%)	0 (0.0%)
Cerebral hemorrhage	1 (0.3%)	0 (0.0%)	3 (1.0%)
Cervicobrachial syndrome	0 (0.0%)	1 (0.3%)	0 (0.0%)
Chest discomfort	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cognitive disorder	3 (1.0%)	2 (0.7%)	3 (1.0%)
Complex partial seizures	1 (0.3%)	0 (0.0%)	1 (0.3%)
Confusion postoperative	2 (0.7%)	0 (0.0%)	3 (1.0%)

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

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

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

	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
Agitation	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Agitation postoperative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Amnesia	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Anxiety	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
Aphasia	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Apraxia	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Asthenia	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Balance disorder	1 (0.8%)	0 (0.0%)	6 (5.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Blepharospasm	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Burning sensation	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebral hemorrhage	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Chest discomfort	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cognitive disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Confusion postoperative	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.5%)	0 (0.0%)
Confusional state	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.1%)	1 (2.6%)
Convulsion	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
Depressed mood	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Depression	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	1 (2.6%)
Device related infection	3 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.5%)	0 (0.0%)
Diplopia	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysarthria	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Dyskinesia	0 (0.0%)	0 (0.0%)	22 (16.5%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Dysphagia	0 (0.0%)	0 (0.0%)	4 (3.3%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Dysphonia	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnoea	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dystonia	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Electrocardiogram change	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Fall	0 (0.0%)	0 (0.0%)	3 (2.5%)	0 (0.0%)	4 (0.8%)	0 (0.0%)
Freezing phenomenon	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Gait disturbance	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Hallucination, auditory	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Hallucination, visual	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	2 (2.6%)
Hiccups	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)

	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
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%)
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%)

	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
Wound haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
TOTALS	**29 (22.20%)**	**11 (28.50%)**	**67 (53.60%)**	**2 (5.20%)**	**76 (58.20%)**	**22 (54.40%)**

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

Serious Adverse Events

Among all 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%)

	Related to Hardware	Related to Stimulation	Related to Procedure
Event	Number of Events (Incidence)	Number of Events (Incidence)	Number of Events (Incidence)
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.

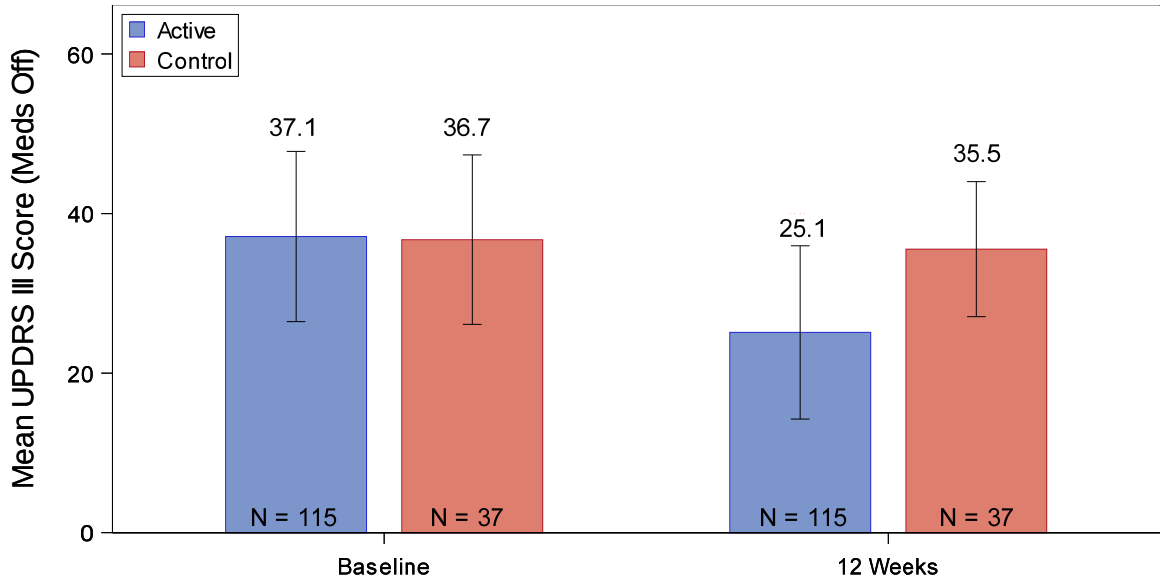


Figure 3: Difference between the Active and Control groups in the mean change in UPDRS-III Score from baseline meds off to 12 weeks post-randomization stim on/meds off.

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.

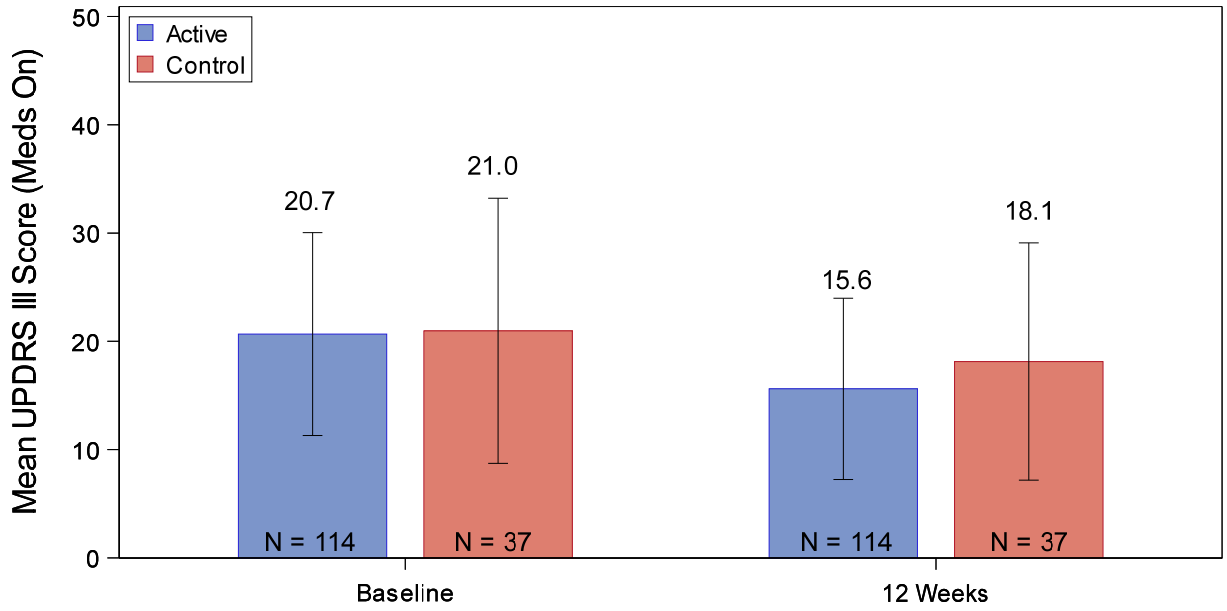


Figure 4: Difference between the Active and Control groups in the mean change in UPDRS-III scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.

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.

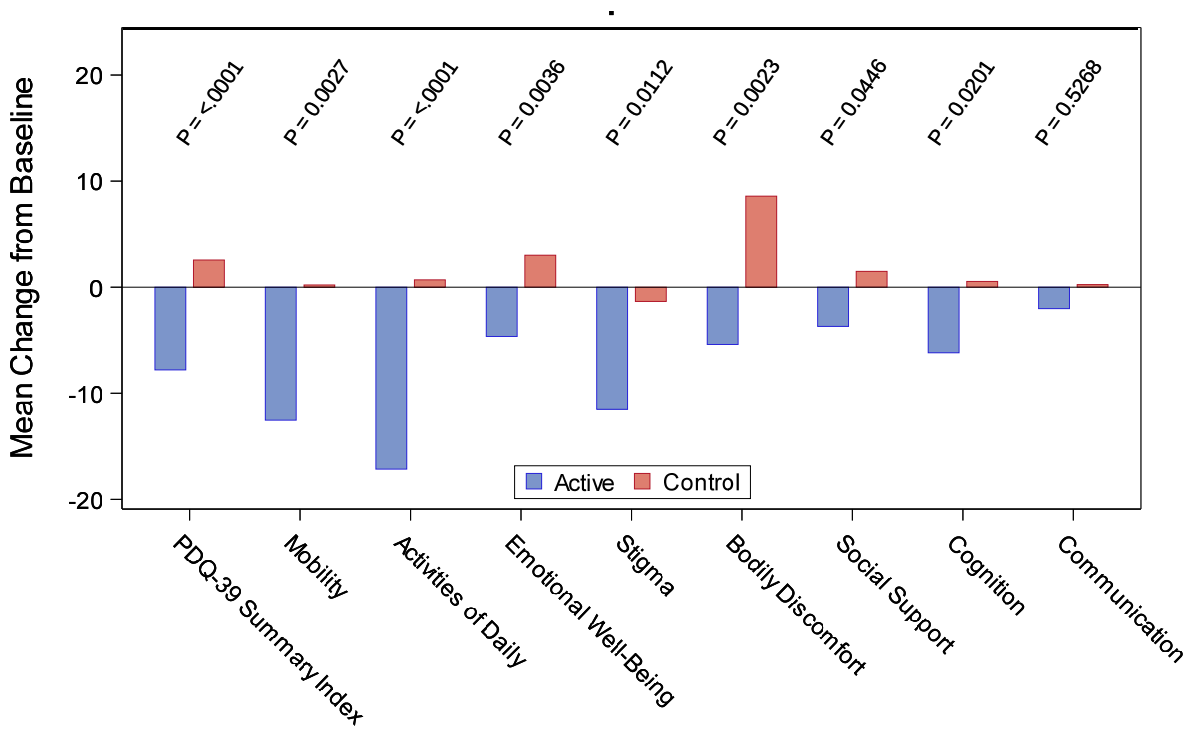


Figure 5: Difference between the Active and Control groups in mean change in PDQ-39 score from baseline to 12 weeks post-randomization. P value from two sample test (Not adjusted for multiplicity).

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.

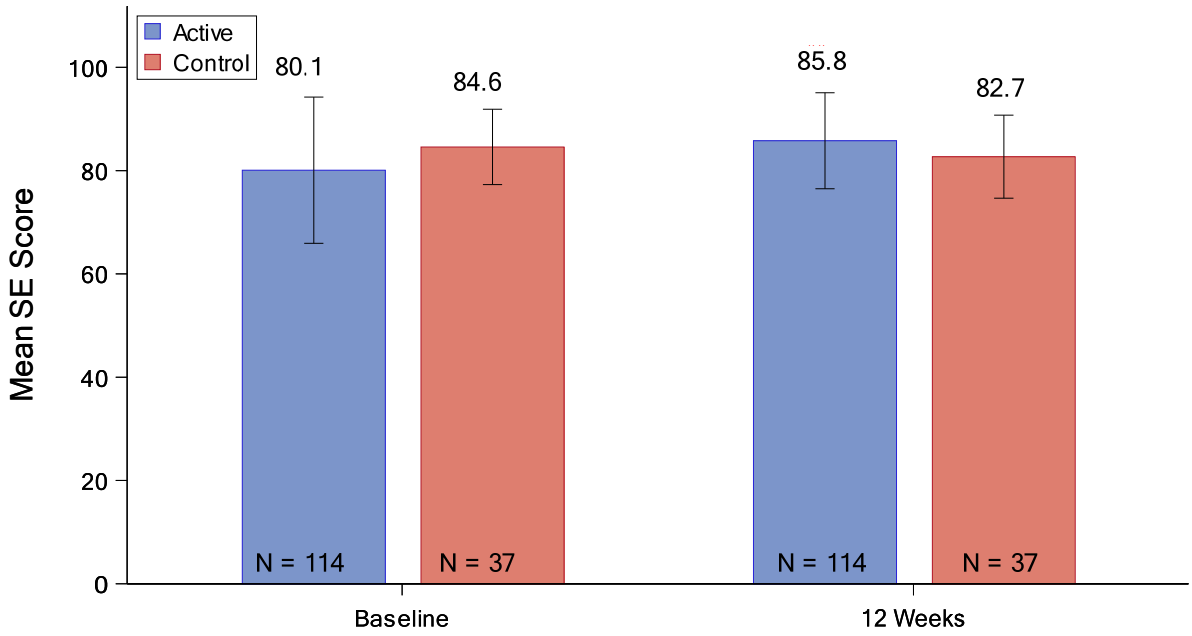


Figure 6: Difference between the Active and Control groups in the mean change in SE scores from baseline to 12 weeks post-randomization.

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

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.

[2] Not adjusted for multiplicity

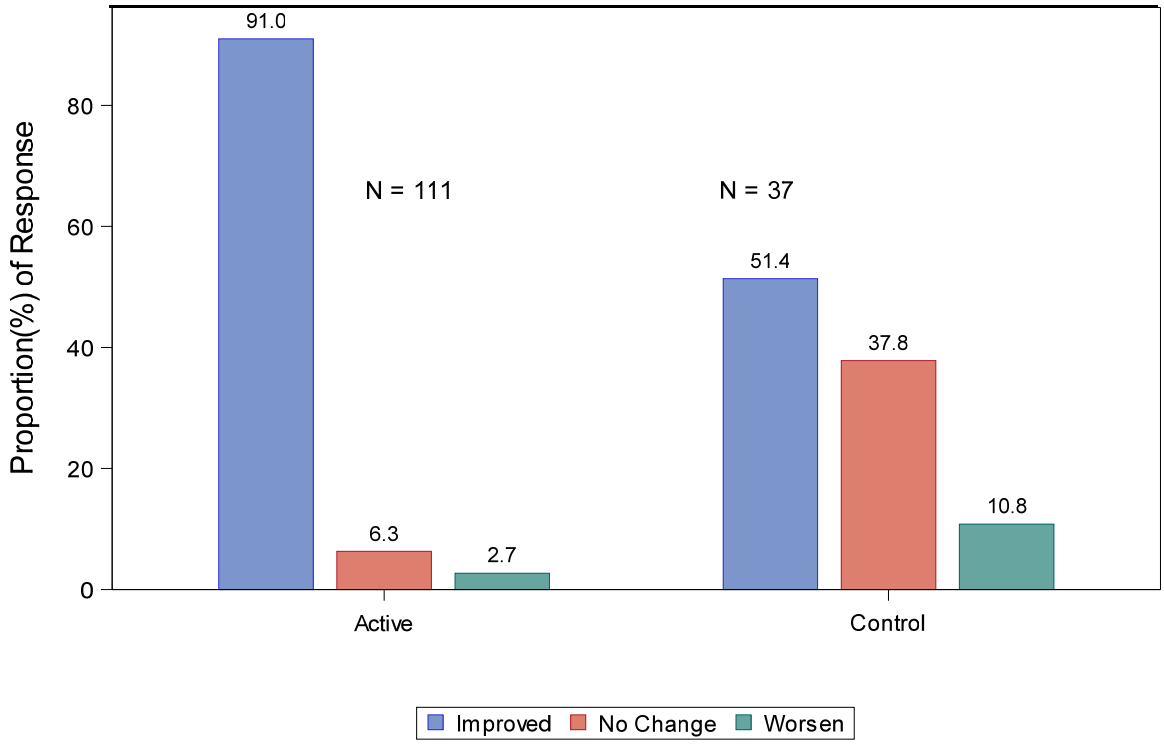


Figure 7: Difference between the Active and Control groups in the mean CGI-C, as assessed by the physician, at Week 12 post-randomization.

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.

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 the graph below.

[3] Not adjusted for multiplicity

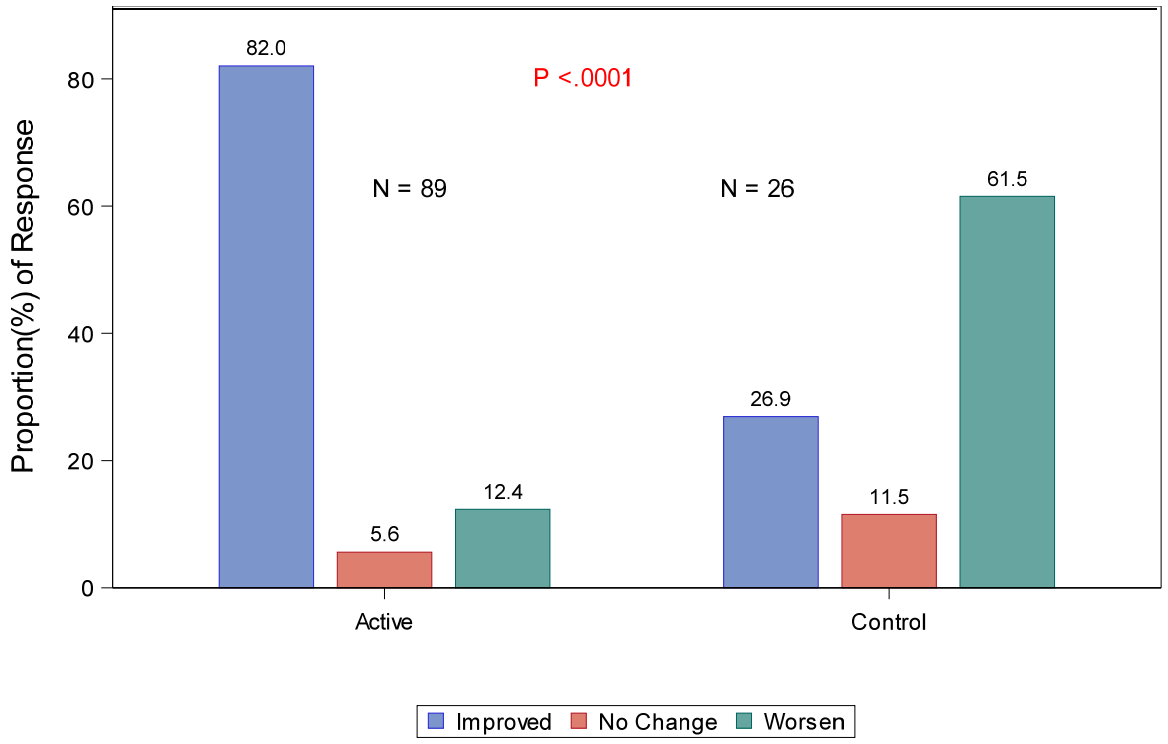


Figure 8: Difference between the Active and Control groups in the mean CGI-C, as assessed by the subject, at Week 12 post-randomization. P value from Fisher's Exact test.

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.

Treatment Satisfaction score

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

The responses of subjects in the Active and Control groups are summarized in the Table 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)

[4] Not adjusted for multiplicity

	Active Group	Control Group
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.

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.

[5] Not adjusted for multiplicity

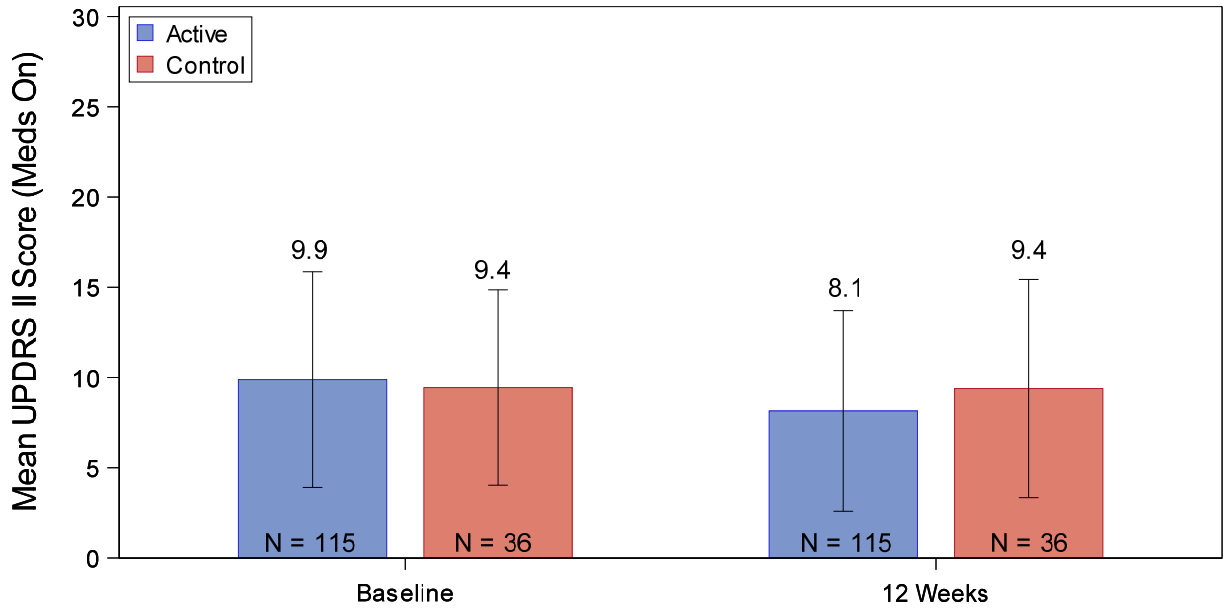


Figure 9: Difference between the Active and Control groups in the mean change in UPDRS-II scores from baseline *meds on* to 12 weeks *stim on/meds on* post-randomization.

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 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.

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