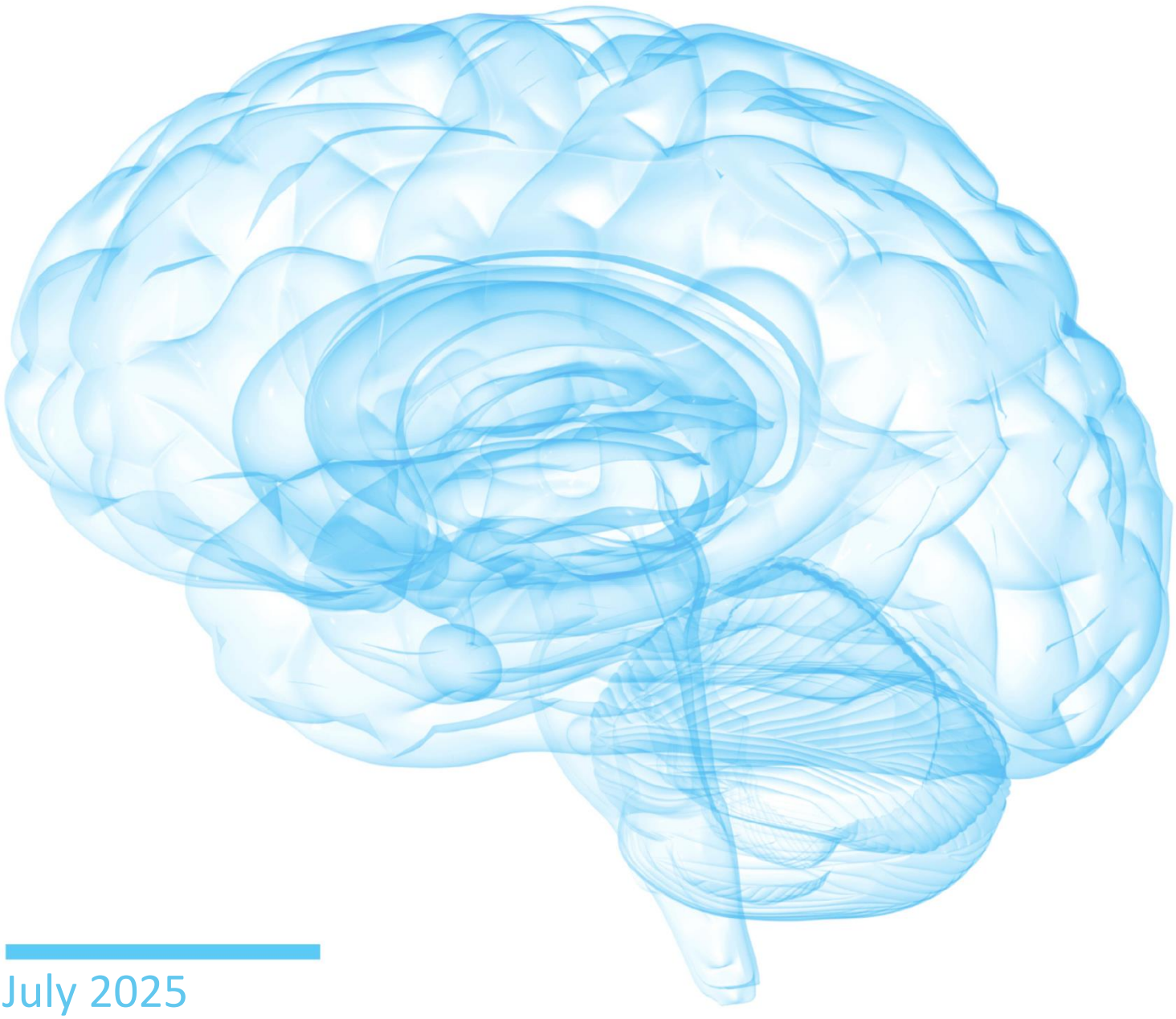

July 2025

EXABLATE MODEL 4000

TYPE 1.0 & TYPE 1.1

APPLICATION: BRAIN INDEX / STAGED CONTRALATERAL UNILATERAL ESSENTIAL TREMOR, TREMOR DOMINANT PARKINSON'S DISEASE, & PALLIDOTOMY MOTOR COMPLICATIONS PARKINSON'S DISEASE

INFORMATION FOR PRESCRIBERS

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CHAPTER 1: OVERVIEW AND LABELING

1.1 Device Description

Insightec's Exablate Neuro delivers focused ultrasound energy into brain tissue through an intact skull. The tissue at the focal spot of the ultrasound beam is increasingly heated to the point of irreversible thermal coagulation, while nearby tissue remains unaffected. Over time, the body gradually absorbs the ablated tissue.

The Exablate Neuro focused ultrasound system operates inside a Magnetic Resonance Imaging (MRI) scanner. The MRI provides images of the patient's anatomy that are used to define the target area and plan the treatment. During the procedure, the MR images are used by the Exablate system to create a real-time thermal map for monitoring of the thermal rise.

Exablate system configuration	
Generic name	Neuro/MRgFUS
Trade Name	Exablate Neuro/Exablate Prime
Model	4000
Cradle Type	1.0 and 1.1
Application	Neuro

For detailed information about each system module, refer to the Exablate Operator's Manual.

1.2 Intended Use / Indications for Use

The Exablate Model 4000 ("Neuro/Prime") is indicated for use:

1. In the unilateral thalamotomy treatment of idiopathic Essential tremor patients with medication-refractory tremor and in the staged (by at least 9 months from the first thalamotomy), unilateral thalamotomy of idiopathic Essential tremor patients with medication-refractory tremor of their contralateral side that was not previously treated in the index unilateral thalamotomy. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (*ventralis intermedius*) must be identified and accessible for targeted thermal ablation by the Exablate device.
2. In the unilateral thalamotomy (*ventralis intermedius*) treatment of tremor-dominant Parkinson's disease with medication-refractory tremor. Patients must be at least age 30.
3. In the unilateral pallidotomy of patients with advanced, idiopathic Parkinson's disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson's disease medication treatment. Patients must be at least age 30. The designated area in the brain responsible for the movement disorder symptoms [*globus pallidus (GPi)*] must be identified and accessible for targeted thermal ablation by the Exablate device.

4. The Exablate Neuro is indicated for use in the unilateral pallidothalamic tractotomy of advanced idiopathic Parkinson's Disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson's disease medication treatment, and in the staged (by at least 6 months from the first pallidothalamic tractotomy), unilateral pallidothalamic tractotomy of idiopathic Parkinson's Disease with medication-refractory motor complications of their contralateral side that was not previously treated in the first unilateral pallidothalamic tractotomy. Patients must be at least age 30. The designated area in the brain responsible for the motor complications symptoms (pallidothalamic tract) must be identified and accessible for targeted thermal ablation by the Exablate device.

CHAPTER 2: PATIENT SELECTION CRITERIA FOR TREATMENT WITH EXABLATE NEURO

2.1 Patient Selection Criteria

Essential Tremor (unilateral thalamotomy)

1. Men and women age 22 years or older;
2. A confirmed diagnosis of Essential tremor refractory to medication therapy such as propranolol or primidone.

Essential Tremor for Bilateral Arm (bilateral thalamotomy)

1. A patient who underwent an Exablate index procedure at least 9 months prior to Contralateral procedure.

Tremor Dominant Parkinson's Disease

1. Men and women age 30 years or older;
2. A confirmed diagnosis of tremor dominant Parkinson's disease as confirmed from clinical history and examination by a movement disorder neurologist/specialist;
3. Tremor remains disabling when medical therapy is optimal or not tolerated for the treatment of other cardinal signs of PD (bradykinesia, rigidity, etc.), as determined by a movement disorders neurologist/specialist;
4. Able to fit into MRI unit;
5. Thalamus / Pallidum visible on MR imaging;
6. Able to tolerate the procedure with or without some form of sedation (e.g., conscious sedation);
7. Able to communicate sensations to the physician during the procedure; and
8. Able to activate **Stop Sonication** button.

Motor Complication Parkinson's Disease (unilateral GPi pallidotomy, pallido-thalamic tractotomy)

1. Men and women, age 30 years and older;
2. Patients with confirmed diagnosis of advanced idiopathic Parkinson's disease with medication-refractory moderate to severe motor complications as determined from clinical history and examination by a movement disorder neurologist/specialist.

Motor Complication Parkinson's Disease for Bilateral Side (bilateral pallido-thalamic tractotomy)

1. A patient who underwent an Exablate index procedure at least 6 months prior to Contralateral procedure.

2.2 Contraindications

The Exablate treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, or allergies to MR contrast agent.
- Patients who are pregnant.
- Patients with advanced kidney disease or on dialysis.
- Patients with unstable cardiac status or severe hypertension.
- Patients exhibiting any behavior(s) consistent with ethanol or substance abuse.
- Patients with history of abnormal bleeding, hemorrhage, and/or coagulopathy.
- Patients receiving anticoagulant or drugs known to increase risk of hemorrhage within one month of focused ultrasound procedure.
- Patients with cerebrovascular disease.
- Patients with brain tumors.
- Patients who are not able or unwilling to tolerate the required prolonged stationary position during treatment. The average treatment time (the time from the first scan to allocate transducer position and ending with the last energy delivery) is 1:56 ± 0.41 hrs (Min: 0.48 hrs, Max: 5:54 hrs).
- Patients who have an Overall Skull Density Ratio of less than 0.40 as calculated from the screening CT.
- Parkinson's disease patients with unstable psychiatric disease, uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation.

For Staged, contralateral Essential Tremor or Parkinson Disease

- Patients with clinically significant dysphagia, abnormal speech function, or gait abnormalities that are moderate to severe following an Exablate unilateral procedure.

2.3 Warnings

- Prolonged immobilization may lead to increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE). In order to avoid this, the patient should be wearing **Thromboembolic Stockings (TEDs),** also referred to as **"anti-embolism"** stockings through the entire procedure time in the MRI.
- The transducer interface must be filled completely with water without air bubbles to provide adequate acoustic coupling.
- Ensure that the patient can activate the Stop Sonication button before initiating treatment. In the event of pain or patient motion, failure to do so may result in serious injury.
- Ensure that the patient's scalp is shaved well, and that any scars or scalp lesions (i.e., eczema or psoriasis) are marked for avoidance in the treatment beam path to minimize heating/burning at the scalp.

- Accurate calibration of the alignment of the transducer at the start of the treatment is critical to proper tissue targeting and to avoid injury to non-targeted tissue. Perform geometrical verification prior to treatment to ensure proper alignment before beginning treatment.
- Failure to monitor the MR thermal maps during the procedure may result in unintended heating of non-targeted tissues, which may cause permanent injury. Operator must cancel/abort the procedure if MR thermometry data are not available.
- Ensure that only degassed water is used in the circulating area between the transducer and the patients' skull to avoid air bubbles in the system which might result in skin burn.
- Prior to the delivery of each sonication throughout the treatment, the beam path should be evaluated to avoid scars or other irregularities in the skin which can cause pain or skin burns.
- Inadequate cooling time between sonications could lead to thermal build-up that may cause serious damage to normal tissues outside the targeted volume. The cooling time between sonications is automatically scaled according to the actual energy applied and sonication parameters and should not be decreased.
- If the skull bone is heated significantly, tissue adjacent to the skull can also absorb heat and may be damaged. To prevent damage to this tissue, heating of the skull should be minimized – this is achieved both by circulating chilled water across the outer surface of the skull (avoid heating of outer skull-skin interface) and choosing target regions at a depth in the brain at least 2.5 cm from the skull (avoid heating of internal skull-tissue interface).

Refer to the Operator's Manual for the Exablate and the MR system for more detailed warnings regarding safe use of this system.

2.4 Precautions

- Before applying energy, the physician must check that water interface is full and that the transducer and head frame are mechanically secured in place.
- The physician should confirm all hair has been shaved from patient's scalp and confirm proper shaving to prevent air trapping that could absorb heat and result in skin burn.
- ACT must be performed prior to this procedure in order to identify all skull configurations and calcifications in the treatment path. These images are loaded into the MR unit and synched with real-time MR images.
- Ensure that the patient has the Stop Sonication button before proceeding in case of emergency. Failure to do so may result in the patient not being able to stop the sonication in case of pain. The attending team must monitor the patient continuously during the procedure, and after each sonication.
- Perform sonication location verification prior to treatment to ensure proper alignment of the transducer. Failure to do so may result in inaccurate focusing of the transducer and/or result in temperatures not capable of ablating the target region.
- Thermal feedback must be monitored throughout the treatment to avoid thermal injury outside the intended treatment volume.
- Do not attempt to use components other than the Exablate hardware, software, and system accessories, and the specified MR imaging system with the device.
- Do not attempt to repair the Exablate System in the event of system failure, malfunction or any evidence of damage to the components. Contact INSIGHTEC Technical Support

Refer to the Operator's Manual for the Exablate and the MR system for more detailed precautions regarding safe use of this system.

2.5 Potential Adverse Reactions

Potential adverse reactions from use of the Exablate device, placement of headframe, or ablative procedure include:

1) Transient events that resolve within or less than three days such as headache, ataxia, dysarthria, pain, dizziness, nausea, diplopia, imbalance, nystagmus, slurred speech, unsteady, numbness/tingling, tilting sensation, and warm sensation.
2) Adverse reactions associated with procedure such as transient fever, oral temperature > 100.4°F/ 38°C, transient skin pain, minor (1° or 2°) skin burns less than 2 cm in diameter, pain during the sonication treatment, tissue damage in area other than the treatment area, hemorrhage in the treated area requiring emergency treatment, skin burns with ulceration of the skin, skin retraction, scar formation, and venous thromboembolic events.
3) Adverse reactions associated with ablative procedure such as numbness/tingling, dysarthria, ataxia, dysgeusia, gait disturbance imbalance, dysphagia, hypogeusia, dysmetria, fatigue, hypoesthesia.

4) Infrequent events (less than 1% occurrence) such as decrease in synchronicity between hands, diplopia, dizziness, dry mouth, facial droop, headache, sialorrhea, voice change, and weakness.

CHAPTER 10: SUMMARY OF PIVOTAL STUDY FOR STAGED, BILATERAL PALLIDOTHALAMIC TRACTOTOMY

10.1 Pivotal Protocol Summary – PD014 (IDE # G200238)

The study was designed as a prospective, open label, single-arm, multi-center pivotal study to evaluate the safety and efficacy of staged bilateral Exablate pallidothalamic tractotomy for patients with motor complications of Parkinson's Disease. Subjects underwent an Exablate procedure (i.e. Treatment-1, "T1") targeting the PTT and were seen at Week 1, and Month 1, 3, and 6 post treatment. At the Month 6 visit, subjects were evaluated for a contralateral Exablate procedure (i.e. Treatment-2, "T2"). Subjects who did not qualify at Month 6 for the second side treatment or did not wish to proceed were seen at Month 12 for their final unilateral follow-up. Subjects who qualified for the staged Pallidothalamic Tractotomy procedure and wished to proceed, underwent a second procedure for the contralateral side and were seen at Week 1, and Month 1, 3, 6, and 12 post-second procedure. In this study, the first patient was enrolled and received initial treatment on July 12, 2021, and the last patient completed second-side treatment on November 1, 2023. The database lock was performed on September 14, 2024, following completion of all data collection.

10.1.1 Eligibility Criteria

The key inclusion and exclusion criteria for this pivotal study are listed below:

10.1.1.1 Inclusion Criteria

1. Men and women, age 30 years and older, desiring bilateral treatment option.
2. Diagnosis of idiopathic PD by UK Brain Bank Criteria.
3. Levodopa responsive (≥ 30% reduction in MDS-UPDRS motor subscale in the ON vs OFF medication state).
4. MDS-UPDRS ≥ 30 in the meds OFF state.
5. Motor complications of PD on optimum medical treatment characterized dyskinesia OR motor fluctuations (MDS-UPRDS 4.2 or 4.4 ≥ 2 in meds ON state).

10.1.1.2 Exclusion Criteria

1. ≥ 3 on the PULL test.
2. Severe premorbid risks per MDS-UPDRS Part II aspects of experiences of daily living (speech, chewing and swallowing, saliva and drooling).
3. Significant cognitive impairment as determined by neuropsychologist.
4. Unstable psychiatric disease.
5. History of abnormal bleeding, hemorrhage, or coagulopathy.
6. Any illness that in the investigator's opinion preclude participation in this study.
7. Contraindications for MR imaging (e.g. implanted metallic devices).

8. Skull Density Ratio (SDR) < 0.40.

Patients were not permitted to receive bilateral treatment if they met the following criteria following the first procedure:

1. Moderate to severe neurological event (e.g. dysphagia, speech, gait imbalance, cognitive impairment, and visual field deficit) following the first unilateral procedure.

10.1.2 Study Follow Up

Subjects were followed-up at Week 1 and at Months 1, 3, 6, and 12. Subjects were evaluated for general health, neurological changes, and PD symptomology measurements, as well as for device/procedure/PD disease progression-related adverse events that may have occurred during the follow-up period.

- Following the index procedure, subjects were evaluated for the second procedure at or after their Month 6 visit. If they did not qualify or did not wish to proceed to the second treatment, they would complete an annual visit at Month 12 ± 60 days and be considered as having completed the study as planned.
- If subjects were eligible and proceeded to the second Exablate procedure, they completed the following visits: Week 1 ± 3 days, Month 1 ± 7 days, Month 3 ± 14 days, Month 6 ± 21 days, and Month 12 ± 60 days.

Analyses of the primary outcome were performed at 3 and 12 months follow-up for efficacy and safety assessments, respectively.

The schedule of events, **Table 1** is shown below:

Table 1. Schedule of Events									
Activity / Visit	Screening/Baseline	Exablate procedure	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 14 days	Month 6 ±21 days	Month 12 ± 60 days	Bilateral Pre-Treatment	Long Term FU (2,3, 4, 5 Years ± 60days)
Informed Consent	X								
Medication Review	X	X	X	X	X	X	X		
Demographics & Medical History	X								
Physical Exam	X	X	X	X	X	X	X		
Neurological Exam	X	X	X	X	X	X	X		
Visual Field Assessment by ophthalmologist	X				X				
TGUG	X			X	X	X	X		
Laboratory Tests	X								
CT	X								
MR *with tractography ●(repeat prior to second procedure)	X	X						X*•	
MDS-UPDRS, Parts I-II	X			X	X	X	X		X
OFF MDS-UPDRS, Part III	X			X	X	X	X		X
ON MDS-UPDRS, Part III	X			X	X	X	X		X
MDS-UPDRS, Part IV	X			X	X	X	X		X
Neuropsychological Assessment	X				X		X		

Table 1. Schedule of Events

Activity \ Visit	Screening/Baseline	Exablate procedure	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 14 days	Month 6 ±21 days	Month 12 ± 60 days	Bilateral Pre-Treatment	Long Term FU (2,3, 4, 5 Years ± 60days)
Dysphagia Handicap Index (DHI) by Speech Pathologist *Assessment will be done prior to Bilateral Treatment and at Month 3 Post Bilateral Treatment					X*			X*	
Speech Function Assessment by Speech Pathologist *Assessment will be done prior to Bilateral Treatment and at Month 3 Post Bilateral Treatment					X*			X*	
Voice Handicap Index (VHI-10) Assessment by Speech Pathologist *Assessment will be done prior to Bilateral Treatment and at Month 3 Post Bilateral Treatment					X*			X*	
Clinician Global Impression of Change					X				X
Patient Global Impression of Change					X				X

Table 1. Schedule of Events									
Activity / Visit	Screening/Baseline	Exablate procedure	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 14 days	Month 6 ±21 days	Month 12 ± 60 days	Bilateral Pre-Treatment	Long Term FU (2,3, 4, 5 Years ± 60days)
Patient Satisfaction Questionnaire					X				X
EQ-5D-5L	X			X	X	X	X		X
WPAI-GH	X			X	X	X	X		X
Exablate procedure		X							
Adverse Events		X	X	X	X	X	X		X

10.1.3 Study Endpoints

10.1.3.1 Primary Safety Endpoint

The primary safety endpoint of this study is the Treatment-Emergent Adverse events (AEs), including serious adverse events (SAEs) and Unanticipated Adverse Device Effects (UADEs) occurring at any time during the trial from the Bilateral treatment through all study visits.

Note that Treatment-Emergent Adverse Events are defined as adverse event starting on or after the day of treatment.

10.1.3.2 Primary Effectiveness Endpoint

The primary efficacy endpoint of the study is the percent change of the bilateral upper and lower extremity motor score from the MDS-UPDRS Part III OFF-Medications at Month 3 post Bilateral treatment (Treatment 2), on both treated sides compared to baseline.

The score of the upper and lower extremity fields will be summed to obtain the total score of the subject at 3 months. The change from Baseline score will also be calculated. The primary endpoint will be calculated for each individual as percent change from Baseline to Month 3 post bilateral procedure for both sides as follows:

% Change = 100*(Baseline score – T2, Month 3 score)/Baseline score

Note: Baseline will be defined as the last assessment prior to the first (unilateral) treatment.

All measurements will be taken in the OFF meds condition for both treated sides and have a maximum total score of 88 points. An individual's score is the sum of the items from the MDS UPDRS Part III as follows:

3.3 rigidity, (upper and lower extremity)

3.4 finger tapping

3.5 hand movements

3.6 pronation-supination movements of hands

3.7 toe tapping

3.8 leg agility

3.15 postural tremor of the hands

3.16 kinetic tremor of the hands

3.17 rest tremor amplitude (upper and lower extremity).

10.1.3.3 Confirmatory Endpoints

This study has two confirmatory effectiveness outcomes that are defined as follows.

1) **MDS-UPDRS Part IV – Motor Complications**

- An individual's score is the sum of the items in the MDS-UPDRS Part IV ON medication (items 4.1 to 4.6).

The motor complication confirmatory endpoint will be calculated for each individual as percent change from Baseline to Month 3 post bilateral procedure as follows:

% Change = 100*(Baseline score – T2, Month 3)/Baseline

The calculated scores, change from Baseline and percent change from Baseline will be presented.

2) **MDS-UPDRS Part III OFF Meds, Total Score**

MDS UPDRS Part III total score is defined as the sum of all items included in part III (items 3.1 to 3.18) taken in the OFF medication state.

Percent change from Baseline to Month 3 post treatment 2 will be calculated as follows:

% Change = 100*(Baseline score – T2, Month 3)/Baseline

The calculated scores, change from Baseline and percent change from Baseline will be presented.

10.1.3.4 Secondary Endpoints

The following secondary efficacy endpoints will also be evaluated, including the calculated scores, change from Baseline and percent change from Baseline for each scheduled visit.

1) MDS-UPDRS Part III – Upper and Lower Extremity Motor Examination

The upper and lower extremity motor examination secondary endpoint will include all upper and lower extremity measurements taken in the OFF meds condition for treatment 1 and for Bilateral treatment as combined sides.

The calculated scores, change from Baseline and percent change from Baseline will be presented.

- Treatment 2 – Bilateral (Combined)

% Change = 100*(Baseline combined extremities score – All Treatment 2 follow-up visits combined extremities score)/Baseline combined extremities score

- Treatment 1 – Unilateral

% Change = 100*(Baseline score treated extremities – All Treatment 1 treated extremities follow-up visits score)/Baseline treated extremities score

Additionally, a *post-hoc* analysis for treatment 2 is performed, based on change from Baseline 2 (B2, defined as score at 6-months post-treatment-1 follow-up visit) and percent change from B2.

2) MDS-UPDRS Part IV – Motor Complication

An individual's score is the sum of the items in the MDS-UPDRS Part IV ON medication (items 4.1 to 4.6).

The motor complication secondary endpoint will be calculated for each individual as percent change from Baseline as follows:

% Change = 100*(Baseline score – All follow-up visits)/Baseline

The calculated scores, change from Baseline and percent change from Baseline will be presented.

3) MDS-UPDRS Part III OFF Meds – Total Score Motor Examination

MDS UPDRS Part III total score is defined as the sum of all MDS-UPDRS part III items (items 3.1 to 3.18) taken in the OFF medication state.

The endpoint will be calculated for each individual as percent change from Baseline:

% Change = 100*(Baseline score – All follow-up visits)/Baseline

The calculated scores, change from Baseline and percent change from Baseline will be presented.

10.1.3.5 Additional Endpoints

The following additional efficacy endpoints will also be evaluated:

1) Clinician Global Impression of Change (CGIC)

The Clinician Global Impression of Change (CGIC) is a 7-point scale requiring the clinician to rate the severity of the patient's condition at the time of assessment, relative to before the Exablate treatment.

2) Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (PGIC) is a 7-point scale requiring the patient to rate the severity of their condition at the time of assessment, relative to before the Exablate treatment.

3) Patient Satisfaction Questionnaire

The Patient Satisfaction Questionnaire comprises of 5 questions assessing patient treatment satisfaction.

10.1.4 Study Statistical Analysis Plan and Analysis Populations

10.1.4.1 Hypothesis Test

Primary Efficacy Endpoint

The primary efficacy analysis was conducted on the Bilateral mITT analysis set and compared the upper and lower extremity motor endpoint from the MDS-UPDRS Part III OFF Meds at Month 3 to Baseline, and tested the following hypothesis:

$$H0: \mu_{\%MDS-UPDRS\ Part\ III\ OFF\ Meds\ at\ 3-mo} \leq 0.056$$

$$H1: \mu_{\%MDS-UPDRS\ Part\ III\ OFF\ Meds\ \ at\ 3-mo} > 0.056$$

10.1.4.2 Study Sample Size

The study was approved for a minimum of 50 and a maximum of 60 treated subjects treated unilaterally from which up to 40 subjects were expected to proceed to bilateral treatment at up to 10 sites. The rationale was that this sample size will allow bilateral ablation to be performed to provide good evidence of the performance/usability across multiple centers.

10.1.4.3 Study Analysis Population

The statistical analysis plan (SAP) identified four analysis populations.

Safety Analysis Populations

- Bilateral Safety Analysis Set
  - The Bilateral Safety analysis set includes all subjects who received at least one sonication at Treatment 2 (T2). This analysis set will be used for the primary safety analysis (N=40)
- Unilateral Safety Analysis Set
  - The Unilateral Safety analysis set includes all subjects who received at least one sonication at Treatment 1 (T1). This analysis set will be used for secondary safety analysis (N=54).

Efficacy Analysis Populations

- Bilateral Efficacy Analysis Set
  - Bilateral Modified Intent to Treat (mITT) Analysis Set: The Bilateral mITT analysis set includes all Bilateral ITT subjects for whom there exists valid baseline MDS-UPDRS Part III OFF meds assessment and at least one post-bilateral treatment MDS-UPDRS Part III OFF meds assessment. This analysis set will be used for the primary analysis and confirmatory secondary analysis.
  - Bilateral Intent to Treat (ITT) Analysis Set: The Bilateral ITT analysis set includes all subjects who received at least one sonication at treatment 2 and who signed informed consent.

  Note: Bilateral ITT (N=40). There were 2 subjects who did not have at least one post-bilateral treatment MDS-UPDRS Off Meds and were excluded from the mITT population (N=38).
- Unilateral Efficacy Analysis Set
  - Unilateral Modified Intent to Treat (mITT) Analysis Set: The Unilateral mITT analysis set includes all Unilateral ITT subjects for whom there exists valid baseline MDS-UPDRS Part III OFF meds assessment and at least one post-unilateral treatment MDS-UPDRS Part III OFF meds assessment. This analysis set will be used for the unilateral outcomes.

- Unilateral Intent to Treat (ITT) Analysis Set: The Unilateral ITT analysis set includes all subjects who received at least one sonication at treatment 1 and who signed informed consent.

Note: Unilateral mITT and ITT population is the same (N=54)

10.1.4.4 Handling of Missing Data

Missing primary and confirmatory secondary data was imputed using multiple imputation.

For MDS-UPDRS Part III Upper / Lower Extremities, if two items or fewer were missing for each one of the extremities (treated and untreated), the missing items were imputed by the observed average and the sum was calculated as usual. If more than 2 items were missing for at least one extremity, then the entire score was considered missing.

For MDS-UPDRS Part III total, if seven items or fewer were missing, the missing item(s) were imputed by the observed average and the sum was calculated as usual. If more than 7 items were missing, then the entire score was considered missing.

For MDS-UPDRS Part IV, if 1 item was missing, the score was calculated as the sum of the available scores multiplied by the number of total items that should have been scored in part IV (6) and this result was divided by the number of items with actual scores (5). If more than 1 item was missing, multiple imputations were used.

10.2 Results

10.2.1 Study Subject Accountability

A total of 84 subjects were consented for the Study as presented in the subject disposition flow chart below (**Figure 1**). Of these potential study candidates, 30 subjects were considered screen fails and 54 subjects were treated Unilaterally (received at least 1 sonication for the index procedure). Of the 54 subjects that were treated Unilaterally, 40 subjects proceeded to Bilateral Treatment (received at least 1 sonication on the contralateral side).

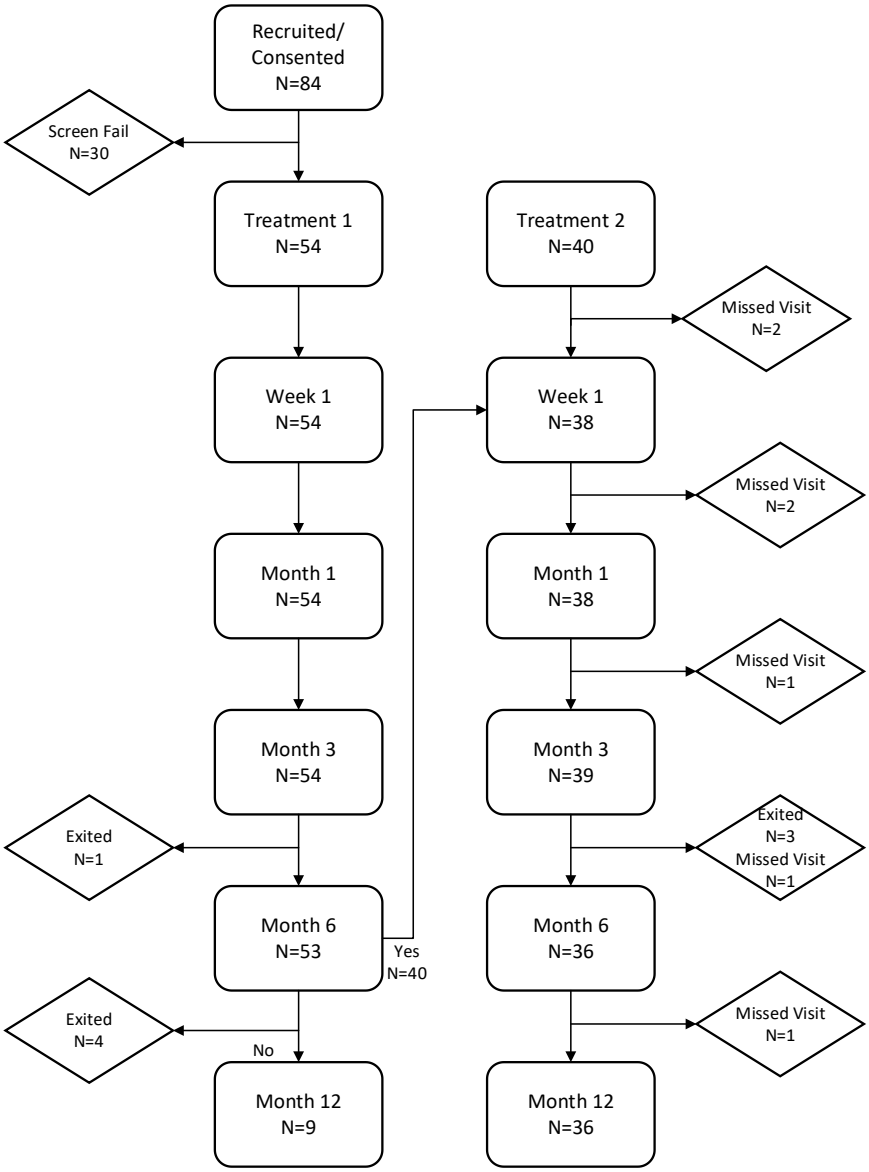

Figure 1 Subject Disposition Flow Chart

Subject accountability for this study is presented in **Table 2** (Unilateral) and in **Table 3** (Bilateral).

Table 2. Subject Disposition – Unilateral

Category	Screening	Treatment 1	Week 1	Month 1	Month 3	Month 6	Month 12
Recruited [1]	84						
Screen Fail/Dropout [2]	30						
Treated [3]		54					
Eligible [4]			54	54	54	54	53
Exited: Death [5]			0	0	0	0	0
Exited: Failure [5]			0	0	0	1	0
Exited: Other Reasons [5]			0	0	0	0	4
Exited: Proceeding to Bilateral Treatment [5]							40
Not Yet Due			0	0	0	0	0
Expected [6]			54	54	54	53	9
Missed Visit			0	0	0	0	0
Actual [7]			54	54	54	53	9
Actual % [8]			100.0	100.0	100.0	100.0	100.0

1 Subject who have signed consent form to enroll in this study.
2 Subjects who have been recruited but did not proceed to treatment.
3 Subjects who have received at least one sonication on the first side.
4 Eligible is equal to total number of subjects expected at each visit (Carry Expected from prior visit).
5 Exited is equal to the number of subjects who have exited the study at specific visit and reason for exit.
6 Expected equals Eligible minus Exited minus Not Due Yet.
7 Actual is the number of subjects who have completed the follow-up visit.
8 Actual % is the number of Actual subjects divided by Expected.

Table 3. Subject Disposition – Bilateral						
Category	**Treatment 2**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	**Month 12**
Treated [1]	40					
Eligible [2]		40	40	40	40	37
Exited: Death [3]		0	0	0	1	0
Exited: Failure [3]		0	0	0	0	0
Exited: Other Reasons [3]		0	0	0	2	0
Not Yet Due		0	0	0	0	0
Expected [4]		40	40	40	37	37
Missed Visit		2	2	1	1	1
Actual [5]		38	38	39	36	36
Actual % [6]		95.0	95.0	97.5	97.3	97.3

1 Subjects who have received at least one sonication on the second side.
2 Eligible is equal to total number of subjects expected at each visit (Carry Expected from prior visit).
3 Exited is equal to the number of subjects who have exited the study at specific visit and reason for exit.
4 Expected equals Eligible minus Exited minus Not Due Yet.
5 Actual is the number of subjects who have completed the follow-up visit.
6 Actual % is the number of Actual subjects divided by Expected.

The reasons for screen failure or drop out prior to unilateral treatment are listed in **Table 4**. The most common reasons were skull density ratio or not being suitable for PTT (PD diagnosis, motor complications, target access), which accounted for nearly two thirds of the screen failures.

Table 4 Screen Fails / Dropouts Prior to Unilateral Treatment	
Number of Subjects	**Coded Reason for Screen Fail**
9	Skull Density Ratio
9	Not suitable for PTT (*PD diagnosis, motor complications, target access*)
4	Levodopa Responsiveness
3	Not suitable for procedure (pre-morbid risk, bleeding risk, claustrophobia)

Table 4 Screen Fails / Dropouts Prior to Unilateral Treatment	
Number of Subjects	**Coded Reason for Screen Fail**
3	Investigator's Decision
1	No interest in bilateral treatment
1	Consent withdrawal
Total: 30	

The majority of unilaterally treated subjects, 40/54 (74%), received a bilateral treatment at least six months after the initial treatment. The reasons for the 14 subjects that did not proceed to bilateral treatment are presented in **Table 5**. The most common reason was that sufficient relief was already obtained with the first treatment.

Table 5. Primary Reasons for not Proceeding to Bilateral Treatment	
Number of Subjects	**Coded Reason for Not Proceeding to Bilateral**
5	Sufficient Relief / Bilateral Effect
2	Lack of Levodopa-induced complications
3	Patient Decision, Unsatisfied
1	*Screen Fail:* Tactile hallucinations
1	*Screen Fail:* Altered mental status
2	Patient Decision, Other
Total: 14	

10.2.2 Study Demographics and Baseline Characteristics

10.2.2.1 Demographics

Baseline and demographic characteristics of the unilateral and bilateral safety populations are presented in **Table 6**. This populations had a mean age of 63, was predominantly male, and was predominantly Caucasian and Asian (primarily due to the participation of one Asian center).

Table 6. Demographics

Demographic Characteristics		Unilateral Safety	Bilateral Safety
Age [Years]	Mean	63.8	63.0
	N	54	40
BMI [kg/m^2]	Mean	25.8	26.0
	N	54	40
Height [cm]	Mean	170.5	170.0
	N	54	40
Weight [kg]	Mean	75.7	75.8
	N	54	40
Gender	Female	17 (31.5%)	14 (35%)
	Male	37 (68.5%)	26 (65%)
	N	54 (100%)	40 (100%)
Race	White	40 (74.1%)	30 (75%)
	Black or African American	1 (1.9%)	1 (2.5%)
	Asian	12 (22.2%)	8 (20%)
	Other	1 (1.9%)	1 (2.5%)
	N	54 (100%)	40 (100%)
Ethnicity	Hispanic	7 (13%)	6 (15%)
	Non-Hispanic	47 (87%)	34 (85%)
	N	54 (100%)	40 (100%)

10.2.2.2 Baseline Characteristics

The baseline characteristics are shown in **Table 7**. On average, subjects had the onset of PD 10 years ago, and were diagnosed and treated for PD around 8 years ago. The Levodopa Equivalent Dosage averaged 1037 mg.

Table 7. Baseline Characteristics		
Time from Initial PD Symptoms [Years]	Mean	10.1
	N	54
Time from Initial PD Diagnosis [Years]	Mean	7.7
	N	54
Time from Initial PD Medical Therapy [Years]	Mean	7.3
	N	54
Levodopa Equivalent Dosage (mg)	Mean	1037.0
	N	54

10.2.3 Safety Outcome

The primary analysis of safety was based upon the collection of all adverse events during the study as collected by the investigators at each site from the time of the Bilateral treatment through all study visits.

10.2.3.1 Adverse Events

The primary analysis of safety population (N=40) was based upon the collection of adverse events during the study as collected by the investigators at each site from the time of the Bilateral treatment through all study visits. Overall, a total of 129 events were recorded in 33 of the 40 bilateral subjects, corresponding to around 3.2 AEs per subject presented in **Table 8**.

Table 8. AE Frequency/Subject (Bilateral Safety)

Experience of at Least One Treatment Emergent AE	N	%
Yes	33	82.5
No	7	17.5
Total	40	100.0

A summary of the safety profile by severity is presented in **Table 9**. Overall, the safety profile was acceptable with about 94% of the 129 AEs being either Mild (63.6% =82/129) or Moderate (30.2% = 39/129) in nature. Five (5) events (5/129, 3.9%) were severe in nature and three (3/129, 2.3%) were life-threatening. None of the severe or life-threatening events were device related.

Table 9. Adverse Events by Severity		
Severity	**Frequency N= 129**	**Incidence N=40**
Mild	82 (63.6%)	28 (70.0%)
Moderate	39 (30.2%)	19 (47.5%)
Severe	5 (3.9%)	4 (10.0%)
Life-Threatening	3 (2.3%)	3 (7.5%)
Total	**129 (100%)**	**33 (82.5%)**
Related SAE	1 (0.8%)	1 (2.5%)
Unrelated SAE	6 (4.7%)	5 (12.5%)

All adverse events were coded by Grouping Term, Body System and Coded Term for analysis. The Grouping terms are: Unrelated, Parkinson's Disease Related, Transient, Pallidothalamic Tract Related, Procedure Related, and Device Related. **Table 10** presents the adverse event safety profile for the study by Grouping Term. Sixty seven percent (67%) of the events were either Unrelated (30%), Parkinson's Disease related (22%), or Transient (15%), which resolved within 72 hours. The Grouping term definitions are defined below and summarized as follows:

- The **Unrelated events** are events that are captured and determined by Investigator(s) to be unrelated to the treatment device (Exablate) or procedure. Included in this category are the i.v., catheter, and frame-related events that occur and are directly attributable to them, as well as any miscellaneous events that occur such as colds, ear infections, miscellaneous musculoskeletal events and positional events.
    - 39 (30%) events in 21 (53%) subjects were Unrelated
- The **PD Disease Related events** are events that are commonly associated with worsening Parkinson's and their PD medications.
    - 28 (22%) events in 12 (30%) subjects were PD disease related
- **Transient events** are those events that last seconds to less than 72 hours and resolve completely.
    - 19 (15%) events in 11 (28%) subjects were Transient (resolved <72 hours)
- The **Pallidothalamic Tract (PTT) related events** are events commonly reported in the literature for this target that may be attributed to the local anatomy effects, such as local edema in adjacent tissue.
    - 33 (26%) events in 17 (43%) subjects were Pallidotomy-related
        - Of the 33 events, 9 (27%) events have resolved.
- The **Procedure related events** are generally those events that are non-transient and related to undergoing the procedure, such as fatigue, a lingering headache, etc.

- 10 (8%) events in 8 (20%) subjects were Procedure-related
  - Of the 10 events, 8 (80%) events have resolved.

- The **Device related events** are events that are caused specifically by device malfunction, or incorrect or inaccurate energy delivery by the Exablate device that causes harm to a subject. In this study there were no persistent or harmful device-related side effects, i.e., non-transient effects related to FUS energy delivery.
  - There were no device related events.

Table 10. Adverse Events by Grouping Term		
Grouping Term	**Frequency (N= 129)**	**Incidence (N=40)**
Unrelated	39 (30.2%)	21 (52.5%)
Parkinson's Disease Related	28 (21.7%)	12 (30.0%)
Subtotal	**67 (51.9%)**	**25* (62.5%)**
Pallidothalamic Tract Related	33 (25.6%)	17 (42.5%)
Procedure Related	10 (7.8%)	8 (20.0%)
Transient Events – (Procedure related - Resolved within 72 hours)	19 (14.7%)	11 (27.5%)
Device Related	0	0
Subtotal	**62 (48.1%)**	**27* (67.5%)**
Grand Total	**129 (100%)**	**33* (82.5%)**
*** Subjects may experience more than one event**		

Table 11 below presents all the adverse events reported by grouping term, body system and coded term. The most common adverse events were hypertension (4.0%), imbalance (3.1%), and fall (3.1%).

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	Body System	Preferred Term	Severity									
			Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40
Pallidothalamic Tractotomy Related	General	Drowsiness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Leg Weakness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Lethargy	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Weight Gain	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
	Nervous	Anarthria	0	0	0	0	1 (0.8)	1 (2.5)	0	0	1 (0.8)	1 (2.5)
		Dysarthria	2 (1.6)	2 (5.0)	1 (0.8)	1 (2.5)	0	0	0	0	3 (2.3)	3 (7.5)
		Dysphagia	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)	0	0	0	0	2 (1.6)	2 (5.0)
		Facial Weakness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Gait Disturbance	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Gait Freezing	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)	0	0	0	0	2 (1.6)	2 (5.0)
		Gait Unsteadiness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Hypophonia	2 (1.6)	2 (5.0)	1 (0.8)	1 (2.5)	0	0	0	0	3 (2.3)	3 (7.5)
		Imbalance	2 (1.6)	2 (5.0)	2 (1.6)	2 (5.0)	0	0	0	0	4 (3.1)	4 (10.0)
		Increased Salivation / Drooling	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E (%$_E$) N=129	**N_S (%$_S$) N=40**	**N_E (%$_E$) N=129**	**N_S (%$_S$) N=40**	**N_E (%$_E$) N=129**	**N_S (%$_S$) N=40**	**N_E (%$_E$) N=129**	**N_S (%$_S$) N=40**	**N_E (%$_E$) N=129**	**N_S (%$_S$) N=40**
		Slurred Speech	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
		Somnolence	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Stutter	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Task Specific Apraxia	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Uncontrolled Laughter	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		VHI Score Elevated	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
	Psychological	Altered Mental Status: Confusion	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
Total Pallidothalamic Tractotomy Related			22 (17.1)	13 (32.5)	10 (7.8)	7 (17.5)	1 (0.8)	1 (2.5)	0	0	33 (25.6)	17 (42.5)
Parkinson's Disease Related	Gastrointestinal	Nausea / Vomiting	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	General	Apathy	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Fall	2 (1.6)	2 (5.0)	2 (1.6)	2 (5.0)	0	0	0	0	4 (3.1)	3 (7.5)
		Fatigue	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Night Sweats	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	Body System	Preferred Term	Severity									
			Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40
	Musculoskeletal	Muscular Weakness	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Musculoskeletal Weakness	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
	Nervous	Apraxia Of Eyelid	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Dizziness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Dysphagia	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Finger Tremor	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Freezing	0	0	2 (1.6)	2 (5.0)	0	0	0	0	2 (1.6)	2 (5.0)
		Gait Freezing	0	0	0	0	1 (0.8)	1 (2.5)	0	0	1 (0.8)	1 (2.5)
		Gait Imbalance	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Hypophonia	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Imbalance	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Increased Salivation / Drooling	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Motor Fluctuations	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Myoclonus	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Paraphonia	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=129	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**
	Psychological	Depression	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)	0	0	0	0	2 (1.6)	2 (5.0)
		Hallucination	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
Total Parkinson's Disease Related			17 (13.2)	9 (22.5)	10 (7.8)	6 (15.0)	1 (0.8)	1 (2.5)	0	0	28 (21.7)	12 (30.0)
Procedure Related	General	Drowsiness	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
		Fatigue	3 (2.3)	3 (7.5)	0	0	0	0	0	0	3 (2.3)	3 (7.5)
		Weakness	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
	Nervous	Decreased Short Term Memory	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Dysarthria	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
		Imbalance	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
Total Procedure Related			8 (6.2)	8 (20.0)	2 (1.6)	2 (5.0)	0	0	0	0	10 (7.8)	8 (20.0)
Transient	Cardiovascular	Fainting	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Hypertension	3 (2.3)	3 (7.5)	2 (1.6)	2 (5.0)	0	0	0	0	5 (3.9)	5 (12.5)
	Gastrointestinal	Nausea/Vomiting	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	General	Fall	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	Nervous	Agitation	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Dizziness	3 (2.3)	2 (5.0)	0	0	0	0	0	0	3 (2.3)	2 (5.0)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=129	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**
		Dyskinesia	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Gait Disturbance	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Hypophonia	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	Pain/Discomfort	Headache	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)	0	0	0	0	2 (1.6)	2 (5.0)
		Positional Pain	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
	Psychological	Anxiety	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
Total Transient			13 (10.1)	8 (20.0)	6 (4.7)	4 (10.0)	0	0	0	0	19 (14.7)	11 (27.5)
Unrelated	Cardiovascular	Pulmonary Embolism	0	0	0	0	0	0	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)
	Dermatologic	Scalp Redness	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	EENT	Double Vision	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Dry Eyes	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Eye Swelling	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Post-Nasal Drip	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Squinting	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	Gastrointestinal	Gastrointestinal Symptoms	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Incontinence	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	Body System	Preferred Term	Severity									
			Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40	N_E ($\%_E$) N=129	N_S ($\%_S$) N=40
		Intestinal Obstruction	0	0	0	0	0	0	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)
	General	Anemia	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Dehydration	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Fall	0	0	0	0	1 (0.8)	1 (2.5)	0	0	1 (0.8)	1 (2.5)
		Fatigue	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Leg Swelling	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	Genitourinary	Urinary Tract Infection	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
	Infection	Covid-19	4 (3.1)	3 (7.5)	0	0	0	0	0	0	4 (3.1)	3 (7.5)
		Flu	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Sepsis	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Viral Infection	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
	Musculoskeletal	Arthritis	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
		Back Sprain	0	0	0	0	1 (0.8)	1 (2.5)	0	0	1 (0.8)	1 (2.5)
		Piriformis	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)
	Nervous	Insomnia	2 (1.6)	2 (5.0)	0	0	0	0	0	0	2 (1.6)	2 (5.0)
		Stroke	0	0	0	0	1 (0.8)	1 (2.5)	1 (0.8)	1 (2.5)	2 (1.6)	2 (5.0)
	Pain/Discomfort	Back Pain	0	0	1 (0.8)	1 (2.5)	0	0	0	0	1 (0.8)	1 (2.5)

Table 11. Adverse Event (Frequency/Incidence) – Bilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=129	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**	**N_E ($\%_E$) N=129**	**N_S ($\%_S$) N=40**
		Sciatica Pain	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
	Stereotactic Frame	Pin Site Bleeding	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Pin Site Edema	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
		Pin Site Pain	1 (0.8)	1 (2.5)	2 (1.6)	2 (5.0)	0	0	0	0	3 (2.3)	3 (7.5)
	Vision	Vision Problem	1 (0.8)	1 (2.5)	0	0	0	0	0	0	1 (0.8)	1 (2.5)
Total Unrelated			22 (17.1)	14 (35.0)	11 (8.5)	9 (22.5)	3 (2.3)	3 (7.5)	3 (2.3)	3 (7.5)	39 (30.2)	21 (52.5)
Grand Total			82 (63.6)	28 (70.0)	39 (30.2)	19 (47.5)	5 (3.9)	4 (10.0)	3 (2.3)	3 (7.5)	129 (100.0)	33 (82.5)

10.2.3.2 Overall Adverse Event Listing

Table 12 below presents a full listing of all adverse events from T1 through Month 12 post T2.

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
Pallidothalamic Tractotomy Related	EENT	Visual Field Deficit	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	General	Drowsiness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Leg Weakness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Lethargy	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Reduced Ld Effect	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Weight Gain	0	0	2 (0.7)	1 (1.9)	0	0	0	0	2 (0.7)	1 (1.9)
	Nervous	Anarthria	0	0	0	0	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)
		Dysarthria	2 (0.7)	2 (3.7)	1 (0.4)	1 (1.9)	0	0	0	0	3 (1.1)	3 (5.6)
		Dyskinesia	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dysphagia	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)	0	0	0	0	2 (0.7)	2 (3.7)
		Facial Weakness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Gait Disturbance	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Gait Freezing	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)	0	0	0	0	2 (0.7)	2 (3.7)
		Gait Unsteadiness	3 (1.1)	3 (5.6)	0	0	0	0	0	0	3 (1.1)	3 (5.6)
		Hypophonia	6 (2.1)	6 (11.1)	1 (0.4)	1 (1.9)	0	0	0	0	7 (2.5)	7 (13.0)
		Imbalance	2 (0.7)	2 (3.7)	2 (0.7)	2 (3.7)	0	0	0	0	4 (1.4)	4 (7.4)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
		Increased Salivation/Drooling	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Slurred Speech	3 (1.1)	3 (5.6)	0	0	0	0	0	0	3 (1.1)	3 (5.6)
		Somnolence	3 (1.1)	2 (3.7)	0	0	0	0	0	0	3 (1.1)	2 (3.7)
		Stutter	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Task Specific Apraxia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Uncontrolled Laughter	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Vhi Score Elevated	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Voice Hoarseness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Word-Finding Difficulty	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Psychological	Altered Mental Status: Confusion	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Cognitive Impairment	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
Total Pallidothalamic Tractotomy Related			**36 (12.9)**	**21 (38.9)**	**13 (4.6)**	**7 (13.0)**	**1 (0.4)**	**1 (1.9)**	**0**	**0**	**50 (17.9)**	**24 (44.4)**
Parkinson's Disease Related	Gastrointestinal	Nausea/Vomiting	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	General	Apathy	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Fall	3 (1.1)	3 (5.6)	3 (1.1)	3 (5.6)	0	0	0	0	6 (2.1)	5 (9.3)
		Fatigue	2 (0.7)	1 (1.9)	0	0	0	0	0	0	2 (0.7)	1 (1.9)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
		Night Sweats	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Musculoskeletal	Arthralgias	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Muscle Cramps	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Muscular Weakness	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Musculoskeletal Weakness	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Restless Abdomen	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Restless Legs	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Slouched Posture	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Nervous	Apraxia Of Eyelid	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Concentration Issues	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Decreased Short Term Recall	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dizziness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Dysphagia	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dystonia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Finger Tremor	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Freezing	2 (0.7)	2 (3.7)	3 (1.1)	2 (3.7)	0	0	0	0	5 (1.8)	4 (7.4)
		Freezing Gait	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
		Gait Disturbance	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Gait Freezing	0	0	0	0	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)
		Gait Imbalance	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Hypophonia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Imbalance	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Increased Salivation/Drooling	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Motor Fluctuations	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Myoclonus	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Paraphonia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Slowness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Visual Hallucinations	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Psychological	Depression	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)	0	0	0	0	2 (0.7)	2 (3.7)
		Hallucination	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)	0	0	2 (0.7)	2 (3.7)
Total Parkinson's Disease Related			**32 (11.4)**	**17 (31.5)**	**15 (5.4)**	**10 (18.5)**	**2 (0.7)**	**2 (3.7)**	**0**	**0**	**49 (17.5)**	**22 (40.7)**
Procedure Related	EENT	Disconjugate Gaze	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Gastrointestinal	Nausea/Vomiting	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
	General	Drowsiness	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Fatigue	7 (2.5)	7 (13.0)	0	0	0	0	0	0	7 (2.5)	7 (13.0)
		Weakness	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
	Nervous	Cerebellar Ataxia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Decreased Short Term Memory	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dysarthria	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Gait Unsteadiness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hiccups	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Imbalance	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Leg Weakness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Numbness/Tingling	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Pain/Discomfort	Head Pain	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Psychological	Confusion	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
Total Procedure Related			**20 (7.1)**	**15 (27.8)**	**3 (1.1)**	**3 (5.6)**	**0**	**0**	**0**	**0**	**23 (8.2)**	**16 (29.6)**
Transient	Cardiovascular	Fainting	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hypertension	7 (2.5)	6 (11.1)	12 (4.3)	10 (18.5)	0	0	0	0	19 (6.8)	16 (29.6)
		Hypotension	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
	Gastrointestinal	Constipation	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Nausea/Vomiting	4 (1.4)	3 (5.6)	1 (0.4)	1 (1.9)	0	0	0	0	5 (1.8)	4 (7.4)
	General	Fall	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Musculoskeletal	Positional Pain	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Nervous	Agitation	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dizziness	8 (2.9)	6 (11.1)	0	0	0	0	0	0	8 (2.9)	6 (11.1)
		Dyskinesia	2 (0.7)	1 (1.9)	0	0	0	0	0	0	2 (0.7)	1 (1.9)
		Gait Disturbance	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hiccups	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hypersalivation	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hypophonia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Pain/Discomfort	Head Pain	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Headache	4 (1.4)	3 (5.6)	2 (0.7)	2 (3.7)	0	0	0	0	6 (2.1)	5 (9.3)
		Positional Pain	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Sonication Head Pain	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Psychological	Anxiety	1 (0.4)	1 (1.9)	4 (1.4)	3 (5.6)	0	0	0	0	5 (1.8)	4 (7.4)
Total Transient			**35 (12.5)**	**14 (25.9)**	**23 (8.2)**	**14 (25.9)**	**0**	**0**	**0**	**0**	**58 (20.7)**	**25 (46.3)**

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
Unrelated	Cardiovascular	Edema - Le	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hypertension	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Pulmonary Embolism	0	0	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)	2 (0.7)	2 (3.7)
	Dermatologic	Livido Reticularis	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Scalp Redness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Skin Rash	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	EENT	Blepharospasm	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Blurry Vision	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Conjunctivitis	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Decreased Visual Acuity	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Double Vision	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Dry Eyes	3 (1.1)	3 (5.6)	1 (0.4)	1 (1.9)	0	0	0	0	4 (1.4)	4 (7.4)
		Eye Redness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Eye Swelling	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Post-Nasal Drip	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Squinting	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Visual Field Deficit	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
		Worsening Eyesight	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Gastrointestinal	Constipation	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Gastrointestinal Symptoms	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Incontinence	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Intestinal Obstruction	0	0	0	0	0	0	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)
	General	Anemia	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dehydration	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Dizziness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Edema - Le	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Fall	3 (1.1)	3 (5.6)	0	0	1 (0.4)	1 (1.9)	0	0	4 (1.4)	4 (7.4)
		Fatigue	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Leg Swelling	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Sleep Apnea	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Syncope	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
	Genitourinary	Kidney Stone	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Renal Insufficiency	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Urinary Tract Infection	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
	Infection	Cold Symptoms	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Covid-19	4 (1.4)	3 (5.6)	2 (0.7)	2 (3.7)	0	0	0	0	6 (2.1)	5 (9.3)
		Flu	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)	0	0	0	0	2 (0.7)	2 (3.7)
		Sepsis	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Viral Infection	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
	Musculoskeletal	Arthritis	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Back Sprain	0	0	0	0	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)
		Bunion Removal	0	0	0	0	1 (0.4)	1 (1.9)	0	0	1 (0.4)	1 (1.9)
		Decreased Mouth Movement	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Hip Injury	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Hypotonia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Muscle Pain	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Neck Pain	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Piriformis	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
	Nervous	Clumsiness	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Insomnia	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
		Paresthesia	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Stroke	0	0	0	0	1 (0.4)	1 (1.9)	1 (0.4)	1 (1.9)	2 (0.7)	2 (3.7)
	Pain/Discomfort	Back Pain	1 (0.4)	1 (1.9)	2 (0.7)	2 (3.7)	0	0	0	0	3 (1.1)	3 (5.6)
		Headache	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Sciatica Pain	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Visual Discomfort	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
	Psychological	Anxiety	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Delusion	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
	Respiratory	Decreased Lung Function	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
	Stereotactic Frame	Eye Swelling	2 (0.7)	2 (3.7)	0	0	0	0	0	0	2 (0.7)	2 (3.7)
		Facial Droop	2 (0.7)	1 (1.9)	0	0	0	0	0	0	2 (0.7)	1 (1.9)
		Head Discomfort	0	0	1 (0.4)	1 (1.9)	0	0	0	0	1 (0.4)	1 (1.9)
		Headache	5 (1.8)	5 (9.3)	0	0	0	0	0	0	5 (1.8)	5 (9.3)
		Numbness/Tingling	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Pin Site Bleeding	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Pin Site Edema	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
		Pin Site Pain	5 (1.8)	5 (9.3)	3 (1.1)	2 (3.7)	0	0	0	0	8 (2.9)	7 (13.0)

Table 12. Adverse Event (Frequency/Incidence) Post T1 and T2 – Full Listing												
			Severity									
Grouping Term	Body System	Preferred Term	Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)	N_E ($\%_E$)	N_S ($\%_S$)
	Vision	Vision Problem	1 (0.4)	1 (1.9)	0	0	0	0	0	0	1 (0.4)	1 (1.9)
Total Unrelated			**70 (25.0)**	**30 (55.6)**	**23 (8.2)**	**13 (24.1)**	**4 (1.4)**	**4 (7.4)**	**3 (1.1)**	**3 (5.6)**	**100 (35.7)**	**36 (66.7)**
Grand Total			**193 (68.9)**	**38 (70.4)**	**77 (27.5)**	**31 (57.4)**	**7 (2.5)**	**6 (11.1)**	**3 (1.1)**	**3 (5.6)**	**280 (100.0)**	**48 (88.9)**

10.2.3.3 Serious Adverse Events

Serious adverse events (SAEs) are summarized in **Table 13**. Out of 129 events, there were 7 SAEs reported. One (0.8% = 1/129) of the 7 SAEs (anarthria) was Pallidothalamic Tractotomy Related. The remaining six (4.7% = 6/129) SAEs were unrelated to device and procedure and consisted of pulmonary embolism, intestinal obstruction, fall, back sprain, and stroke. All these SAEs were reviewed and adjudicated by the Data Safety Monitoring Board.

Table 13. Serious Adverse Event – Bilateral Safety

Subject ID	Grouping Term	Body System	Preferred Term	Severity
Related to PTT Procedure				
134003*	Pallidothalamic Tractotomy Related	Nervous	Anarthria	Severe
Unrelated to Device and Procedure				
246006	Unrelated	Gastrointestinal	Intestinal Obstruction	Life-threatening
126001	Unrelated	Nervous	Stroke	Life-threatening
43004	Unrelated	Nervous	Stroke	Severe
126001	Unrelated	General	Fall	Severe
150002	Unrelated	Cardiovascular	Embolism	Life-threatening
150014	Unrelated	Infection	Sepsis	Moderate

* Anarthria was due to user error.

10.2.3.4 Speech Assessment

All patients were assessed for their overall status, including and not limited for potential Speech impairment. During the course of the study, three additional speech assessments by Speech Pathologists were introduced: Dysphagia Handicap Index (DHI), Voice Handicap Index (VHI-10), and Speech Function assessments. These 3 additional speech assessments were repeated at two separate time points, one prior to the bilateral treatment and one at the Month 3 post bilateral follow-up visit. Due to the timing of the additional Speech assessments introduction, ten (10) subjects had already completed their Month 3 post bilateral visit schedule. Hence, these 10 subjects did not have the additional speech assessments, however they were evaluated for speech and for other requirements per study protocol. Hence, the additional assessment is limited to 30 patients within the mITT Bilateral population.

Speech Function was assessed as Clinically Significant (CS) or Non-Clinically Significant (NCS) based on DHI, VHI, language assessment, and speech assessment. The overall results of each of these assessments are provided in **Table 14**.

Table 14. Speech Assessment Results						
Speech Function Category / Assessment / Result			**Pre Treatment 2**		**Post Treatment 2**	
			N	**%**	**N**	**%**
Swallowing Assessment	Dysphagia Handicap Index (DHI) Results	Normal	24	80.0	14	50.0
		Abnormal NCS	2	6.7	5	17.9
		Abnormal CS	4	13.3	9	32.1
		Total	30	100.0	28	100.0
Voice Assessment	Voice Handicap Index (VHI-10) Results	Normal	15	60.0	8	29.6
		Abnormal NCS	1	4.0	3	11.1
		Abnormal CS	9	36.0	16	59.3
		Total	25	100.0	27	100.0
Language Assessment	Patient exhibits the inability to express and comprehend language	No	29	96.7	26	92.9
		Yes NCS	1	3.3	2	7.1
		Yes CS	0	0.0	0	0.0
		Total	30	100.0	28	100.0
	Patient exhibits slurred or slow speech that is difficult to comprehend	No	23	76.7	12	42.9
		Yes NCS	1	3.3	2	7.1
		Yes CS	6	20.0	14	50.0
		Total	30	100.0	28	100.0
Product of Speech Assessment	Articulation	Normal	23	76.7	9	32.1
		Abnormal NCS	2	6.9	5	17.9
		Abnormal CS	5	16.7	14	50.0
		Total	30	100.0	28	100.0
	Phonation	Normal	16	55.3	6	21.4
		Abnormal NCS	6	20.0	5	17.9
		Abnormal CS	8	26.7	17	60.7
		Total	30	100.0	28	100.0

Table 14. Speech Assessment Results						
Speech Function Category / Assessment / Result			Pre Treatment 2		Post Treatment 2	
			N	%	N	%
	Respiration	Normal	27	90.0	24	85.7
		Abnormal NCS	0	0.0	1	3.6
		Abnormal CS	3	10.0	3	10.7
		Total	30	100.0	28	100.0
	Resonance	Normal	29	96.7	23	82.1
		Abnormal NCS	0	0.0	1	3.6
		Abnormal CS	1	3.3	4	14.3
		Total	30	100.0	28	100.0
	Prosody	Normal	17	56.7	15	53.6
		Abnormal NCS	5	16.7	3	10.7
		Abnormal CS	8	26.7	10	35.7
		Total	30	100.0	28	100.0
*NCS = Not clinically significant; CS = Clinically Significant Note: subjects may experience more than one event						

All "additional" Clinically Significant findings that are presented in **Table 14** from the Speech Pathologist in each of the evaluated areas were added to the review within the context of each subject's overall safety based on applicable medical records and study assessments (e.g. Neurologist assessments, PD disease progression, etc.) to compile the complete list of all adverse events presented in **Table 11** above.

Overall, a total of 19 speech events in 15 of the 40 subjects were reported in this study (see **Table 11** above). Out of the 19, 14 speech events in 11 (11/40, 28%) were related to bilateral PTT lesioning. In this study, only 5 events in 4 of the 40 (4/40, 10%) subjects were reported with clinically significant (moderate to severe) speech worsening:

- Four moderate events in four subjects (1 Dysphagia, 1 Dysarthria, 1 Hypophonia, 1 Stutter), and
- One severe event (Anarthria) in one subject

The Severe event was the result of operator error. It should be noted that the Exablate system offers several safety mitigating tools and features to mitigate these types of events.

10.2.4 Effectiveness Outcomes

10.2.4.1 Primary Effectiveness Outcome

The primary efficacy analysis was performed on the bilateral mITT and ITT population to compare the percent change from Baseline to the Month 3 visit. The primary endpoint (PE) reflects the average percent change in MDS-UPDRS part III motor (lower/upper extremities) scores of PD subjects. As shown in **Table 15** and **Figure 2**, the data demonstrate a median 32.7% improvement in the MDS-UPDRS part-III score compared to Baseline, with the calculated median score dropping from 32.5 at baseline to 21.0 at Month 3, which corresponds to a 10.2-point median score from Baseline. This percent change statistically and clinically significantly exceeded the performance goal of 5.6% ($p < 0.0001$), demonstrating that the Primary Efficacy Endpoint was successfully met. For the 14/54 enrolled subjects that did not proceed to bilateral treatment, effectiveness endpoints reflecting post-unilateral-treatment outcomes are reported in Table 29 of Section 10.2.5.4.

Table 15. Primary Efficacy Endpoint: MDS-UPDRS Part III OFF Medication Upper / Lower Extremity Motor Score

Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	34.7	N/A	N/A
	SD	9.7	N/A	N/A
	Min	19.0	N/A	N/A
	Median	32.5	N/A	N/A
	Max	57.0	N/A	N/A
	Mean Lower 95%I CL	31.5	N/A	N/A
	Mean Upper 95% CL	37.9	N/A	N/A
Month 3	Mean	21.5	13.2	34.0
	SD	7.9	12.4	27.0
	Mean Lower 95% CL	18.9	9.2	25.0
	Mean Upper 95% CL	24.1	17.2	42.9
	Median	21.0	10.2	32.7
	Median Lower 95% CL			21.8
	Median Upper 95% CL			43.6
	P-Value			<.0001

Table 15. Primary Efficacy Endpoint: MDS-UPDRS Part III OFF Medication Upper / Lower Extremity Motor Score				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	34.8	N/A	N/A
	Median	33.0	N/A	N/A
	SD	9.5	N/A	N/A
Month 3	Mean	21.6	13.1	33.9
	Median	21.0	10.4	32.6
	SD	8.1	12.3	26.9
	P-Value			<.0001
Lower scores are better. Higher percent change demonstrates improvement. NOTE: For all endpoints, the hypothesis test was done on the median rather than the mean.				

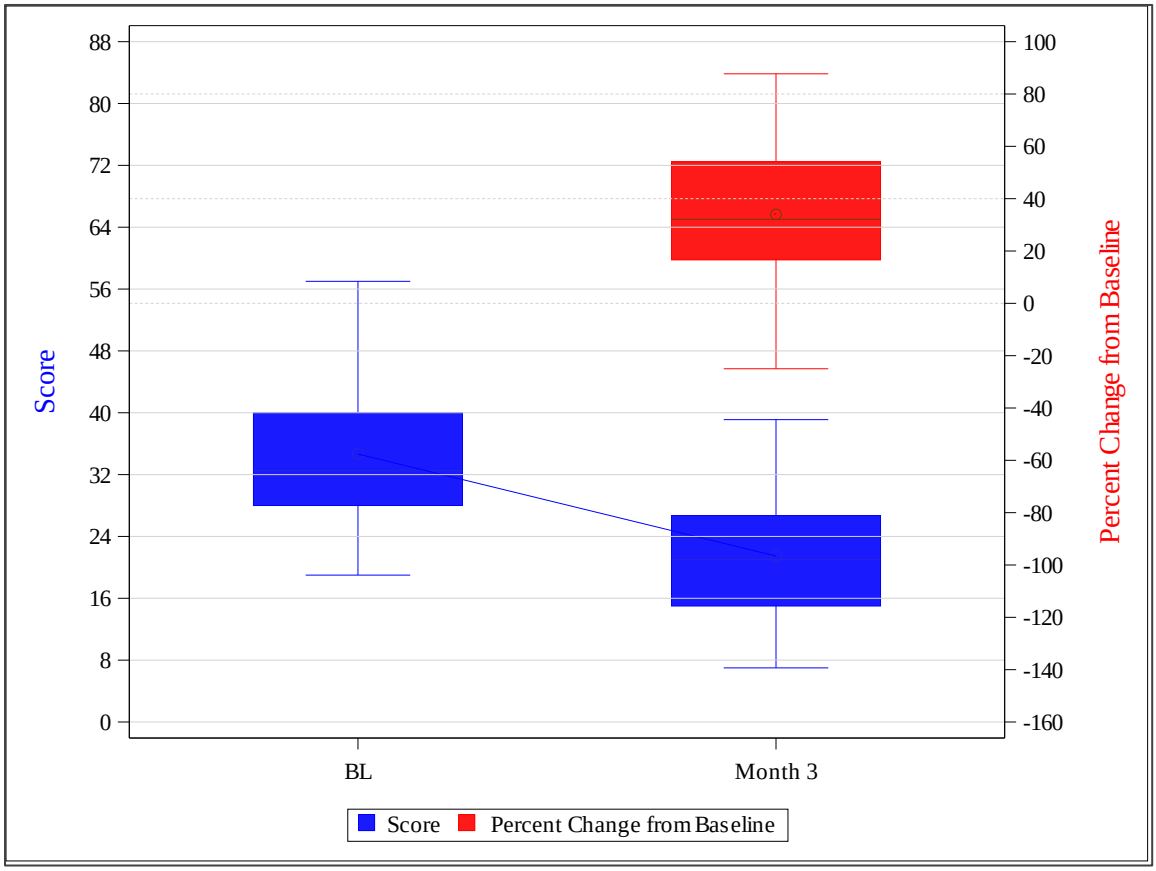

Figure 2. Primary Endpoint – MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score for Both Treated Side – Score and Percent Change from Baseline (Bilateral mITT).

10.2.4.2 Confirmatory Endpoints

There are two confirmatory analyses performed using the Bilateral mITT population comparing change from Baseline to Month 3 post Bilateral Treatment.

Confirmatory Endpoint 1:

One analysis assessed motor complications by comparing the MDS-UPDRS Part IV between baseline and Month 3, see **Table 16** and **Figure 3.** This analysis also showed a clinically meaningful median percent reduction in median score of 66.1% . The calculated median score dropped from 11.5 at baseline to 4.0 at Month 3.

Table 16. Confirmatory Endpoint 1: MDS-UPDRS Part IV

Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	10.6	N/A	N/A
	SD	3.2	N/A	N/A
	Min	5.0	N/A	N/A
	Median	11.5	N/A	N/A
	Max	17.0	N/A	N/A
Month 3	Mean	3.6	7.0	67.9
	Median	4.0	7.0	66.1
	SD	3.0	3.0	25.3
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	10.7	N/A	N/A
	Median	12.0	N/A	N/A
	SD	3.2	N/A	N/A
Month 3	Mean	3.6	7.1	68.1
	Median	3.9	7.0	66.8
	SD	2.9	3.0	24.9

Table 16. Confirmatory Endpoint 1: MDS-UPDRS Part IV				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Lower scores are better. Higher percent change demonstrates improvement.				

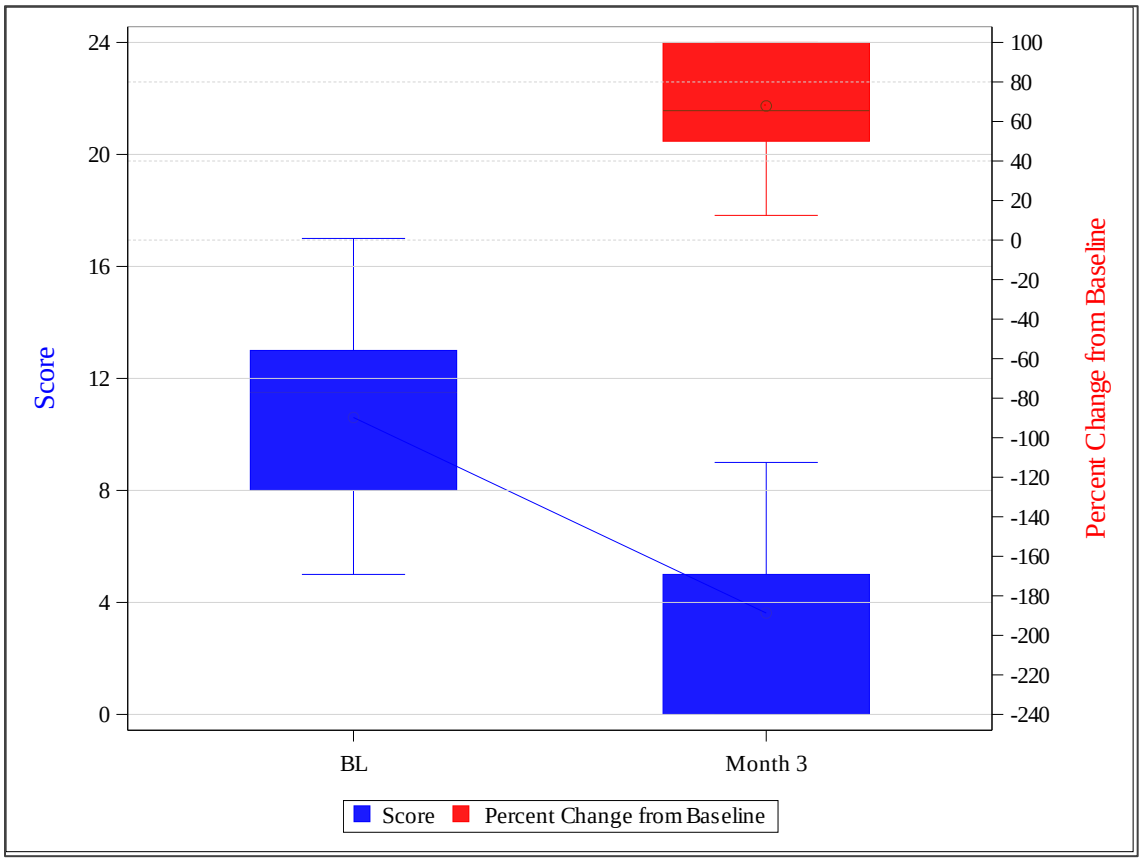

Figure 3. Confirmatory Endpoint 1:MDS-UPDRS Part IV Score and Percent Change from Baseline (Bilateral mITT)

Confirmatory Endpoint 2:

A second confirmatory endpoint was also performed that assessed the MDS-UPDRS Part III Total Score OFF medication, see **Table 17** and **Figure 4**. Here too a clinically significant median percent reduction in score of 33.0% was observed. The calculated median score dropped from49.5 at Baseline to 32.5 at Month 3.

Table 17. Confirmatory Endpoint 2: MDS-UPDRS Part III Total Score				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	51.0	N/A	N/A
	SD	12.6	N/A	N/A
	Median	49.5	N/A	N/A
Month 3	Mean	33.3	17.7	31.8
	Median	32.5	16.0	33.0
	SD	11.3	15.8	24.7
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	51.3	N/A	N/A
	Median	49.5	N/A	N/A
	SD	12.4	N/A	N/A
Month 3	Mean	33.4	17.8	32.0
	Median	32.7	16.0	33.0
	SD	11.4	15.7	24.7
Lower scores are better. Higher percent change demonstrates improvement.				

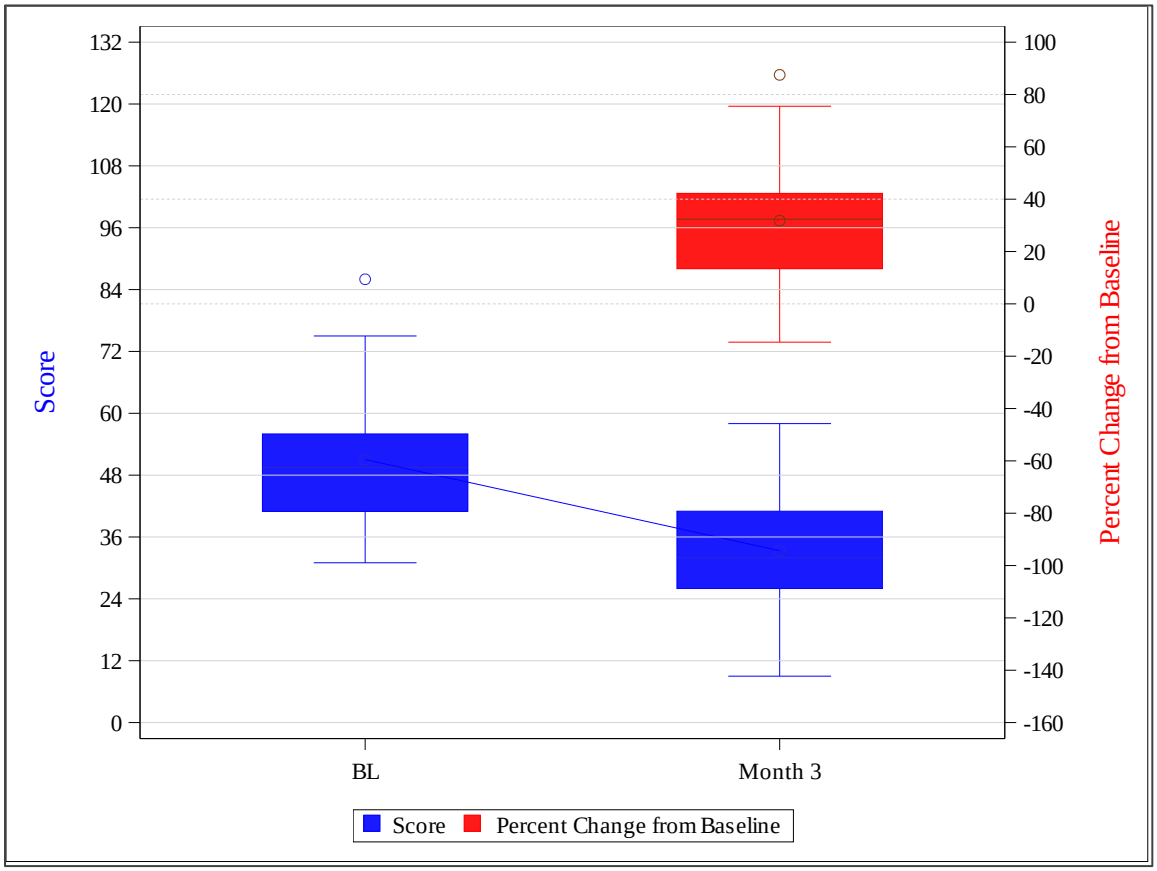

Figure 4. Confirmatory Endpoint 2: MDS-UPDRS Part III Total Score – Score and Percent Change from Baseline (Bilateral mITT)

10.2.4.3 Secondary Endpoints

There are three secondary efficacy analyses performed on the Bilateral mITT population out to Month 12. These are the same analyses performed for the primary and confirmatory endpoints, except that they are being assessed to reflect the outcomes through the follow up visits. As described below, the results show that a clinically significant and effective improvement can be achieved immediately following treatment, and the results are sustained through the twelve months of follow-up.

MDS-UPDRS Part III Upper and Lower Extremity

Change as compared to baseline for MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Bilateral Effect through Month 12 is shown in **Table 18** and **Figure 5**. This analysis also shows a clinically meaningful mean reduction in symptoms of 44.5%, 34.0%, 35.5%, and 35.0% at 1, 3, 6, and 12 months, respectively. The calculated mean score dropped from 34.7 at baseline to 18.4, 21.5, 21.7, and 21.9 at 1, 3, 6, and 12 months, respectively.

Table 18. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Bilateral Effect through Month 12				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	34.7	N/A	N/A
	Median	32.5	N/A	N/A
	SD	9.7	N/A	N/A
Month 1	Mean	18.4	16.3	44.5
	Median	17.0	15.0	43.8
	SD	8.6	12.0	27.0
Month 3	Mean	21.5	13.2	34.0
	Median	21.0	10.2	32.7
	SD	7.9	12.4	27.0
Month 6	Mean	21.7	13.0	35.5
	Median	21.9	11.0	36.9
	SD	8.6	11.0	25.6
Month 12	Mean	21.9	12.8	35.0
	Median	21.7	10.6	35.5
	SD	7.9	9.8	22.2
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	34.8	N/A	N/A
	Median	33.0	N/A	N/A
	SD	9.5	N/A	N/A
Month 1	Mean	18.5	16.2	44.3
	Median	17.3	15.0	43.8
	SD	8.7	11.9	26.9
Month 3	Mean	21.6	13.1	33.9
	Median	21.0	10.4	32.6
	SD	8.1	12.3	26.9
Month 6	Mean	21.9	12.9	35.1

Table 18. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Bilateral Effect through Month 12				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
	Median	21.9	11.0	36.4
	SD	8.7	10.9	25.6
Month 12	Mean	22.2	12.6	34.4
	Median	21.9	10.5	34.2
	SD	8.1	9.8	22.4
Lower scores are better. Higher percent change demonstrates improvement.				

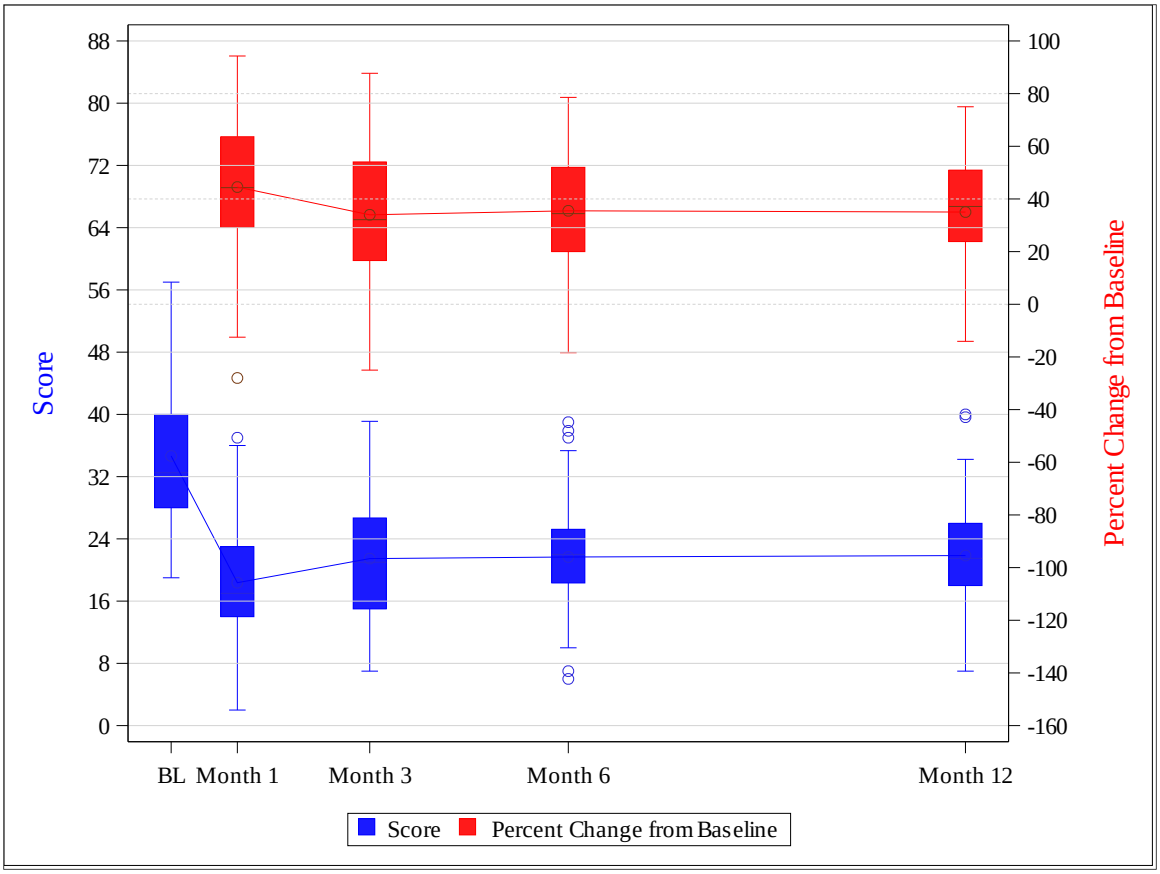

Figure 5. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Bilateral Effect – Score and Percent Change from Baseline (Bilateral mITT)

MDS-UPDRS Part IV

Change as compared to baseline for MDS-UPDRS Part IV – Motor Complications through Month 12 is shown in **Table 19** and **Figure 6**. This analysis also showed a clinically meaningful mean reduction in symptoms of 62.1%, 67.9%, 62.6%, and 67.1% at 1, 3, 6, and 12 months, respectively. The calculated mean score dropped from 10.6 at baseline to 4.1, 3.6, 4.0, and 3.8 at 1, 3, 6, and 12 months, respectively.

Table 19. Secondary Endpoint 2: MDS-UPDRS Part IV through Month 12

Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	10.6	N/A	N/A
	SD	3.2	N/A	N/A
	Median	11.5	N/A	N/A
Month 1	Mean	4.1	6.5	62.1
	Median	3.8	6.1	69.9
	SD	3.7	4.0	35.2
Month 3	Mean	3.6	7.0	67.9
	Median	4.0	7.0	66.1
	SD	3.0	3.0	25.3
Month 6	Mean	4.0	6.6	62.6
	Median	4.0	6.5	66.8
	SD	3.4	3.9	33.5
Month 12	Mean	3.8	6.8	67.1
	Median	3.2	6.4	71.0
	SD	3.7	3.5	31.1
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	10.7	N/A	N/A
	Median	12.0	N/A	N/A
	SD	3.2	N/A	N/A
Month 1	Mean	4.2	6.5	61.9
	Median	3.8	6.1	69.9

Table 19. Secondary Endpoint 2: MDS-UPDRS Part IV through Month 12				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
	SD	3.6	3.9	34.6
Month 3	Mean	3.6	7.1	68.1
	Median	3.9	7.0	66.8
	SD	2.9	3.0	24.9
Month 6	Mean	4.0	6.7	62.4
	Median	4.0	6.7	66.8
	SD	3.4	3.8	32.9
Month 12	Mean	3.8	6.9	67.3
	Median	3.2	6.7	71.9
	SD	3.6	3.5	30.5
Lower scores are better. Higher percent change demonstrates improvement.				

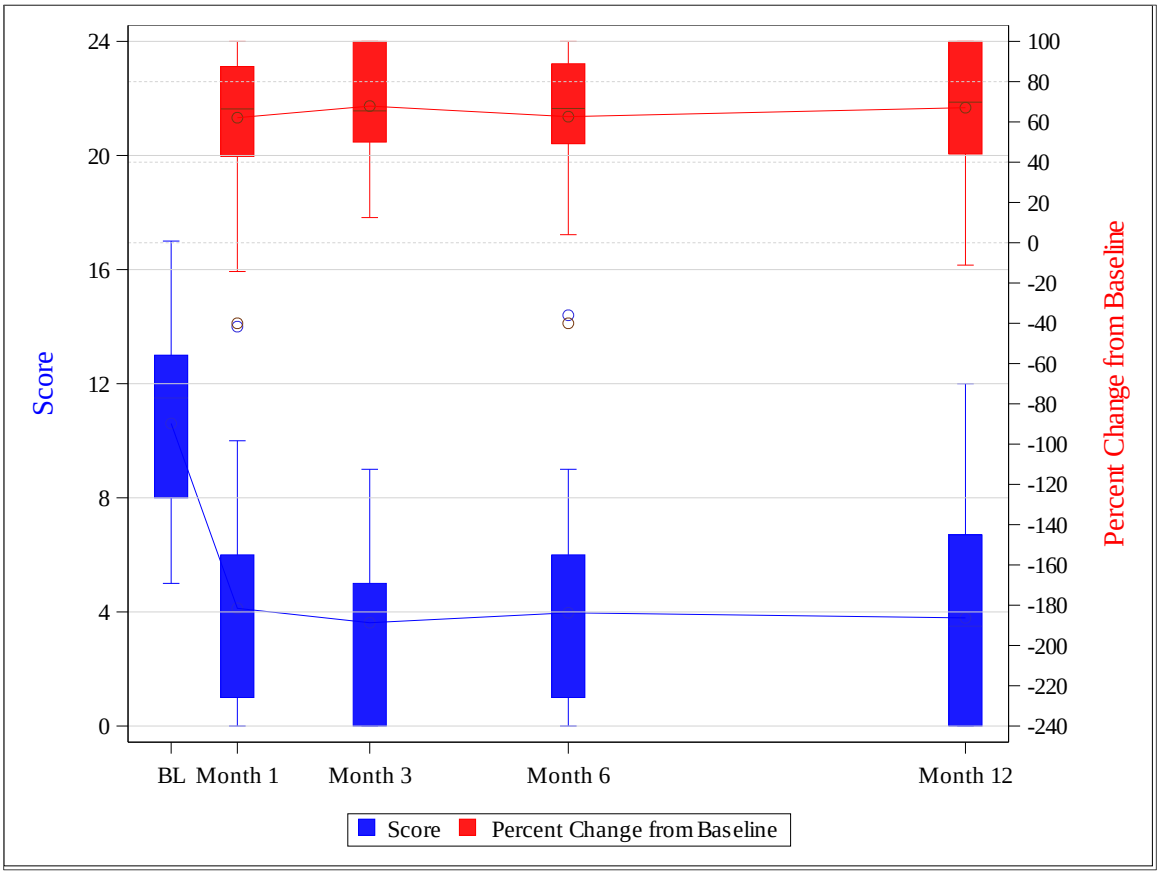

Figure 6. Secondary Endpoint 2: MDS-UPDRS Part IV – Score and Percent Change from Baseline (Bilateral mITT)

MDS-UPDRS Part III – Total Score

Change as compared to baseline for MDS-UPDRS – Part III OFF Medication Total Score through Month 12 is shown in **Table 20** and **Figure 7**. This analysis also showed a clinically meaningful mean reduction in symptoms of 40.0%, 31.8%, 34.4%, and 30.5% at 1, 3, 6 and 12 months, respectively. The calculated mean score dropped from 51.0 at baseline to 29.5, 33.3, 32.8, and 34.7 at 1, 3, 6, and 12 months, respectively.

Table 20. Secondary Endpoint 3: MDS-UPDRS Part III OFF Med Total Score through Month 12 (Bilateral mITT)

Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline
Bilateral mITT Analysis Set (N=38)				
Baseline	Mean	51.0	N/A	N/A
	SD	12.6	N/A	N/A

Table 20. Secondary Endpoint 3: MDS-UPDRS Part III OFF Med Total Score through Month 12 (Bilateral mITT)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
	Median	49.5	N/A	N/A
Month 1	Mean	29.5	21.5	40.0
	Median	28.1	18.7	39.8
	SD	12.5	16.8	27.4
Month 3	Mean	33.3	17.7	31.8
	Median	32.5	16.0	33.0
	SD	11.3	15.8	24.7
Month 6	Mean	32.8	18.2	34.4
	Median	32.7	16.5	36.8
	SD	12.2	14.3	23.7
Month 12	Mean	34.7	16.3	30.5
	Median	35.2	16.1	33.6
	SD	11.1	12.9	21.3
Bilateral ITT Analysis Set (N=40)				
Baseline	Mean	51.3	N/A	N/A
	Median	49.5	N/A	N/A
	SD	12.4	N/A	N/A
Month 1	Mean	29.5	21.7	40.1
	Median	28.3	18.9	40.1
	SD	12.4	16.7	27.3
Month 3	Mean	33.4	17.8	32.0
	Median	32.7	16.0	33.0
	SD	11.4	15.7	24.7
Month 6	Mean	33.0	18.2	34.3
	Median	32.8	16.6	36.7
	SD	12.2	14.1	23.5
Month 12	Mean	35.0	16.2	30.2

Table 20. Secondary Endpoint 3: MDS-UPDRS Part III OFF Med Total Score through Month 12 (Bilateral mITT)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
	Median	35.4	15.8	32.8
	SD	11.3	12.9	21.4
Lower scores are better. Higher percent change demonstrates improvement.				

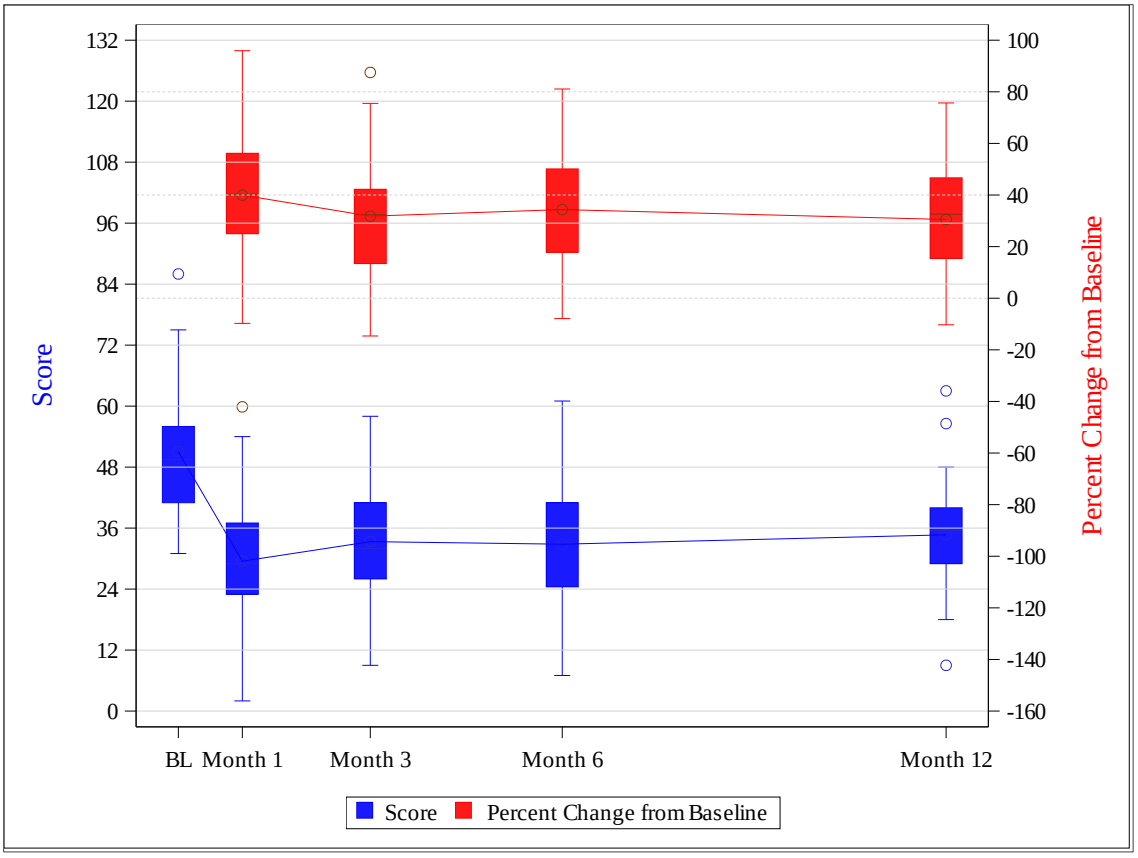

Figure 7. Secondary Endpoint 3: MDS-UPDRS Part III OFF Med Total Score – Score across Visits and Percent Change from Baseline (Bilateral mITT)

10.2.4.4 Additional Endpoints

There were 3 additional efficacy endpoint analyses performed to evaluate bilateral efficacy.

Clinician Global Impression of Change

The clinician-reported rating of subject overall change at the Month 3 post contralateral procedure showed that 97% of the patients (**Figure 8**) that underwent the contralateral procedure had at least some improvement, with 70% being rated as having been much or very much improved. The full details of the CGIC results are presented in **Table 21** below.

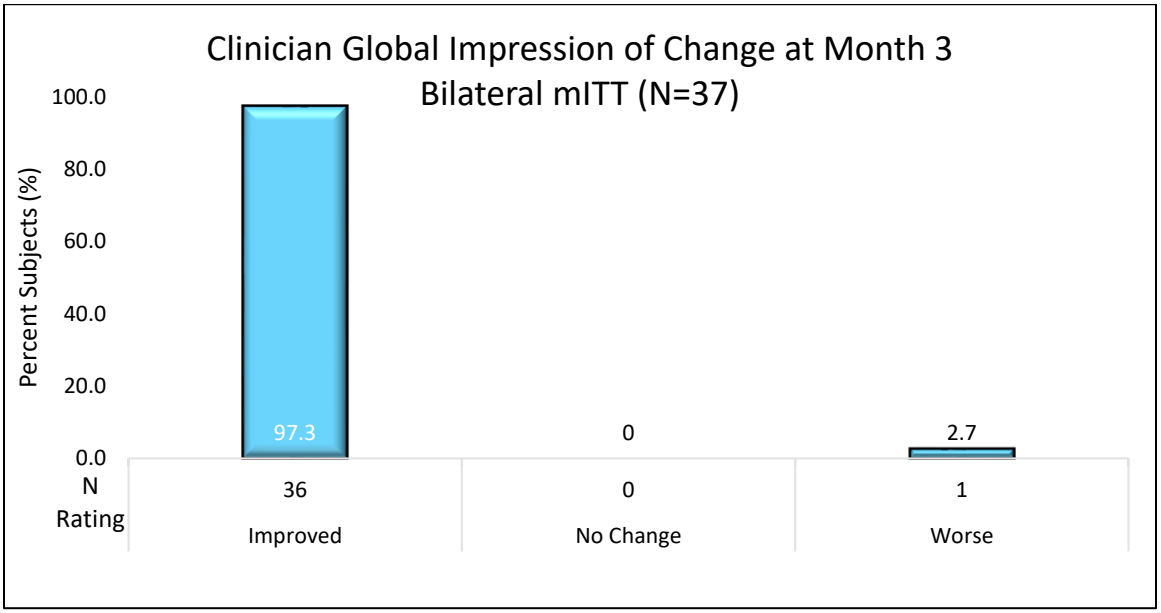

Figure 8: Clinician Global Impression of Change at Month-3 in the Bilateral mITT population with available data

Table 21. Additional Efficacy Endpoint – Clinician Global Impression of Change at Month 3 post bilateral treatment (Bilateral mITT)		
Rating	**Bilateral mITT population with available data (N=37)**	
	Number	**Percent (%)**
1 = Very Much Improved	8	21.6 %
2 = Much Improved	18	48.6 %
3 = Minimally Improved	10	27.0 %
4 = No Change	0	0.0 %
5 = Minimally Worse	0	0.0 %
6 = Much Worse	0	0.0 %
7 = Very Much Worse	1	2.7 %

Patient Global Impression of Change

The self-reported patient Global Impression of change (PGIC) rating of overall change at the Month 3 post contralateral procedure showed that 86% of the patients (see **Figure 9)** that underwent the contralateral procedure felt they had at least some improvement, with 43% rating themselves as having much or very much improved. The full details of the PGIC results are presented in **Table 22** below.

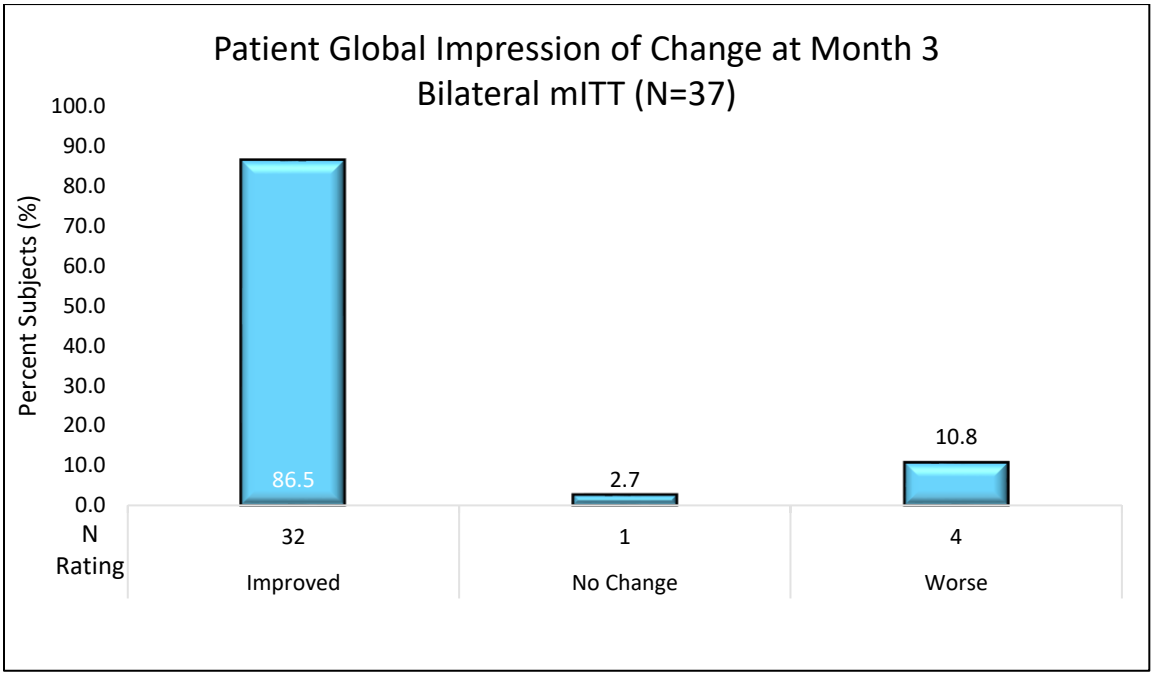

Figure 9: Patient Global Impression of Changes at Month-3 in the Bilateral mITT population with available data

Table 22. Additional Efficacy Endpoint – Patient Global Impression of Change at Month 3 post bilateral treatment (Bilateral mITT)

Rating	Bilateral mITT population with available data (N=37)	
	Number	Percent (%)
1 = Very Much Improved	2	5.4 %
2 = Much Improved	14	37.8 %
3 = Minimally Improved	16	43.2 %
4 = No Change	1	2.7 %
5 = Minimally Worse	2	5.4 %
6 = Much Worse	2	5.4 %
7 = Very Much Worse	0	0 %

Patient Satisfaction Questionnaire

The self-reported patient questionnaire (see **Figure 10**) showed that at the Month 3 post contralateral procedure, 65% of the patients that underwent the contralateral procedure felt that, taking everything into account, they would have the procedure again, 62% felt satisfied that the good things outweighed the bad things, 62% of the patients were overall satisfied with the procedure, 76% felt that the procedure reduced PD symptoms well on one side and 68% felt that the procedure reduced their PD symptoms well at least to some degree on both sides.

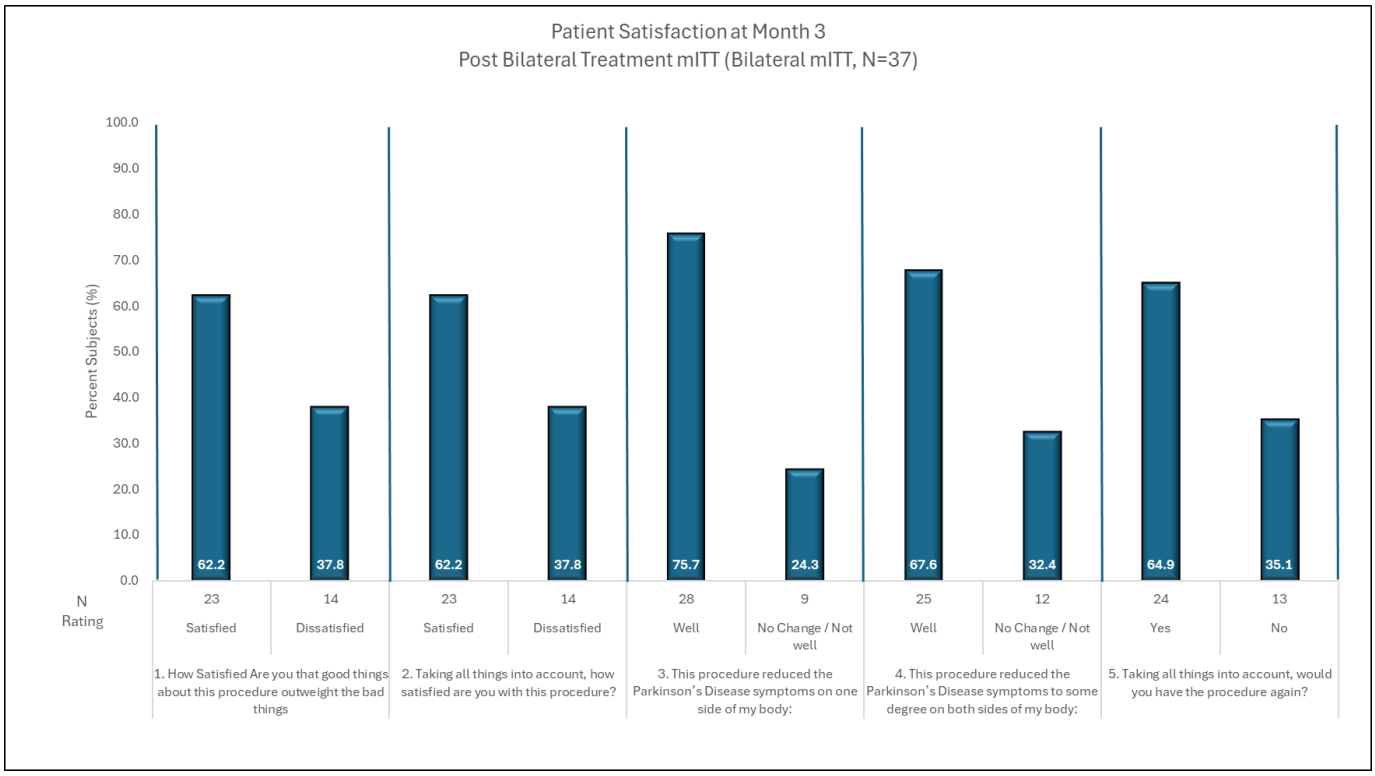

Figure 10 Patient Satisfaction Assessments at Month-3 in the Bilateral mITT population with available data

10.2.4.5 Post-hoc Analysis

Additional post-hoc effectiveness analyses were conducted for the primary effectiveness endpoint (MDS-UPDRS Part III Off Medication Upper and Lower Extremity) on the bilateral mITT population to isolate improvement observed for the second treatment of the bilateral PTTractotomy. These analyses evaluated the primary effectiveness endpoint using a the 6-month post-unilateral timepoint as the baseline comparison (B2). The percent change of the primary endpoint was recalculated for each patient as follows:

$$\% \text{ Change} = 100*(\text{B2 score} - \text{T2, month 3 score})/(\text{B2 score})$$

Results of this analysis are presented descriptively as shown in **Table 23** and for percent change (Figure 11) and score change (Figure 12). Larger improvements are observed for the second side treated in comparison to first side treated and both sides at timepoints following the bilateral treatment. Percent change in score (Figure 11) and change in score (Figure 12) indicate improvement in median MDS-UPDRS Part III Off Medication Upper and Lower Extremity Scores for second side treated and both sides following the bilateral treatment. The percent and score changes in "Both Sides" are smaller than changes in the side treated at the second procedure, because percent/score change for the side treated in the first procedure was negative, i.e., the first treatment side worsened during the period of the second treatment.

The MDS-UPDRS Part III OFF Meds Upper and Lower Extremity score was repeated for Treated side and Combined Side. Changes from Baseline 2 (B2) using Month 6 post unilateral as re-baseline is shown in **Table 23**.

Table 23. MDS-UPDRS Part III Off Medication Upper and Lower Extremity Motor Score for Treated Side & Combined Sides Compared to Month 6 post Unilateral Treatment (Bilateral mITT)

		Side Treated During Second Procedure			Total Score – Both Procedures		
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Bilateral mITT (N=38)							
Unilateral Stage - Month 6 (Baseline for Bilateral Stage)	Mean	15.2	N/A	N/A	24.7	N/A	N/A
	Median	15.5	N/A	N/A	26.0	N/A	N/A
	SD	5.9	N/A	N/A	9.1	N/A	N/A
Bilateral Stage - Month 1	Mean	9.2	6.1	32.4	18.4	6.3	21.5
	Median	8.9	5.1	44.0	17.0	6.8	33.8
	SD	5.0	6.5	45.7	8.6	8.0	36.1
Bilateral Stage - Month 3	Mean	11.1	4.1	16.4	21.5	3.2	2.9
	Median	10.2	3.8	19.6	21.0	2.9	10.4
	SD	5.3	6.5	55.3	7.9	8.6	44.4
Bilateral Stage - Month 6	Mean	10.5	4.8	22.6	21.7	3.0	5.3
	Median	10.5	5.0	29.3	21.9	3.3	15.4
	SD	5.0	6.2	46.9	8.6	7.5	42.0
	Mean	11.6	3.6	13.1	21.9	2.8	2.1

Table 23. MDS-UPDRS Part III Off Medication Upper and Lower Extremity Motor Score for Treated Side & Combined Sides Compared to Month 6 post Unilateral Treatment (Bilateral mITT)							
		Side Treated During Second Procedure			Total Score – Both Procedures		
Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline	Calculated Score	Change from Baseline	Percent Change from Baseline
Bilateral mITT (N=38)							
Bilateral Stage - Month 12	Median	11.9	4.5	29.2	21.7	3.6	12.5
	SD	4.7	6.0	52.2	7.9	8.0	44.8
Lower scores are better. Higher percent change demonstrates improvement. Note: The treated 1 brain side scores at Month 6 post T1 was used as Baseline for both side evaluation post treatment 2.							

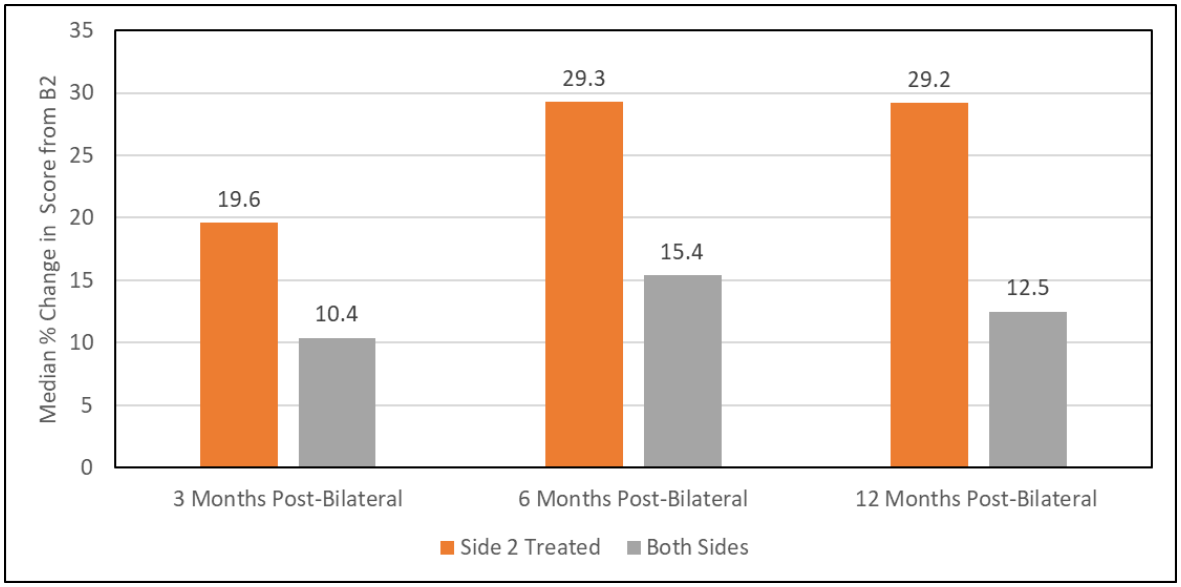

Figure 11: Percent change in Median MDS-UPDRS Part III Off Medication Upper and Lower Extremity Scores with respect to median score at B2 for first side treated, second side treated, and both sides. Baseline is defined as B2 (6-month post-unilateral timepoint).

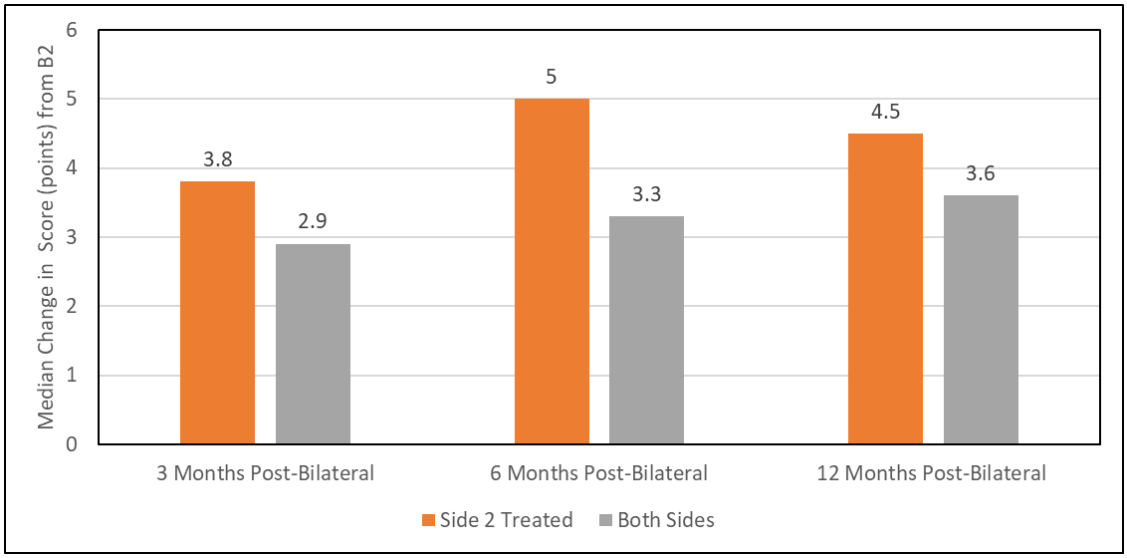

Figure 12: Median improvement in MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score after T2 with respect to median score at B2 for second side treated and both sides. Baseline is defined as score at B2 (6-month post-unilateral timepoint). Positive values indicate reduction in score (improvement).

(Figure 13) presents the median improvement in MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score for the side treated and both sides at 3 months after the unilateral and bilateral procedures. Figure 13demonstrates that a larger improvement was observed for the treated side and both sides after the unilateral procedure compared to the bilateral procedure. A responder rate analysis was conducted on the MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score using a minimal clinical important difference (MCID) of 3 points. The responder rate for T2 on the second treated side (when compared to B2) is 61.43% (N=38). In comparison, the responder rate of T1 on the first treated side (when compared to B1) is 90.7% (49/54). This finding is not unexpected given the higher magnitude of symptoms occurring on the side treated during the unilateral procedure.

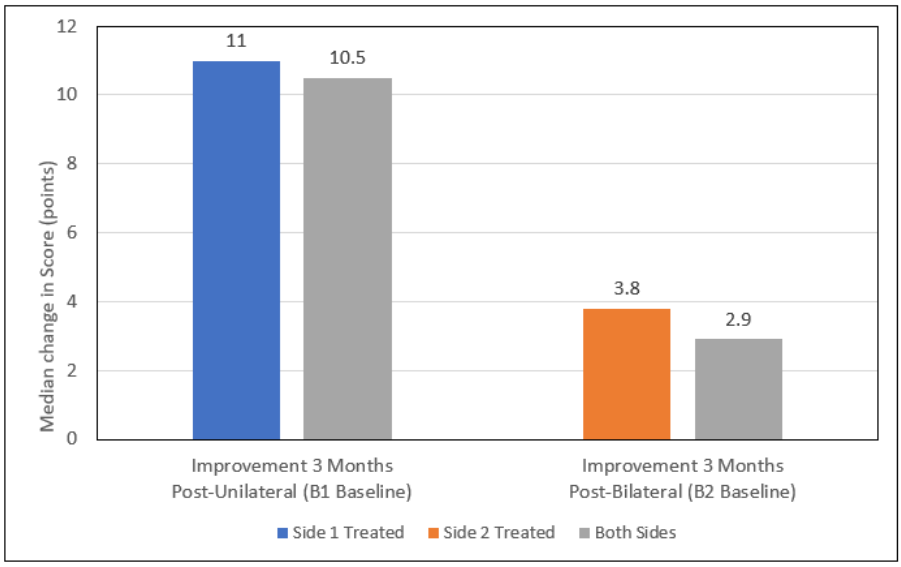

Figure 13: Median improvement in MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score for the side treated and both sides 3 months after unilateral and bilateral procedures. Scores at B1 and B2 were used as baseline scores for the unilateral and bilateral procedures, respectively.

10.2.5 Unilateral Safety and Effectiveness Results

Unilateral safety and efficacy results of the 54 treated subjects out to six months post Index Procedure are summarized in the sections below. This summary also includes the Month 12 data of those subjects who did not qualify or proceed to Treatment 2 (N=14).

10.2.5.1 Unilateral Safety Endpoint

The safety analysis of the Unilateral safety population included all the subjects treated Unilaterally, N=54.

As presented in **Table 24** , in this study, 10 out of the 54 (18.5%) subjects experienced no adverse events and 44 out of the 54 (81.5%) subjects experienced at least one adverse event following Index procedure and prior to Contralateral procedure.

Table 24. AE Frequency/Subject (Unilateral Safety)		
Experience of at Least One Treatment Emergent AE	**N**	**%**
Yes	44	81.5
No	10	18.5
Total	54	100.0

Overall, a total of 151 events were recorded in 44 of the 54 treated subjects, which corresponds to 2.8 events per subject. **Table 25** presents the adverse event safety profile for the study by severity. Approximately 99% of all the adverse events were either Mild (73.5%=111/151) or Moderate (25.2% =38/151). The two events that were Severe (2/151=1.3%) were neither Device nor Procedure related. In this study, there were no life-threatening events.

Table 25. Adverse Events by Severity (Unilateral Safety)

Severity	Frequency N= 151	Incidence N=54
Mild	111 (73.5%)	33 (61.1%)
Moderate	38 (25.2%)	22 (40.7%)
Severe	2 (1.3%)	2 (3.7%)
Life-Threatening	0 (0%)	0 (0%)
Total	**151 (100%)**	**44 (81.5%)**
Related to Device or Procedure SAE	0 (0%)	0 (0%)
Unrelated to Device or Procedure SAE	3 (2.0%)	2 (3.7%)

Table 26 presents the adverse event safety profile for the study by Grouping Term. Eighty percent (80%) of the events were either Unrelated (40%), underlying Parkinson's Disease related (14%), or Transient (26%); Transient events are those events that resolved within 72 hours.

Table 26. Adverse Events by Grouping Term (Unilateral Safety)

Grouping Term	Frequency (N= 151)	Incidence (N=54)
Unrelated	61 (40.4%)	32 (59.3%)
Parkinson's Disease Related	21 (13.9%)	13 (24.1%)
Subtotal	**82 (54.3%)**	**35 (64.8%)**
Transient	**39 (25.8%)**	**23 (42.6%)**
Pallidothalamic Tract Related	17 (11.3%)	13 (24.1%)
Procedure Related	13 (8.6%)	10 (18.5%)
Device Related	0 (0%)	0 (0%)

Table 26. Adverse Events by Grouping Term (Unilateral Safety)		
Grouping Term	**Frequency (N= 151)**	**Incidence (N=54)**
Subtotal	**30 (19.9%)**	**21 (38.9%)**
Grand Total	**151 (100%)**	**44 (81.5%)**

To Summarize the unilateral safety data:

- The **Unrelated events** are events that are captured and determined by Investigator(s) to be unrelated to the treatment device (Exablate) or procedure.
    - 61 (40%) events in 32 (59%) subjects were Unrelated
- The **PD Disease Related events** are events that are commonly associated with worsening Parkinson's and their PD medications.
    - 21 (14%) events in 13 (24%) subjects were PD disease related
- **Transient events** are those events that last seconds to less than 72 hours and resolve completely.
    - 39 (26%) events in 23 (43%) subjects were Transient (resolved <72 hours)
- The **Pallidothalamic Tract (PTT) related events** are events commonly reported in the literature for this target.
    - 17 (11%) events in 13 (24%) of subjects were Pallidotomy-related
        - Of the 17 events, 15 (88%) events have resolved.
- The **Procedure related events** are generally those events that are non-transient and related to undergoing the procedure, such as fatigue, headache, etc.
    - 13 (9%) events in 10 (19%) of subjects were Procedure-related
        - Of the 13 events, 11 (85%) events have resolved.
- The **Device related events** are events that are caused specifically by incorrect or inaccurate energy delivery by the Exablate device and cause safety events to a subject.
    - There were no device related events.

Table 27 below presents all the adverse events for unilateral subjects reported by grouping term, body system and coded term. The most common adverse events were hypertension (9.2%), dizziness (3.3%), and stereotactic frame-related headache (3.3%) or pin-site pain (3.3%).

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety

Grouping Term	Body System	Preferred Term	Severity									
			Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54
Pallidothalamic Tractotomy Related	EENT	Visual Field Deficit	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	General	Reduced Ld Effect	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Weight Gain	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Nervous	Dyskinesia	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Gait Disturbance	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Gait Unsteadiness	2 (1.3)	2 (3.7)	0	0	0	0	0	0	2 (1.3)	2 (3.7)
		Hypophonia	4 (2.6)	4 (7.4)	0	0	0	0	0	0	4 (2.6)	4 (7.4)
		Slurred Speech	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Somnolence	2 (1.3)	2 (3.7)	0	0	0	0	0	0	2 (1.3)	2 (3.7)
		Voice Hoarseness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Word-Finding Difficulty	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Psychological	Cognitive Impairment	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
Total Pallidothalamic Tractotomy Related			14 (9.3)	11 (20.4)	3 (2.0)	2 (3.7)	0	0	0	0	17 (11.3)	13 (24.1)
Parkinson's Disease Related	General	Fall	1 (0.7)	1 (1.9)	1 (0.7)	1 (1.9)	0	0	0	0	2 (1.3)	2 (3.7)
		Fatigue	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Musculoskeletal	Arthralgias	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Muscle Cramps	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Restless Abdomen	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Restless Legs	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Slouched Posture	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Nervous	Concentration Issues	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Decreased Short Term Recall	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Dystonia	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Freezing	2 (1.3)	2 (3.7)	1 (0.7)	1 (1.9)	0	0	0	0	3 (2.0)	3 (5.6)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
		Freezing Gait	2 (1.3)	2 (3.7)	0	0	0	0	0	0	2 (1.3)	2 (3.7)
		Gait Disturbance	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Imbalance	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Slowness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Visual Hallucinations	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Psychological	Hallucination	0	0	0	0	1 (0.7)	1 (1.9)	0	0	1 (0.7)	1 (1.9)
Total Parkinson's Disease Related			15 (9.9)	10 (18.5)	5 (3.3)	5 (9.3)	1 (0.7)	1 (1.9)	0	0	21 (13.9)	13 (24.1)
Procedure Related	EENT	Disconjugate Gaze	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Gastrointestinal	Nausea/Vomiting	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	General	Fatigue	4 (2.6)	4 (7.4)	0	0	0	0	0	0	4 (2.6)	4 (7.4)
	Nervous	Cerebellar Ataxia	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Gait Unsteadiness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
		Hiccups	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Leg Weakness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Numbness/Tingling	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Pain/Discomfort	Head Pain	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Psychological	Confusion	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
Total Procedure Related			12 (7.9)	9 (16.7)	1 (0.7)	1 (1.9)	0	0	0	0	13 (8.6)	10 (18.5)
Transient	Cardiovascular	Hypertension	4 (2.6)	4 (7.4)	10 (6.6)	10 (18.5)	0	0	0	0	14 (9.3)	14 (25.9)
		Hypotension	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Gastrointestinal	Constipation	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Nausea/Vomiting	3 (2.0)	3 (5.6)	1 (0.7)	1 (1.9)	0	0	0	0	4 (2.6)	4 (7.4)
	Musculoskeletal	Positional Pain	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Nervous	Dizziness	5 (3.3)	5 (9.3)	0	0	0	0	0	0	5 (3.3)	5 (9.3)
		Dyskinesia	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Hiccups	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
		Hypersalivation	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Pain/Discomfort	Head Pain	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Headache	3 (2.0)	3 (5.6)	1 (0.7)	1 (1.9)	0	0	0	0	4 (2.6)	4 (7.4)
		Sonication Head Pain	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Psychological	Anxiety	1 (0.7)	1 (1.9)	3 (2.0)	3 (5.6)	0	0	0	0	4 (2.6)	4 (7.4)
Total Transient			22 (14.6)	12 (22.2)	17 (11.3)	13 (24.1)	0	0	0	0	39 (25.8)	23 (42.6)
Unrelated	Cardiovascular	Edema - Le	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Hypertension	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Pulmonary Embolism	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Dermatologic	Livido Reticularis	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Skin Rash	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	EENT	Blepharospasm	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Blurry Vision	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	Body System	Preferred Term	Severity									
			Mild		Moderate		Severe		Life-Threatening		Any	
			N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54	N_E ($\%_E$) N=151	N_S ($\%_S$) N=54
		Conjunctivitis	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Decreased Visual Acuity	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Dry Eyes	3 (2.0)	3 (5.6)	0	0	0	0	0	0	3 (2.0)	3 (5.6)
		Eye Redness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Visual Field Deficit	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Worsening Eyesight	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Gastrointestinal	Constipation	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	General	Dizziness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Edema - Le	2 (1.3)	2 (3.7)	0	0	0	0	0	0	2 (1.3)	2 (3.7)
		Fall	3 (2.0)	3 (5.6)	0	0	0	0	0	0	3 (2.0)	3 (5.6)
		Sleep Apnea	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Syncope	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Genitourinary	Kidney Stone	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Renal Insufficiency	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Infection	Cold Symptoms	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
		Covid-19	0	0	2 (1.3)	2 (3.7)	0	0	0	0	2 (1.3)	2 (3.7)
		Flu	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Musculoskeletal	Bunion Removal	0	0	0	0	1 (0.7)	1 (1.9)	0	0	1 (0.7)	1 (1.9)
		Decreased Mouth Movement	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Hip Injury	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Hypotonia	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Muscle Pain	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Neck Pain	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Nervous	Clumsiness	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Paresthesia	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Pain/Discomfort	Back Pain	1 (0.7)	1 (1.9)	1 (0.7)	1 (1.9)	0	0	0	0	2 (1.3)	2 (3.7)
		Headache	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Visual Discomfort	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
	Psychological	Anxiety	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)

Table 27. Adverse Event (Frequency/Incidence) – Unilateral Safety												
Grouping Term	**Body System**	**Preferred Term**	**Severity**									
			Mild		**Moderate**		**Severe**		**Life-Threatening**		**Any**	
			N_E ($\%_E$) N=151	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**	**N_E ($\%_E$) N=151**	**N_S ($\%_S$) N=54**
		Delusion	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Respiratory	Decreased Lung Function	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
	Stereotactic Frame	Eye Swelling	2 (1.3)	2 (3.7)	0	0	0	0	0	0	2 (1.3)	2 (3.7)
		Facial Droop	2 (1.3)	1 (1.9)	0	0	0	0	0	0	2 (1.3)	1 (1.9)
		Head Discomfort	0	0	1 (0.7)	1 (1.9)	0	0	0	0	1 (0.7)	1 (1.9)
		Headache	5 (3.3)	5 (9.3)	0	0	0	0	0	0	5 (3.3)	5 (9.3)
		Numbness/Tingling	1 (0.7)	1 (1.9)	0	0	0	0	0	0	1 (0.7)	1 (1.9)
		Pin Site Pain	4 (2.6)	4 (7.4)	1 (0.7)	1 (1.9)	0	0	0	0	5 (3.3)	5 (9.3)
Total Unrelated			48 (31.8)	27 (50.0)	12 (7.9)	9 (16.7)	1 (0.7)	1 (1.9)	0	0	61 (40.4)	32 (59.3)
Grand Total			**111 (73.5)**	**33 (61.1)**	**38 (25.2)**	**22 (40.7)**	**2 (1.3)**	**2 (3.7)**	**0**	**0**	**151 (100.0)**	**44 (81.5)**

10.2.5.2 Serious Adverse Events

Serious adverse events (SAEs) for unilateral subjects are summarized in **Table 28**. Out of the 151 adverse events reported in this study, there were 3 SAEs reported. All these SAEs were Unrelated to Device and Procedure and were related to the subject's underlying medical conditions. Two Serious events (hallucinations) were Parkinson's Disease Related and one (pulmonary embolism) was unrelated.

Table 28. Serious Adverse Event – Unilateral Safety				
Subject ID	**Grouping Term**	**Body System**	**Preferred Term**	**Severity**
Unrelated to Device and Procedure				
424011	Parkinson's Disease Related	Nervous	Visual Hallucination	Mild
43001	Unrelated	Cardiovascular	Pulmonary Embolism	Moderate
	Parkinson's Disease Related	Psychological	Hallucination	Severe

10.2.5.3 Unilateral Efficacy Results

In line with the above analyses, there are two key efficacy analyses performed on the unilateral mITT population out to Month 6:

- MDS-UPDRS Part III OFF Medications Upper and Lower Extremity
- Unilateral MDS-UPDRS Part IV

Note: Per study design, all unilateral results are based on the Month 6 data. The analyses also included those subjects (N=14) who did not proceed to the bilateral procedure and continued to Month-12 follow up. Month 12 data for these 14 subjects is presented in the Tables below only.

As described below, the results demonstrate effective improvement on the first side of the patient achieved immediately following treatment, and the results are sustained through Month-6, and through Month-12 of follow-up for those subjects who did not receive the contralateral Exablate procedure.

Unilateral MDS-UPDRS Part III OFF Medications Upper and Lower Extremity Score

Change as compared to baseline for MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Unilateral Effect through Month 12 is shown in **Table 29**. This analysis shows a clinically significant reduction in symptoms of 49.8%, 50.4%, and 50.3% at Month 1, 3, and 6 respectively, see **Figure 14**. The corresponding calculated score dropped from 20.9 at baseline to 10.1, 10.0, and 9.8 at Month 1, 3, and 6 respectively.

Table 29. MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Unilateral treatment effect-mITT/ITT				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Baseline	Mean	20.9	N/A	N/A
	SD	5.3	N/A	N/A
	Median	20.0	N/A	N/A
	N	54	N/A	N/A
Month 1	Mean	10.1	10.8	49.8
	Median	9.3	9.9	50.8
	SD	5.8	7.1	29.2
	N	54	54	54
Month 3	Mean	10.0	10.9	50.4
	Median	9.5	11.0	52.6
	SD	5.4	6.8	27.4
	N	54	54	54
Month 6	Mean	9.8	11.0	50.3
	Median	10.5	11.0	56.7
	SD	5.0	7.2	28.6
	N	54	54	54
Month 12	Mean	12.4	8.2	35.5
	Median	11.4	8.7	40.6
	SD	6.3	8.7	38.0
	N*	14	14	14
Lower scores are better. Higher percent change demonstrates improvement.*: 14 subjects did not proceed to bilateral at the 6-months timepoint. Continued with study requirement through Month-12.				

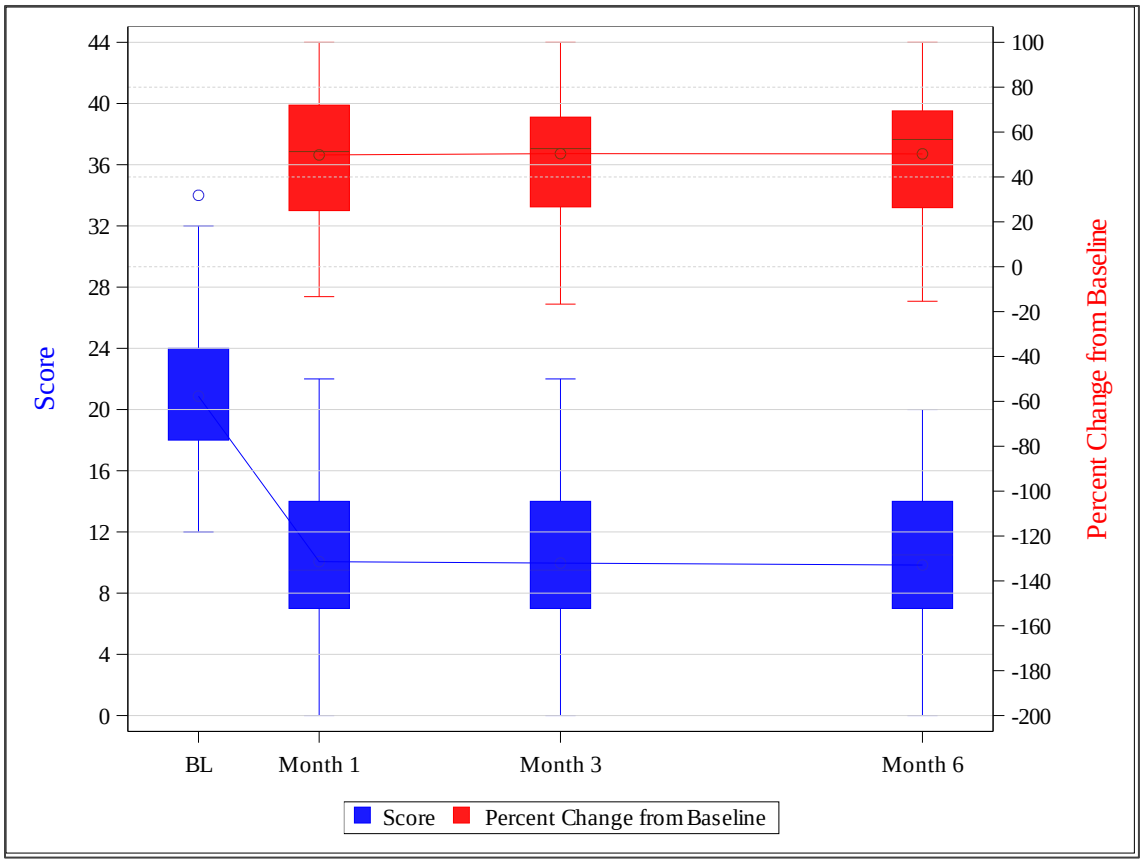

Figure 14. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Treated Side – Score across visits and Percent Change from Baseline (Unilateral mITT)

Unilateral MDS-UPDRS Part IV

Change as compared to baseline for MDS-UPDRS Part IV – Motor Complications for the unilateral subjects is shown in **Table 30**. This analysis shows also a clinically significant reduction in symptoms of 51.2%, 56.3%, and 46.1% at Month 1, 3, and 6, respectively, see **Figure 15**. The calculated score dropped from 10.5 at baseline to 5.0, 4.6, and 5.7 at Month 1, 3, and 6, respectively.

Table 30. Secondary Endpoint 2: MDS-UPDRS Part IV (Unilateral mITT/ITT)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Baseline	Mean	10.5	N/A	N/A
	Std	3.5	N/A	N/A
	Median	12.0	N/A	N/A
	N	54	N/A	N/A
Month 1	Mean	5.0	5.5	51.2
	Median	4.9	5.5	53.9
	SD	3.5	3.6	37.6
	N	54	54	54
Month 3	Mean	4.6	5.9	56.3
	Median	4.1	5.9	61.6
	SD	3.7	3.9	34.9
	N	54	54	54
Month 6	Mean	5.7	4.8	46.1
	Median	5.0	5.0	50.0
	SD	3.9	3.7	35.5
	N	54	54	54
Month 12	Mean	4.7	5.2	59.3
	Median	2.7	5.3	70.5
	SD	5.4	4.4	43.9
	N*	14	14	14
Lower scores are better. Higher percent change demonstrates improvement. *: 14 subjects did not proceed to bilateral at the 6-months timepoint. Continued with study requirement through Month-12.				

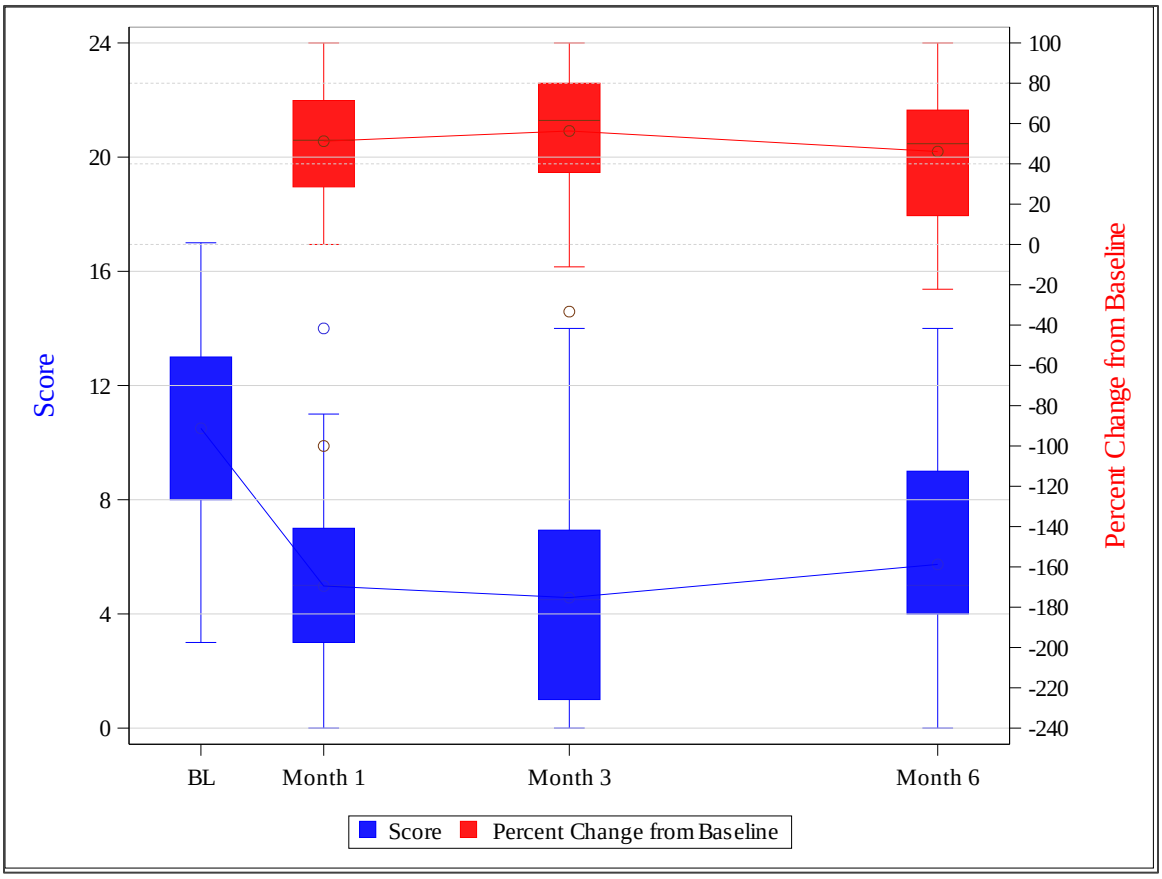

Figure 15. Secondary Endpoint 2: MDS-UPDRS Part IV – Score and Percent Change from Baseline (Unilateral mITT)

10.2.5.3.1 Additional Endpoints

There were 3 additional efficacy endpoint analyses performed using the Unilateral mITT population:

Clinician Global Impression of Change

The clinician-reported CGIC rating of subject overall change at the Month 3 post Index procedure showed that 98% of the study patients had at least some improvement after the first unilateral treatment, with 81% being rated as having much or very much improved.

Patient Global Impression of Change

The self-reported patient PGIC rating of overall change at the Month 3 post Index procedure showed that 94% of the patients felt they had at least some improvement after the first unilateral treatment, with 72% rating themselves as having much or very much improved.

Patient Satisfaction Questionnaire

The self-reported patient questionnaire showed that at the Month 3 post Index procedure 93% of the patients felt that, taking everything into account, they would have the procedure again, 85% felt satisfied that the good things outweighed the bad things, 85% of the patients were overall satisfied with the procedure, 85% felt that the procedure reduced PD symptoms well on one side and 28% felt that the procedure reduced their PD symptoms well at least to some degree on both sides.

10.2.5.4 Unilateral Treated Only Analysis (N=14)

There were 14 subjects who discontinued treatment after the first unilateral treatment procedure. For those 14 subjects, the following additional analysis was performed:

- MDS-UPDRS Part III OFF Medication Lower and Upper Extremity Score for side treated, side not treated, and both sides **Table 31.**

Table 31. MDS-UPDRS Part III Off Medication Lower and Upper Extremity Motor Score (Unilateral Treated Only – N=14)

Visit	Statistic	Side Treated During First Procedure			Side Not Treated During First Procedure			Both Sides		
		Calculated Score	Change from Baseline	Percent Change from Baseline	Calculated Score	Change from Baseline	Percent Change from Baseline	Calculated Score	Change from Baseline	Percent Change from Baseline
Unilateral Stage - Baseline	Mean	20.6	N/A	N/A	13.6	N/A	N/A	34.1	N/A	N/A
	Median	20.0	N/A	N/A		N/A	N/A		N/A	N/A
	SD	5.1	N/A	N/A	6.6	N/A	N/A	9.6	N/A	N/A
Unilateral Stage - Month 1	Mean	11.6	9.0	41.8	10.9	2.7	0.2	22.4	11.7	31.0
	Median	9.5	9.0	38.9	10.5	1.0	7.4	20.5	11.0	33.3
	SD	6.0	6.8	29.6	4.8	5.4	57.9	7.1	9.0	23.6
Unilateral Stage - Month 3	Mean	10.8	9.8	45.2	11.3	2.3	0.7	22.1	12.1	32.8
	Median	9.0	11.0	53.5	11.0	3.0	20.4	20.5	9.5	33.4
	SD	6.0	7.0	32.7	4.9	5.3	49.9	7.8	9.2	22.2
	Mean	10.1	10.5	47.7	11.0	2.6	15.5	21.1	13.1	36.3
	Median	11.0	11.0	52.8	11.0	0.5	13.9	20.5	12.5	41.5

Table 31. MDS-UPDRS Part III Off Medication Lower and Upper Extremity Motor Score (Unilateral Treated Only – N=14)										
		Side Treated During First Procedure			Side Not Treated During First Procedure			Both Sides		
Visit	Statistic	Calculated Score	Change from Baseline	Percent Change from Baseline	Calculated Score	Change from Baseline	Percent Change from Baseline	Calculated Score	Change from Baseline	Percent Change from Baseline
Unilateral Stage - Month 6	SD	5.1	7.5	30.6	6.4	5.1	37.7	9.2	10.2	23.8
Unilateral Stage - Month 12	Mean	12.4	8.2	35.5	9.4	4.2	-3.0	21.8	12.4	30.1
	Median	11.4	8.7	40.6	9.4	3.3	25.8	20.8	13.3	39.1
	SD	6.3	8.7	38.0	5.9	7.8	134.7	11.8	14.8	46.4
Lower scores are better. Higher percent change demonstrates improvement.										

- MDS-UPDRS Part IV total score for Unilateral Treated Only **Table 32**.

Table 32. MDS-UPDRS Part IV Motor Complications Score (Unilateral Treated Only – N=14)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Unilateral Stage - Baseline	Mean	9.9	N/A	N/A
	Median	11.0	N/A	N/A
	SD	4.2	N/A	N/A
Unilateral Stage - Month 1	Mean	5.1	4.7	39.8
	Median	4.7	5.0	52.5
	SD	3.8	4.4	51.5
Unilateral Stage - Month 3	Mean	4.2	5.7	53.8
	Median	3.7	5.0	62.0
	SD	4.3	5.0	44.2
Unilateral Stage - Month 6	Mean	4.3	5.5	62.2
	Median	4.0	4.9	64.7

Table 32. MDS-UPDRS Part IV Motor Complications Score (Unilateral Treated Only – N=14)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
	SD	4.3	3.7	33.8
Unilateral Stage - Month 12	Mean	4.7	5.2	59.3
	Median	2.7	5.3	70.5
	SD	5.4	4.4	43.9
Lower scores are better. Higher percent change demonstrates improvement.				

- MDS-UPDRA Part III Total Score for Unilateral Treated Only Subjects **Table 33**.

Table 33. MDS-UPDRS Part III Off Medication Total Score (Unilateral Treated Only – N=14)				
Visit	**Statistic**	**Calculated Score**	**Change from Baseline**	**Percent Change from Baseline**
Unilateral Stage - Baseline	Mean	52.0	N/A	N/A
	Median	47.5	N/A	N/A
	SD	14.0	N/A	N/A
Unilateral Stage - Month 1	Mean	34.3	17.7	31.6
	Median	34.5	16.5	31.2
	SD	9.6	13.7	19.1
Unilateral Stage - Month 3	Mean	34.1	17.9	31.6
	Median	32.0	17.5	37.2
	SD	11.5	15.6	23.5
Unilateral Stage - Month 6	Mean	32.1	19.9	36.5
	Median	29.5	21.0	41.7
	SD	12.9	15.4	23.1
Unilateral Stage - Month 12	Mean	31.8	20.2	34.1
	Median	31.6	21.0	41.8
	SD	15.7	21.7	35.5
Lower scores are better. Higher percent change demonstrates improvement.				

10.3 Regional Analysis

Improvement from baseline was observed in every region for the primary and confirmatory secondary endpoints **Table 34**. Heterogeneity across regions may exist, based on exploratory regional poolability analysis; however, limited sample sizes in regions outside of the US limits the interpretability of this regional subgroup analysis.

Table 34 By Region Analysis

Region	Statistic	Primary Endpoint	Confirmatory Secondary Efficacy Endpoint	
		MDS-UPDRS Part III Off Medication Upper and Lower Extremity Motor Score	MDS-UPDRS Part III Off Medication Total Score	MDS-UPDRS Part IV Motor Complications Score
US (N=29)	Mean percent change from baseline at 3 months	32.2	30.7	65.1
	Median percent change from baseline at 3 months	29.7	32.3	65.6
	Median 95% CI	16.4, 43.1	20.6, 44.0	54.3, 76.9
Taiwan (N=6)	Mean percent change from baseline at 3 months	54.9	48.8	90
	Median percent change from baseline at 3 months	59.9	53.3	100.0
	Median 95% CI	45.0, 64.8	26.8, 62.3	40.0, 100.0
Spain (N=3)	Mean percent change from baseline at 3 months	9.6	8.5	50
	Median percent change from baseline at 3 months	9.5	11.5	50
	Median 95% CI	-8.0, 27.3	-7.9, 21.9	42.9, 57.1

*CIs are not adjusted for multiplicity

10.4 Conclusion Drawn from the Study

10.4.1 Effectiveness conclusions

The Effectiveness Analysis in this study was performed on the modified Intent to Treat (mITT) population, which included all treated subjects who received staged contralateral (i.e. bilateral) Exablate procedure and had at least one post-bilateral treatment MDS-UPDRS Part III OFF meds assessment.

- **Primary Efficacy Endpoint**

  Primary effectiveness analysis was conducted on the bilateral mITT analysis population and reflects the average change in MDS-UPDRS Part III OFF Medication Upper / Lower Extremity Motor Score from Baseline (prior to any Exablate procedure) to Month 3 after the second Exablate procedure of the contralateral side.

  - **Endpoint Analysis**

    At Month 3, the primary effectiveness analysis showed an median score improvement of 10.2, a 32.7% improvement. This result is statistically significantly greater than the prespecified performance goal of 5.6%, with p <0.0001.

- **Confirmatory Secondary Effectiveness Endpoints**

  There were two additional effectiveness endpoint analyses performed using the bilateral mITT population to evaluate change from Baseline (prior to any Exablate procedure) at Month 3 Follow-up after the second Exablate procedure of the contralateral side.

  - **MDS-UPDRS Part IV – Motor Complications**

    Additional effectiveness endpoint measure of MDS-UPDRS Part IV demonstrated an average decrease of 7.0, a 67.9% improvement at Month 3 compared to Baseline.

  - **MDS-UPDRS Part III OFF Medication – Total Score**

    Additional effectiveness endpoint measure of MDS-UPDRS Part III Total Score demonstrated an average decrease of 17.7, a 31.8% improvement at Month 3 compared to Baseline.

- **Secondary Efficacy Endpoints**

  There are three secondary effectiveness analyses performed on the Bilateral mITT population out to Month 12.

  - **MDS-UPDRS Part III OFF Medication – Upper and Lower Extremity Score**

    Additional effectiveness endpoint measure of MDS-UPDRS Part III Upper and Lower Extremity demonstrated an average decrease of 12.8 , a 35.0% improvement at Month 12 compared to Baseline.

  - **MDS-UPDRS Part IV – Motor Complications**

    Additional effectiveness endpoint measure of MDS-UPDRS Part IV demonstrated an average decrease of 6.8, a 67.1% improvement at Month 12 compared to Baseline.

  - **MDS-UPDRS Part III OFF Medication – Total Score**

    Additional effectiveness endpoint measure of MDS-UPDRS Part III Total Score demonstrated an average decrease of 16.3 , a 30.5% improvement at Month 12 compared to Baseline.

- **Additional** effectiveness **Endpoints**

  Three additional effectiveness analyses were collected on the Bilateral mITT population.

- **Clinician Global Impression of Change**
  Clinicians reported that the vast majority (97.3%) of patients improved, with most (70%) being at least much improved. No subjects showed no change, while only a single patient was very much worse.

- **Patient Global Impression of Change**
  The vast majority (86.5%) of patients believed that they had improved. One subject reported no change, and four subjects (10.8%) reported being minimally or much worse.

- **Patient Satisfaction Questionnaire**

  The majority (62%) of subjects were at least satisfied that the benefits of the procedure outweighed its costs and were overall satisfied with the procedure. About twice as many subjects reported reduced PD symptoms on both sides of their body and were willing to have the procedure again as were not.

Subjects in this study showed a clinically significant and immediate response in their reduction in Parkinson's Disease symptoms, with bilateral symptom relief especially when both sides are treated. With the results being sustained through Month 12.

In summary, the primary effectiveness endpoints statistically significantly exceeded the prespecified performance goal of 5.6% and were clinically significant. At Month 3, the primary efficacy analysis showed a 32.7% improvement as compared to Baseline MDS-UPDRS Part III OFF Medication Upper / Lower Extremity Motor Score. Both confirmatory secondary endpoints show meaningful improvement in PD symptoms, demonstrating durable symptom improvement through Month 12. Nearly all subjects were reported by their clinician (97.3%) or by themselves (86.5%) to have improved. In sum, the treatment is shown to be effective.

10.4.2 Safety Conclusion

Overall, the summary of safety demonstrated that no adverse events related to device occurred, nor were there any Unanticipated Adverse Device Effects.

Of the 129 events reported following the contralateral Exablate procedure, 94% were categorized as Mild (63.6%) or Moderate (30.2%) and 6.2% were categorized as Severe (3.9%) or Life-threatening (2.3%) in nature. Of the 8 (6.2%) events that were categorize as Severe or Life-threatening, 7 events were unrelated to device and procedure. There was only 1 Severe event (that was also an SAE out of the 7 SAEs) reported as PTT-related. This event (anarthria) was caused by user error and could have been mitigated with proper use of the Exablate system tools and mitigation steps. No Life-threatening events related to Device or Procedure occurred.

In this study, each subject was evaluated for speech impairment. During the course of the study, additional speech assessments by a Speech-Language Pathologist (SLP) were introduced. Out of the 40 bilateral subjects, 30 subjects were evaluated additionally by a Speech-Language Pathologist (SLP) to determine the presence of clinically significant speech-language dysfunction at baseline (qualification to proceed to Bilateral), prior to bilateral treatment, as well as to evaluate any clinically significant change in function at Month 3 post bilateral treatment. All these additional Clinically Significant findings from the Speech Pathologist in each of the evaluated areas were reviewed within the context of each subject's overall medical records (e.g. Neurologist assessments, PD disease progression, etc.) to compile the complete list and assess severity of speech adverse events. A total of 19 speech events in 15 of the 40 subjects were reported post-contralateral procedure. Out of the 19, 14 speech events in 11 subjects (11/40, 28%) were related to bilateral PTT lesioning.

- 2 slurred speech
- 2 dysphagia
- 3 dysarthria
- 1 anarthria
- 3 hypophonia
- 2 VHI score elevated
- 1 stutter

Only 5 of those events (1 dysarthria, 1 anarthria, 1 dysphagia, 1 hypophonia, 1 stutter) in 4 of the 40 (4/40, 10%) subjects were reported with clinically significant (Moderate to Severe) speech deficiency.

Additionally, a total of 151 events in 44 out of 54 subjects were reported in this study (2.8 events per subject) after the first unilateral procedure. Ten (10) of the 54 subjects (18.5%) experienced no adverse events at all after the first procedure. Of the 151 events, 99% were Mild (74%) or Moderate (25%) in nature.

Overall, the occurrence of the events, in particular speech related events, remains consistent with the literature reporting in other surgical procedures for the same PD population. The safety profile of this device remains favorable.

The Exablate provides a safe and effective staged, bilateral treatment option for treatment of symptoms related to Parkinson's Disease. The risks are balanced with the benefit of substantial symptom reduction.

10.4.3 Risk-Benefit Conclusions

Probable benefit, as shown in the clinical study, demonstrates a statistically significant improvement (i.e. score reduction) in the MDS-UPDRS Part III OFF Meds Upper/Lower Extremity Score, Part III OFF Meds Total Score, and Part IV scores that included an objective measure.

Potential Risks of bilateral procedures (Pallidothalamic Tractotomy or DBS) include adverse events that have been reported in the literature such as dysarthria, dysphagia, imbalance/unsteadiness, ataxia/gait disturbance, and numbness/tingling.

Overall, the safety profile of the Exablate shows 94% of all events being either Mild or Moderate following the contralateral procedure, with 99% of events being Mild or Moderate following the first Unilateral procedure.

The risk (safety profile) vs. benefit (clinical benefit) ratio should be taken into account for each subject. In subjects with no clinically significant complications from the first procedure, the second procedure demonstrates high clinical benefit and minimal safety risk.

10.4.4 Overall Conclusion

The data in this section supports the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

For this population of patients suffering from Parkinson's Disease symptoms, the Exablate Neuro treatment is a reasonable alternative to existing treatments. The results from the pivotal study demonstrate that it is efficacious, and the safety profile is reasonable and does not cause any increased risks for this population who are at high risk due to the nature of the disease.

In conclusion, the treatment benefits of the device for the target population outweigh the risks when used in accordance with the directions for use.