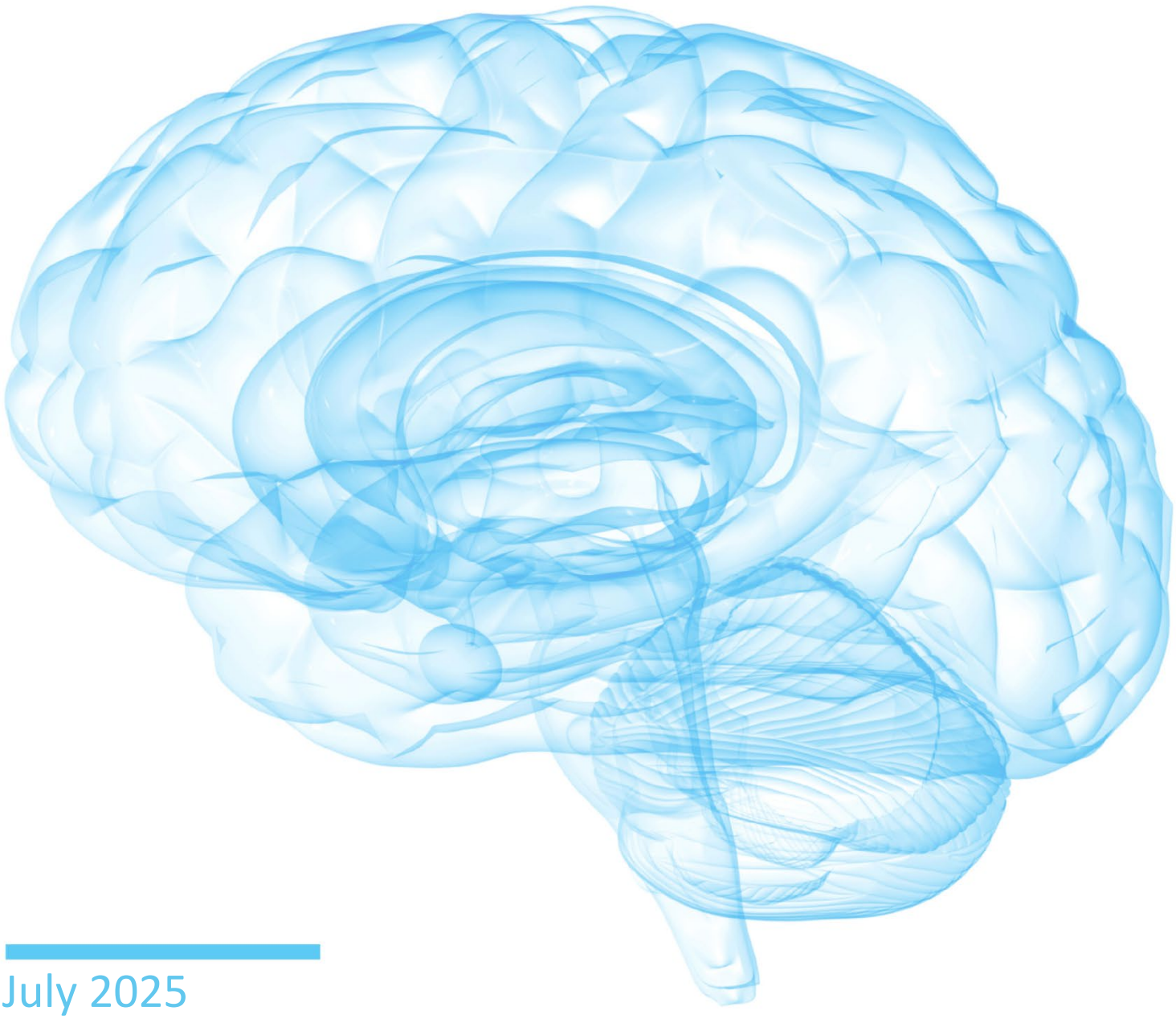

July 2025

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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PUB41002923, Rev 14

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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 (SDR) as calculated from the screening CT, of:
    - **Essential Tremor Only**: less than 0.35±(0.05)
    - **Parkinsons Disease Only**: less than 0.45±(0.05)
- 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 3: SUMMARY OF PIVOTAL CLINICAL STUDY – ESSENTIAL TREMOR

3.1 Study Design

The Pivotal study was a prospective, randomized, double-blind (to subjects, local site assessors, and Tremor Core Lab assessors), crossover, multi-site, two-arm study (Exablate treated arm versus Exablate Sham treated control arm) in the treatment of medication-refractory tremor in subjects with Essential Tremor (ET) using the Exablate Neuro.

Subjects with idiopathic Essential Tremor with medication-refractory tremor who are at least 22 years old were recruited into the study at 8 clinical sites. Qualified subjects were randomized at a 3:1 ratio to either Exablate treatment arm or sham control arm and preceded to MR/CT screening and geometric target verification where further subjects were ruled ineligible for study participation.

Subjects who were randomized to the sham treatment arm and passed the Screen Fail criteria underwent a sham Exablate treatment with sonication energy disabled. Subjects randomized to the Exablate treatment arm and passed the Screen Fail criteria preceded in normal fashion to Exablate treatment.

3.1.1 Eligibility Criteria

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

3.1.1.1 Inclusion Criteria

1. Men and women aged 22 years or older
2. Subjects who are able and willing to give consent and able to attend all study visits,
3. A diagnosis of ET as confirmed from clinical history and examination by a neurologist or neurosurgeon specialized in movement disorder
4. Tremor refractory to adequate trials of at least two medications, one of which should be a first line therapy of either propranolol or primidone. An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
5. Following the 1-month medication stability period, subject must be on stable medication for tremor

a. The 1-Month stability period visit will be 1-month post consent date

6. Vim nucleus of thalamus can be target by the Exablate device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
7. Able to communicate sensations during the Exablate Neuro treatment
8. Postural or intention tremor severity score of greater than or equal to 2 in the dominant hand/arm as measured by the CRST rating scale while stable on medication.
9. May have bilateral appendicular tremor

10. Significant disability due to Essential tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])
11. Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
12. Subjects on stable antidepressant medications for at least 3 months may be enrolled into this study (i.e., no change in medication drug or dosage for 3 months).

3.1.1.2 Exclusion criteria

Subjects were excluded from the study if they had any of the following:

1. Subjects with unstable cardiac status including:
   a) Unstable angina pectoris on medication
   b) Subjects with documented myocardial infarction within six months of protocol entry
   c) Significant congestive heart failure defined with ejection fraction < 40
   d) Subjects with unstable ventricular arrhythmias
   e) Subjects with atrial arrhythmias that are not rate-controlled
2. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within a 12 month period:
   a) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
   b) Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
   c) Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
   d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).
3. Severe hypertension (diastolic BP > 100 on medication)
4. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
5. Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease
6. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m^2 (or per local standards should that be more restrictive) and/or who is on dialysis;

7. History of abnormal bleeding and/or coagulopathy
8. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
9. Active or suspected acute or chronic uncontrolled infection
10. History of immunocompromise including those who are HIV positive.
11. History of intracranial hemorrhage
12. Cerebrovascular disease (multiple CVA or CVA within 6 months)
13. Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).
14. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment. (can be up to 4 hrs of total table time.)
15. Are participating or have participated in another clinical trial in the last 30 days
16. Significant claustrophobia that cannot be managed with mild medication.
17. Subjects unable to communicate with the investigator and staff.
18. Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
19. Anyone suspected to have the diagnosis of idiopathic Parkinson's disease. Anyone with the presence of parkinsonian features including bradykinesia, rigidity, or postural instability will be excluded. Subjects who exhibit only mild resting tremor but no other symptoms or signs of PD may be included.
20. Presence of significant cognitive impairment as determined with a score ≤ 24 on the Mini Mental Status Examination (MMSE)
21. Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
22. Subjects with a history of seizures within the past year
23. Subjects with presence or history of psychosis will be excluded. Subjects with significant or active mood disorders including depression will be excluded. For the purpose of this study, we consider a significant mood disorder to include any subject who:
    a) Scores ≥ 20 on the PHQ-9 questionnaire
    b) Is currently under the care of a psychiatrist
    c) Is currently participating in cognitive-behavioral therapy
    d) Has been hospitalized for the treatment of a psychiatric illness within 12 months
    e) Has ever received transcranial magnetic stimulation
    f) Has ever received electroconvulsive therapy

24. Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimeter, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
25. Subjects with brain tumors
26. Any illness that in the investigator's opinion preclude participation in this study.
27. Pregnancy or lactation.
28. Legal incapacity or limited legal capacity.
29. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
30. Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
31. Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening CT.

3.1.2 Patient Treatment

Patients who were randomized to sham treatment underwent a sham Exablate treatment with the sonication energy output disabled. The entire procedure was to last only approximately 45 minutes.

Patients randomized to active treatment underwent pre-treatment planning. Any patient deemed not to have a device accessible lesion was considered a screen failure and was exited from the study. If the subject remained eligible, i.e., the lesion was device accessible, the patient had the planned treatment.

3.1.3 Study Follow Up

All participating patients were consented for 5 years. Both active and sham treatment patients were seen for follow-up at 1-day, 1 week and 1, and 3 months, at which time all patients were un-blinded for primary endpoint analyses. Subjects were evaluated for general health, efficacy measurements as well as for device/procedure related AEs that occurred during the follow-up period.

Following the Month-3 visit, study subjects in both arms were first evaluated per study requirements, and then unblinded. The Exablate Arm subjects continued with their planned long-term follow up that included 6-month and 12 months follow ups, followed with 2, 3, 4, and 5 years planned follow up visits. The Sham Arm subjects were permitted to opt for a cross-over treatment with the Exablate. All the cross-over subjects will be followed up in the same manner as the active treatment group.

Analyses of the Primary endpoint were performed at 3 months and 12 months follow-up for the active Exablate Arm subjects.

provides the full schedule of evaluations in the study.

TABLE 1: SUMMARY OF STUDY SCHEDULE AND MEASUREMENTS									
	SCREENING	BASELINE ASSESSMENT	TREATMENT	1 DAY	1 WEEK	1 MONTH	3 MONTH	6 MONTH	12 MONTH
CONSENT	X								
ELIGIBILITY EVALUATION WITH LABS	X	X							
MEDICATIONS	X	X	X	X	X	X	X	X	X
30 DAY MEDS STABILIZATION		X							
MEDICAL HISTORY	X								
PHYSICAL EXAM	X	X		X	X	X	X	X	X
NEUROLOGICAL STATUS	X		X	X	X	X	X	X	X
CRST (UNBLINDED)	X							X	X
SITE BLINDED ASSESSOR CRST		X				X	X		
BLINDED TREMOR CORE LAB CRST		X				X	X	X	X
QOL (QUEST)	X	X				X	X	X	X
PHQ-9	X					X	X	X	X
CT	X								
MR		X	X						X
TREATMENT			X						
ADVERSE EVENTS			X	X	X	X	X	X	X
EXIT FORM									X

3.1.4 Study Endpoints

Safety Endpoint

The safety of the Exablate was determined by an evaluation of the incidence and severity of device-related adverse events and serious adverse events from treatment day through the Month 12 post-treatment time point.

Primary Effectiveness Endpoint

The Primary Effectiveness (PE) was evaluated using a validated, tremor rating scale: the Clinical Rating Scale for Tremors (CRST) for ET subjects, based upon subjects in whom unilateral Exablate lesioning is attempted (i.e., Intent-to-Treat analysis; "ITT"). The specific study hypothesis was as follows:

At 3-months post-treatment, the treated (contralateral) upper limb CRST subscore (CRST Part-A & B applicable to upper limb) in the Exablate -treated group will be statistically lower compared to that in the Exablate sham-treated control group.

This primary endpoint (PE) is comparing the percent improvement (between Month 3 and Baseline) of the CRST score between Study groups:

PE =% Improvement = (〖CRST_ [contralateral, Baseline] - 〖CRST〗_ [contralateral, 3 month FU])/ 〖CRST〗_ [contralateral, Baseline] x 100

Where the CRST score implemented for this study is the average of 8 components, combining the 3-components of the tremor CRST Part-A with the 5-components of the Motor Functions of the CRST Part-B from the treated side of the body:

〖CRST〗_[Contralateral] = (PART_(_A) + PART_B)/(Max Score)

- **Part A** = Rest + **Posture** + Action/Intention
- **Part B** = **all** 5 motor functions:

Writing + Drawing A (large spiral) + Drawing B (small spiral) + Drawing C (straight lines) + Pouring (transfer of water between 2 glasses).

The primary efficacy endpoint in this study is referred to hereinafter as the "Composite Tremor/Motor Function Score".

Hence, this PE characterizes the impact of Essential Tremor on the "clinical disability" level of an ET patient. The robustness of this matrix parameter is further enhanced by the fact that it undergoes a normalization procedure allowing a true comparison between patients. Hence, this combined **"Composite Tremor/Motor Function"** score, i.e., study PE, is a robust measure of the impact of Essential Tremor in the subject's life.

Secondary Effectiveness Endpoint

The secondary endpoints of the study are as follows:

1. Quality life claims: Questionnaire for Essential Tremor (QUEST) outcome (upper extremity questions) at Months 3 change from Baseline as compared between treatment groups
2. Durability (as measured by CRST upper arm extremity questions) of the procedure as reflected by the efficacy data through change from baseline measures through Month 12 follow up
3. Subject daily functionalities: as measured by CRST Part-C (subscales) Month 12 as compared to Baseline, and between treatment groups through Month 3.
4. Crossover cohort treatment outcome (perform 1-3 as above for the Crossover cohort)

3.1.5 Study Statistical Analysis Plan and Analysis Population

3.1.5.1 Study Sample Size

The study was approved for a minimum of 72 and a maximum of 80 randomized subjects in a 3:1 (Exablate: Sham control) ratio at up to 8 sites. This minimum sample size provides a 20% increase due to potential subject dropout from the below rationale for 60 evaluable subjects.

The rational for this sample size is based upon the observation from the pilot study of a sample size of 15 of a 78% drop in Total CRST from a mean of 20.4 to 4.7 while the untreated sample dropped 4%. Based upon these data, the power to detect a change in the treated vs sham control is greater than 99% with a sample size of 60 subjects. In the crossover paired comparison, the power also is greater than 99%.

In order to detect the occurrence of side effects with at least a 5% frequency, the sample size was selected. With the proposed study design a total of 60 subjects would be expected have safety data. With 45 subjects the probability of observing an event rate of 5% is 0.95 for the 60 subjects total, 0.90 for 45 subjects (treated vs control arm) and is 0.52 for the 15 subjects in the crossover arm. The probability of observing an event rate of 0.01 is 45% with 60 subjects.

The additional 8 subjects above 72 was requested in order to accommodate treatment of subjects who had undergone the extensive screening and baseline evaluations from confirmation of eligibility to scheduling treatment within the center based upon availability of MR time.

NOTE:

It should be noted that a score of one represents the worst case scenario, whereas the score of “zero” represents the best case scenario in the Essential Tremor impact on the subject’s life. An improvement in the combined Tremor/Motor Function matrix at follow-up will reflect scores with decreasing values.

3.1.5.2 Study Analysis Population

The following analysis populations were used to evaluate study results:

Intent to Treat (ITT)

The ITT analysis population included all Safety subjects (subjects with at least one sonication in either the Exablate or the Sham arm) for whom there exist valid baseline measurement and at least one post-baseline measurement on the primary efficacy data. The Crossover population is not included in the ITT population.

Per Protocol (PP)

The PP analysis population included all ITT subjects who have observed primary efficacy data at three months and have no major protocol violations likely to affect outcome. The Crossover population is not included in the PP population.

Crossover Analysis Population

The Crossover analysis population included all subjects who received at least one sonication in the Crossover stage of the study.

3.1.6 Study Subject Accountability

At the time of database lock, of the 121 patients enrolled in the PMA study, 33 were screen failures and 7 declined to participate prior to randomization. An additional 5 subjects were screening failures after randomization. Thus, 76 subjects received treatment (i.e. Exablate or sham), of which 74 (97.4%) completed follow-up through the primary endpoint (Month 3) and that data is available for analysis. Two Exablate subjects who withdrew prior to the Month 3 follow-up visit did so for reasons unrelated to their participation in the study. All 20 Sham subjects completed the primary end point visit.

As discussed above, the Exablate subjects were scheduled for follow-up visits at Month 6 and Month 12 post-treatment. Three Exablate subjects withdrew from the study following the Month 3 follow-up visit due to: 1) one subject chose to have DBS treatment; 2) the other 2 subjects withdrew for personal reasons unrelated to the study. In addition, 2 other Exablate subjects were moved to the Crossover study, which is discussed in more detail below. Thus, 49 (49/56 = 88%) Exablate subjects continued, un-blinded, in their original treatment arm after the primary endpoint was assessed. Currently, 48 (48/56 = 86%) Exablate subjects have completed their Month 6 follow-up visit and 49 (49/56 = 88%) Exablate subjects have completed their Month 12 follow-up visit

At the Month 3 follow-up visit, Sham subjects were given the option of crossing over to the Exablate treatment if they still met the enrollment criteria. Of the 20 Sham subjects, 19 became Crossover subjects. One Sham subject was undecided for several months, then withdrew from the study. In addition, as stated above, 2 non-responding Exablate subjects were placed in the Crossover group and re-treated with Exablate with FDA's permission. Thus, the Crossover portion of the study, which was un-blinded, had 21 subjects. Of the Crossover subjects, 21 out of 21 (100%) have completed their follow up visits through Month 6. Through September 30, 2015, 9 out of the 21 subjects have completed their Month 12 follow up visit. The other 12 subjects have not yet reached their Month-12 follow up visit as of September 30, 2015.

A subject accountability **TABLE 2** and study flowchart (**Figure 1**) are provided below.

TABLE 2: PATIENT DISPOSITION BY TREATMENT GROUP AND SCHEDULED VISIT

CATEGORY	BASELINE		1 MONTH FU		3 MONTHS FU		6 MONTHS FU	12 MONTHS FU
	EXABLATE	SHAM	EXABLATE	SHAM	EXABLATE	SHAM	EXABLATE	EXABLATE
Recruited	121							
SF 1[1]	33							
Discontinued for Reasons Other than SF (not yet randomized)	7							
Randomized[2]	61	20						
SF 2[3]	5	0						
Theoretical[4]	56	20	56	20	56	20	56	56
Death	0	0	0	0	0	0	0	0
Failure[5]	0	0	0	0	0	0	1	1
Exited –Other Reasons[6]	0	0	0	0	2	0	4	6
Expected[7]	56	20	56	20	54	20	51	49
Actual[8]	56	20	56	20	54	20	48	49
Actual %[9]	100%	100%	100%	100%	100%	100%	94%	100%

[1] SF 1 – Those subjects Recruited, but not meeting enrollment criteria

[2]Randomized equals those Recruited minus SF 1 minus Discontinued for Reasons Other than SF (not yet randomized)

[3]SF 2 – Randomized subjects who have not received any sonication and did not meet inclusion/exclusion criteria

[4]Theoretical is equal to the number of subjects Recruited minus SF 1 minus Discontinued for Reasons Other than SF minus SF 2. Therefore, theoretical is equal to the number of subjects eligible to receive treatment in either group

[5]Failures include any subjects (Exablate or Sham) who discontinued the study due to beginning another treatment for their condition

[6]Exited the Main Analysis for reasons other than Failure

[7]Expected equals Theoretical minus Exited-Other Reasons minus Failures minus Death

[8]Actual is the number of subjects actually returning for the follow-up visit

[9]Actual % is the number of Actual subjects divided by Expected

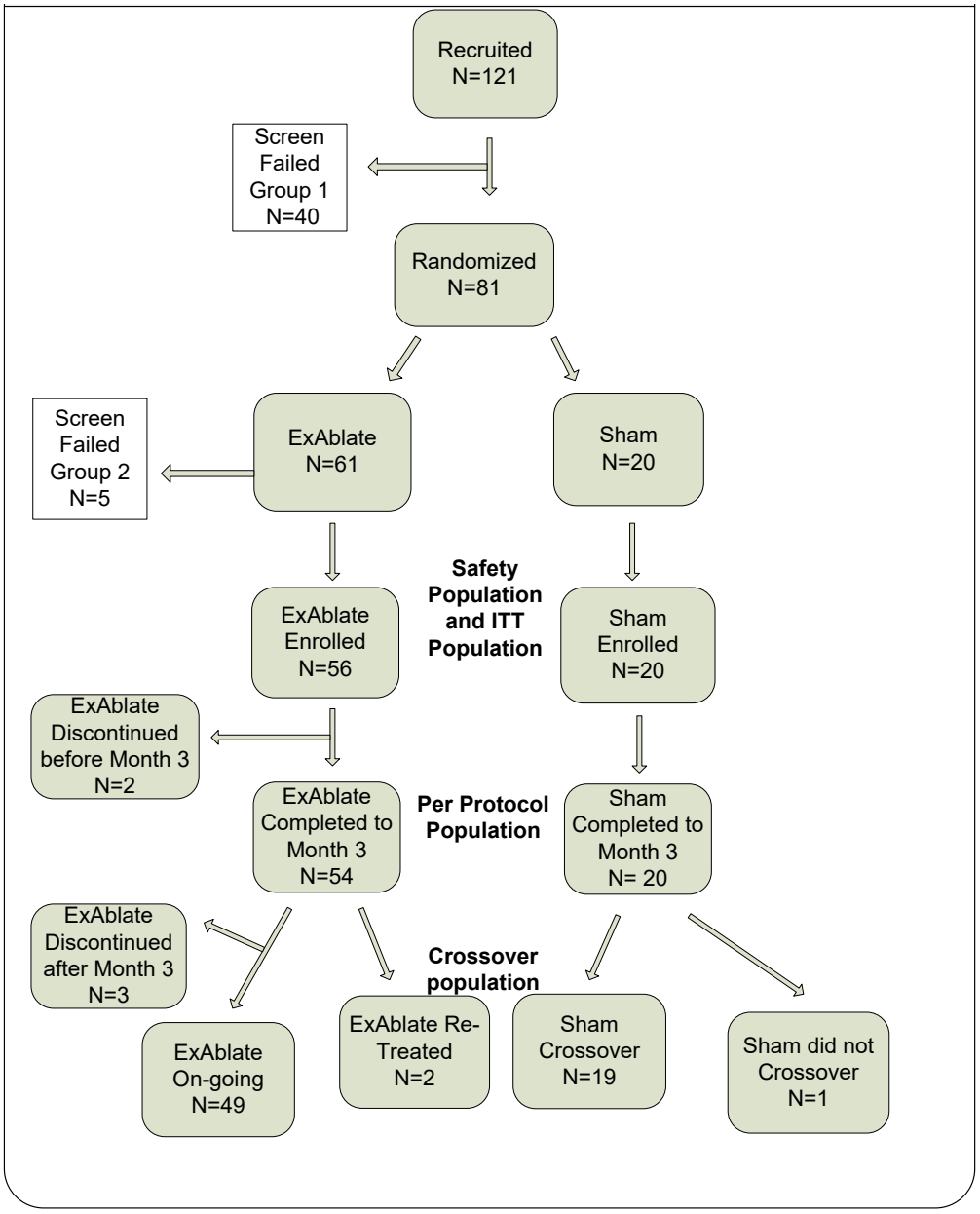

Figure 1: ET002 Study Flow Chart

3.1.7 Study Demographics and Baseline Characteristics

The demographics of the study population are typical for an Essential Tremor study performed in the United States. The demographics, baseline, and operative characteristics were similar between the two treatment groups, as shown in **TABLE 3** below.

TABLE 3: BASELINE AND DEMOGRAPHIC INFORMATION BY TREATMENT GROUP

DEMOGRAPHIC CHARACTERISTICS		TREATMENT GROUP	
		EXABLATE N=56	SHAM N=20
Age [Years]	Mean	70.8	71.4
BMI [kg/m²]	Mean	26.9	27.9
Height [cm]	Mean	171.9	173.3
Weight [kg]	Mean	79.6	85.5
Gender	Male	37 (66%)	15 (75%)
	Female	19 (34%)	5 (25%)
Race	Caucasian	41 (73%)	16 (80%)
	African-American	0	0
	Asian	14 (25%)	4 (20%)
	Hispanic	0	0
	Other	1 (2%)	0
Family History of ET	Yes	39 (70%)	16 (80%)
	No	17 (30%)	4 (20%)
Average Years ET History (yrs)	Mean	13.9	14.7
Skull Density Ratio "SDR"	Mean	0.6	0.5
Treated (Contralateral UE CRST Primary Endpoint Subscore	Mean	0.57	0.51
QUEST Summary of Dimensions Total Score*	Mean	42.55	42.76
Functional Disabilities CRST Part C Total Score	Mean	2.07	2.01

Note: None of the above baseline/demographic characteristics showed statistical differences between treatment groups.

*Quest is missing at Baseline for one Sham subject, so N = 19.

3.2 Study Results

3.2.1 Safety Results

The analysis of safety was based on the ITT/Safety Population cohort of 76 subjects (56 Exablate subjects and 20 Sham subjects), available through the Month 12 evaluation. Note that the Sham subjects' AE data was only collected out to the Month 3 follow-up visit (i.e., primary endpoint), after which all Sham subject either crossed over to the Exablate treatment or withdrew. Thus, **TABLE 5** below reflects data through the Month 12 follow-up visit for the Exablate group and data through the Month 3 follow-up visit for Sham group.

Table 8 below shows the prevalence of AEs, with post-treatment onset reported on or before the Month 3 visit, by duration and onset for the Exablate and Sham groups.

A total of 210 AEs in 76 subjects were reported in this study, 209 (99.5%) of which were either Mild or Moderate. There was also 1 (0.5%) unrelated Severe event. Of all these events, there were only 2 serious events reported: one was an Unrelated Transient Ischemia Attack "TIA" (severe) and one was related to the Thalamotomy procedure (moderate). The breakdown of these events per study group is described below.

In the Exablate group, 184 AEs were reported by 49 Exablate subjects: 137 (74%) of these events were Mild, and 46 (25%) were Moderate. Seven Exablate subjects reported no AEs. There were no reports of device or procedure-related severe events or deaths.

In the Sham group, which underwent all the procedural preparations including shave, head frame, catheter and I.V., a total of 26 AEs in 14 subjects were reported, and all (100%) of them were Mild or Moderate: 18 (70%) of these events were Mild, and 8 (30%) were Moderate. Thus, 6 subjects in the Sham group reported no AEs.

AEs are reported in **TABLE 4** and **TABLE 6** below. See **TABLE 4** for a summary of safety by severity between groups.

TABLE 4: SUMMARY OF SAFETY (ADVERSE EVENTS) BETWEEN GROUPS BY SEVERITY

SEVERITY OF AE	EXABLATE		SHAM	
	FREQUENCY N=184	INCIDENCE N=56	FREQUENCY N=26	INCIDENCE N=20
Mild	137 (74.4%)	46 (82%)	18 (70%)	10 (50%)
Moderate	45 (24.4%)	27 (48%)	8 (30%)	6 (30%)
Thalamotomy Related SAE	1 (0.6%)	1 (2%)	0 (0%)	0 (0%)
Severe				
Unrelated SAE	1 (0.6%)	1 (2%)	0 (0%)	0 (0%)
Total	184 (100%)	49 (88%)	26 (100%)	14 (70%)

Two adverse events were reported as serious in the Main Analysis (**TABLE 5**). In this study, there were 2 AEs that met the definition of SAE as per FDA regulation. Both occurred in the Exablate group. Both were reviewed by the DSMB and adjudicated, and FDA was notified of the occurrence of these events. The second Exablate subject experienced an embolic peripheral cortical stroke likely due to left carotid artery disease or a cardiac event. The stroke specialist, the treating physician, and the DSMB concurred that the event was unrelated to Exablate and not due to the study intervention

- One event recorded as starting post-procedure that was moderate (Numbness/tingling) was elevated to the status of an SAE at Month 3 because the Numbness/tingling interfered with his ability to hold a pen and write at work (i.e., physical impairment). Worst severity was always Moderate. The DSMB adjudicated the event and agreed that it was thalamotomy-related.
- The other SAE that was a Transient Ischemia Attack (TIA) that occurred 6 weeks after the procedure and was deemed Unrelated to the Exablate procedure. Due to the potential nature of event, it was captured as a severe event, but the patient was treated early with no sequelae. The experienced an embolic peripheral cortical stroke likely due to left carotid artery disease or a cardiac event. The stroke specialist, the treating physician, and the DSMB concurred that the event was unrelated to Exablate and not due to the study intervention.

TABLE 5. SERIOUS ADVERSE EVENTS BY RELATION AND TREATMENT ARM

SERIOUS ADVERSE EVENTS (SAEs)	EXABLATE		SHAM	
	FREQUENCY N=184	INCIDENCE N=56	FREQUENCY N=26	INCIDENCE N=20
Thalamotomy Related	1 (0.6%)	1(2%)	0 (0%)	0 (0%)
Unrelated	1 (0.6%)	1(2%)	0 (0%)	0 (0%)
Total SAE's	2 (1.2%)	2 (4%)	0 (0%)	0 (0%)

The frequency and incidence of all adverse events is presented by treatment group and severity and by body system and coded term in .

TABLE 6: FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP AND SEVERITY											
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS) = 184; # PTS = 56)						SHAM (N EVENTS = 26; # PTS = 20)			
		MILD		MODERATE		SEVERE		MILD		MODERATE	
		FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)
Cardiovascular	Bradycardia	1 (0.5%)	1 (2%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Hypertension	1 (0.5%)	1 (2%)	4 (2%)	4 (7%)	0	0	0	0	1 (4%)	1 (5%)
	Hypotension	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	TIA	0	0	0	0	1 (0.5%)	1 (2%)	0	0	0	0
ENT	Tinnitus	3 (2%)	3 (5%)	0	0	0	0	0	0	0	0
Eye	Vision problems	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Watering Eyes	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
Gastrointestinal	Dysphagia	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Increased salivation	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Nausea/Vomiting	6 (3%)	6 (11%)	7 (4%)	7 (13%)	0	0	2 (8%)	2 (10%)	0	0
General	Fatigue	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Generalized Weakness	0	0	1 (0.5%)	1 (2%)	0	0	1 (4%)	1 (5%)	0	0
	Impatience	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Restlessness	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
Infection	Common Cold	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Ear Infection	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
Musculoskeletal	Gait Disturbance	2 (1 %)	2 (4%)	2 (1%)	2 (4%)	0	0	0	0	0	0
	Dysergia	1 (0.5%)	1 (2%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0

TABLE 6: FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP AND SEVERITY											
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS) = 184; # PTS = 56)						SHAM (N EVENTS = 26; # PTS = 20)			
		MILD		MODERATE		SEVERE		MILD		MODERATE	
		FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)
	Imbalance	7 (4%)	7 (13%)	3 (2%)	3 (5%)	0	0	1 (4%)	1 (5%)	0	0
	Musculoskeletal Weakness	1 (0.5%)	1 (2%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Other Musculoskeletal Pain	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Positional Pain	5 (3%)	5 (9%)	0	0	0	0	1 (4%)	1 (5%)	0	0
	Unsteady	5 (3%)	5 (5%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0
Nervous	Anxiety	2 (1%)	2 (4%)	0	0	0	0	1 (4%)	1 (5%)	1 (4%)	1 (5%)
	Ataxia	6 (3%)	6 (11%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Dizziness	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Dysesthesia	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Dysgeusia	3 (2%)	2 (2%)	0	0	0	0	0	0	0	0
	Dysgnosia	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Dysmetria	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Involuntary Movements-UE	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0

TABLE 6: FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP AND SEVERITY											
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS) = 184; # PTS = 56)						SHAM (N EVENTS = 26; # PTS = 20)			
		MILD		MODERATE		SEVERE		MILD		MODERATE	
		FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)
	Memory Deterioration	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Numbness/Tingling	24 (13%)	16 (29%)	3 (2%)	2 (4%)	0	0	2 (8%)	2 (10%)	1 (4%)	1 (5%)
	Slurred speech	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Paresthesia	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Somnolence	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
Pain/Discomfort	Ankle pain	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Foot pain	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Headache	10 (5%)	9 (16%)	5 (3%)	5 (9%)	0	0	4 (15%)	4 (20%)	1 (4%)	1 (5%)
	Sonication-related Head pain	7 (4%)	7 (13%)	7 (4%)	7 (13%)	0	0	0	0	0	0
Respiratory	Hiccups	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
Skin	Bruising	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Skin Rash	1 (0.5%)	1 (2%)	0	0	0	0	0	0	1 (4%)	1 (5%)
Stereotactic Frame	Eyelid Ptosis	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Facial edema	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Numbness/Tingling	1 (0.5%)	1 (2%)	0	0	0	0	1 (4%)	1 (5%)	1 (4%)	1 (5%)
	Bruising – Stereotactic Frame	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Pin Site Edema	1 (0.5%)	1 (2%)	0	0	0	0	1 (4%)	1 (5%)	1 (4%)	1 (5%)

TABLE 6: FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP AND SEVERITY											
BODY SYSTEM	**PREFERRED TERM**	**EXABLATE (N EVENTS) = 184; # PTS = 56)**						**SHAM (N EVENTS = 26; # PTS = 20)**			
		MILD		**MODERATE**		**SEVERE**		**MILD**		**MODERATE**	
		FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)	FREQ N (%)	INCIDENCE # (%)
	Pin Site Abrasion	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Pin site bleeding	0	0	0	0	0	0	0	0	1 (4%)	1 (5%)
	Pin site pain	7 (4%)	7 (13%)	1 (0.5%)	1 (2%)	0	0	4 (15%)	3 (15%)	0	0
Urinary	Catheter Irritation	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	Urinary Urgency	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
	BHP	0	0	1 (0.5%)	1 (2%)	0	0	0	0	0	0
Vestibular Disorder	Vertigo	2 (1%)	2 (4%)	0	0	0	0	0	0	0	0
	Dizziness	11 (6%)	10 (18%)	0	0	0	0	0	0	0	0
	Paroxysmal Vertigo Episodes	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
Vision	Vision change	1 (0.5%)	1 (2%)	0	0	0	0	0	0	0	0
TOTAL		**137 (74%)**	**46 (82%)**	**46 (25%)**	**28 (50%)**	**1 (0.5%)**	**1 (2%)**	**18 (69%)**	**19 (50%)**	**8 (31%)**	**6 (30%)**

As shown in **TABLE 7**, the majority (89% Exablate; 96% Sham) of all events begin within 30 days of the procedure and nearly all resolved.

TABLE 7: ADVERSE EVENTS ONSET VERSUS ADVERSE EVENTS DURATION BY TREATMENT GROUP

ONSET/ DURATION	EXABLATE			SHAM		
	ONSET < 30 DAYS	ONSET 31-90 DAYS	ONSET > 90 DAYS	ONSET < 30 DAYS	ONSET 31-90 DAYS	ONSET > 90 DAYS
	FREQ N=184	FREQ N=184	FREQ N=184	FREQ N=27	FREQ N=27	FREQ N=27
<30 days	88 (48%)	2 (1%)	4 (2%)	24 (92%)	0	0
31-90 days	14 (8%)	2 (1%)	1 (1%)	2 (8%)	0	0
> 90 days	25 (14%)	2 (1%)	4 (2%)	0	0	0
Ongoing	35 (20%)	2 (1%)	5 (3%)	0	0	0
TOTAL	162 (88%)	8 (4%)	14 (8%)	26 (100%)	0	0

The safety profile indicates, as expected, that adverse events related to the device, procedure or thalamotomy are observed shortly after the procedure and mostly resolved within 30 days of the procedure.

Adverse events were categorized by relation into groups. Out of the 184 AEs in the Exablate group, 53 (29%) events were categorized as Transient (i.e., resolved right after the sonication or same day up to 3 days post-procedure) and 57 (31%) AEs were determined to be Unrelated to the study.

TABLE 8 summarizes the Transient and Unrelated AEs by body system, coded term, and treatment arm.

TABLE 8: FREQUENCY OF EXABLATE ADVERSE EVENTS CATEGORIZED AS TRANSIENT OR UNRELATED TO EXABLATE

RELATION / BODY SYSTEM / AE CODED TERM			EXABLATE: N=184		SHAM: N=26	
			N	%	N	%
Transient Events	Gastrointestinal	Nausea/Vomiting	12	7%	2	8%
	Nervous	Anxiety	1	0.5%	2	8%
		Dysgnosia	1	0.5%	0	0%
		Dysgeusia	1	0.5%	0	0%
		Numbness/Tingling	4	2%	2	8%
	Pain/Discomfort	Headache	10	5%	4	15%
		Sonication-Related Head Pain	13	7%	0	0%
	Vestibular Disorder	Dizziness	9	5%	0	0%
		Vertigo	2	1%	0	0%
TRANSIENT SUBTOTAL			53	29%	10	39%
	Cardiovascular	Bradycardia	2	1%	0	0%

TABLE 8: FREQUENCY OF EXABLATE ADVERSE EVENTS CATEGORIZED AS TRANSIENT OR UNRELATED TO EXABLATE

RELATION / BODY SYSTEM / AE CODED TERM			EXABLATE: N=184		SHAM: N=26	
			N	%	N	%
Unrelated Events		Hypertension	5	3%	2	8%
		Hypotension	1	0.5%	0	0%
		TIA	1	0.5%	0	0%
	Eye	Vision Problem	1	0.5%	0	0%
		Watering Eyes	1	0.5%	0	0%
	Gastrointestinal	Increased Salivation/Drooling	1	0.5%	0	0%
		Nausea/Vomiting	1	0.5%	0	0%
	General	Impatience	1	0.5%	0	0%
		Restlessness	1	0.5%	0	0%
	Infection	Common Cold	1	0.5%	0	0%
		Ear Infection	1	0.5%	0	0%
	Musculoskeletal	Other Musculoskeletal Pain	1	50.5%	0	0%
		Positional Pain	5	2.7%	0	0%
		Unsteady	2	1.1%	0	0%
	Nervous	Anxiety	1	0.5%	0	0%
		Dizziness	1	0.5%	0	0%
		Dysgeusia	1	0.5%	0	0%
		Involuntary Movements - UE	1	0.5%	0	0%
		Memory Deterioration	1	0.5%	0	0%
		Somnolence	1	0.5%	0	0%
	Pain/Discomfort	Positional pain	2	1%	1	4%
		Ankle pain	1	0.5%	0	0%
		Foot pain	1	0.5%	0	0%
	Respiratory	Hiccups	1	0.5%	0	0%
	Skin	Bruising	1	0.5%	0	0%
		Skin Rash	1	0.5%	1	4%
	Stereotactic Frame	Bruising - Stereotactic Frame	1	0.5%	0	0%

TABLE 8: FREQUENCY OF EXABLATE ADVERSE EVENTS CATEGORIZED AS TRANSIENT OR UNRELATED TO EXABLATE						
RELATION / BODY SYSTEM / AE CODED TERM			EXABLATE: N=184		SHAM: N=26	
			N	%	N	%
		Eyelid Ptosis	2	1.1%	0	0%
		Facial edema	1	0.5%	0	0%
		Numbness/Tingling	1	0.5%	2	8%
		Pin Site Abrasion	2	1.1%	0	0%
		Pin site bleeding	0	0.0%	1	4%
		Pin Site Edema	1	0.5%	1	0%
		Pin Site Pain	8	4.3%	5	29%
	Urinary	Catheter Irritation	1	0.5%	0	0%
		Urinary Urgency	1	0.5%	0	0%
	Urogenital	Benign Prostate Hypertrophy	1	0.5%	0	0%
SUBTOTAL UNRELATED			57	31%	13	50%
TOTAL			110	60%	23	88.5%

The remaining events were categorized into Procedure-related and Thalamotomy-related categories (TABLE 9). Of the AEs that resolved, resolution generally occurred within 1 week to 3 months. AEs categorized as Procedure-related (e.g., fatigue, weakness, headache, and sonication-related head pain) are rather minor, but lasted longer than 3 days. Other AEs listed as Thalamotomy-related are similar to the types of events that have been reported in the literature as accompanying radiofrequency lesioning. AEs with the greatest frequency were numbness/tingling (22; 12%), imbalance (10; 5%), unsteady (4; 2%), and gait disturbance (4, 2%). These events are usually coincident with thalamotomy as reported in the literature.

TABLE 9: FREQUENCY OF ADVERSE EVENTS CATEGORIZED AS RELATED TO THE PROCEDURE/ DEVICE/ THALAMOTOMY						
RELATION/BODY SYSTEM, AE CODED TERM			EXABLATE ARM N=184		SHAM ARM N=26	
			N	%	N	%
Procedure-related	ENT	Tinnitus	3	2%	1	0%
	Gastrointestinal	Dysphagia	1	0.5%	0	0%
	General	Fatigue	2	1%	0	0%
		Generalized Weakness	1	0.5%	1	4%
	Musculoskeletal	Imbalance	0	0%	1	4%
	Nervous	Dysgnosia	1	0.5%	0	0%
		Numbness/ Tingling	1	0.5%	0	0%
	Pain/Discomfort	Headache	5	3%	0	0%
		Sonication-Related Head Pain	1	0.5%	0	0%
	Vestibular Disorder	Dizziness	1	0.5%	0	0%
Thalamotomy related	Musculoskeletal	Dysergia	2	1%	0	0%
		Gait Disturbance	4	2%	0	0%
		Imbalance	10	5%	0	0%
		Musculoskeletal Weakness	2	1.1%	0	0%
		Unsteady	4	2.2%	0	0%
	Nervous	Ataxia	7	3.8%	0	0%
		Dysesthesia	1	0.5%	0	0%

TABLE 9: FREQUENCY OF ADVERSE EVENTS CATEGORIZED AS RELATED TO THE PROCEDURE/ DEVICE/ THALAMOTOMY						
RELATION/BODY SYSTEM, AE CODED TERM			EXABLATE ARM N=184		SHAM ARM N=26	
			N	%	N	%
		Dysgeusia	1	0.5%	0	0%
		Dysmetria	2	1.1%	0	0%
		Numbness/ Tingling	22	12%	0	0%
		Paresthesia	1	0.5%	0	0%
		Slurred Speech	1	0.5%	0	0%
TOTAL			74	100%	3	12%

3.2.1.1 Mental Status Assessment - PHQ-9

An additional safety measure that was captured in this study was mental status of patients using the PHQ-9 for depression. Per protocol, subjects with a score of 20 or higher were excluded until their depression was managed. Any subject who scored a 20 or more on follow-up was to be referred out for psychiatric evaluation and treatment. Any treatment beyond medication would be counted as a SAE. The follow-up PHQ-9 scores show no study subject scoring a 20 or higher on the PHQ-9 ( ) at any time during the study. This outcome indicates that the Exablate treatment does not induce depression.

TABLE 10: FREQUENCY DISTRIBUTION OF PHQ9 EXAM RESULTS (SAFETY)								
VISIT	TOTAL SCORE OF PHQ9 TESTS ABOVE 20							
	EXABLATE				SHAM			
	YES		NO		YES		NO	
	N	%	N	%	N	%	N	%
Screening	0	0.0	56	100.0	0	0.0	18	100.0
1 Month FU	0	0.0	56	100.0	0	0.0	20	100.0
3 Months FU	0	0.0	54	100.0	0	0.0	20	100.0
6 Months FU	0	0.0	47	100.0	0	0	0	0
12 Months FU	0	0.0	34	100.0	0	0	0	0

3.2.2 Effectiveness Results

The primary analysis of effectiveness was based on the ITT population, i.e., the 76 evaluable subjects at the Month 3 time point, while some secondary efficacy endpoints continued to Month 12. Key effectiveness outcomes are presented in **TABLE 11** to **TABLE 15**.

Follow-up for all subjects was performed at Day 1 (prior to discharge), Week 1, and Months 1, 3, 6, and 12, per the schedule of events.

Efficacy analyses are presented below on the analysis populations described above. The primary efficacy endpoint is presented first with the secondary confirmatory efficacy endpoints and additional secondary endpoints following.

3.2.2.1 Primary Endpoint

As shown in **TABLE 11**, the Exablate group demonstrated nearly a 50% improvement in the Composite Tremor/Motor Function score compared to baseline, while the Sham group demonstrated virtually no improvement to slight worsening by Month 3. This difference in the percent change between treatment groups was highly significant (46.9% versus -0.1%, $p<0.001$). Hence, this demonstrates that the Composite Tremor/Motor Function Primary Endpoint was successfully met.

TABLE 11: PRIMARY ENDPOINT (COMPOSITE TREMOR/MOTOR SCORE): MEAN SCORE AND PERCENT CHANGE FROM BASELINE AT THREE MONTHS BY TREATMENT GROUP (ITT)					
PE	TREATMENT GROUP				P-VALUE*
	EXABLATE: N =56		SHAM: N = 20		
	MEAN SCORE	% CHANGE	MEAN SCORE	% CHANGE	
ITT Mean	0.30	46.9%	0.50	-0.1%	<0.001
Lower 95% CI		40.3%		-9.6%	
Upper 95% CI		53.5%		9.5%	
1. SE1 was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher SE1 values represent improvement *p-value reflects testing between groups.					

3.2.2.2. Confirmatory Secondary Endpoints Safety Results

3.2.2.2.1. PE Calculation (Composite Tremor/Motor Function Score) as Compared to Exablate Baseline through Month 12

PE Composite Tremor/Motor Function Score was recorded through Month 12 to assess the treatment response over time. As shown in **TABLE 12** below the mean difference between baseline and each scheduled visit was highly significant ($p<0.001$) through the Month 12 visit. This demonstrates that the secondary endpoint involving the change in PE Composite score compared to baseline was successfully met through Month-12.

The data of **TABLE 12** is also presented in **Figure 2.**

TABLE 12: CONFIRMATORY ENDPOINT: PERCENT CHANGE IN THE COMPOSITE TREMOR/MOTOR FUNCTION IN EXABLATE ARM BY VISIT (ITT)			
VISIT		TREATMENT GROUP	P-VALUE*
	SE2	EXABLATE	
3 Months FU	Mean (%)	46.9	<0.001
	Lower 95% CI	40.3	
	Upper 95% CI	53.5	
	N	56	
6 Months FU	Mean (%)	43.1	<0.001
	Lower 95% CI	36.4	
	Upper 95% CI	49.9	
	N	56	
12 Months FU	Mean (%)	39.6	<0.001
	Lower 95% CI	34.0	
	Upper 95% CI	45.3	
	N	56	
Notes: 1. SE2 was calculated as Percent Change ({(Baseline - Visit)/Baseline}*100) 2. Higher SE2 values represent improvement *p-value reflects testing vs. baseline			

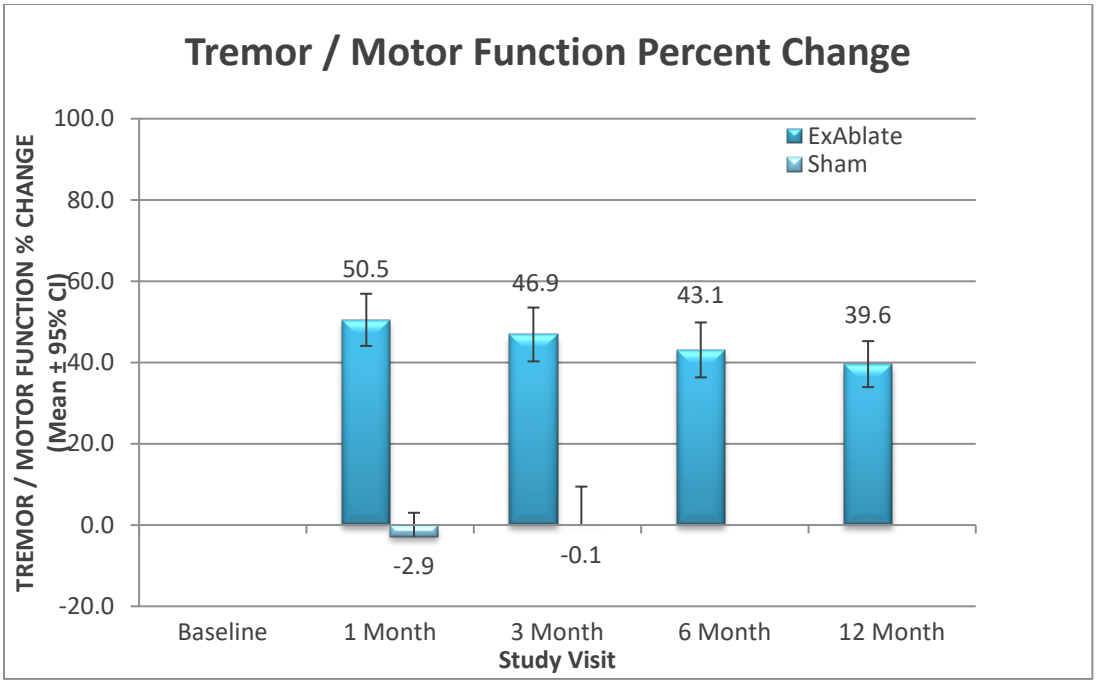

Figure 2: Tremor / Motor Function percent of change as defined by the Primary Endpoint of the study

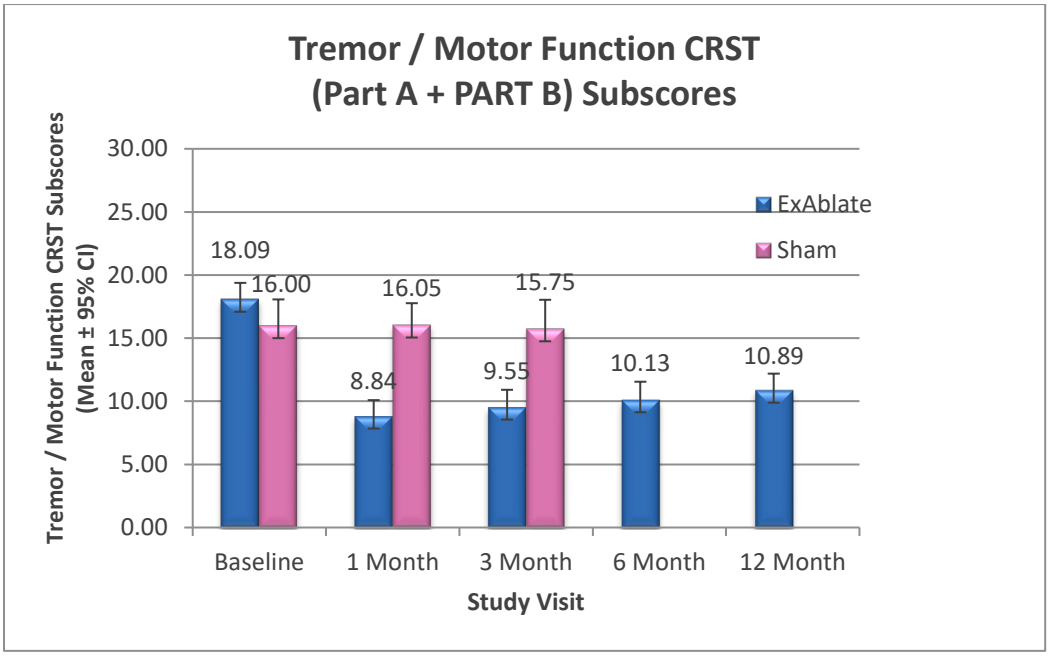

Figure 3: Tremor / Motor Function CRST Actual Subscore (Part A + Part B) through Month-12 for both Exablate and Sham study Arms. The maximum score of the 8-components of the CRST subscore is either 32 or 28 depending on the treated hand.

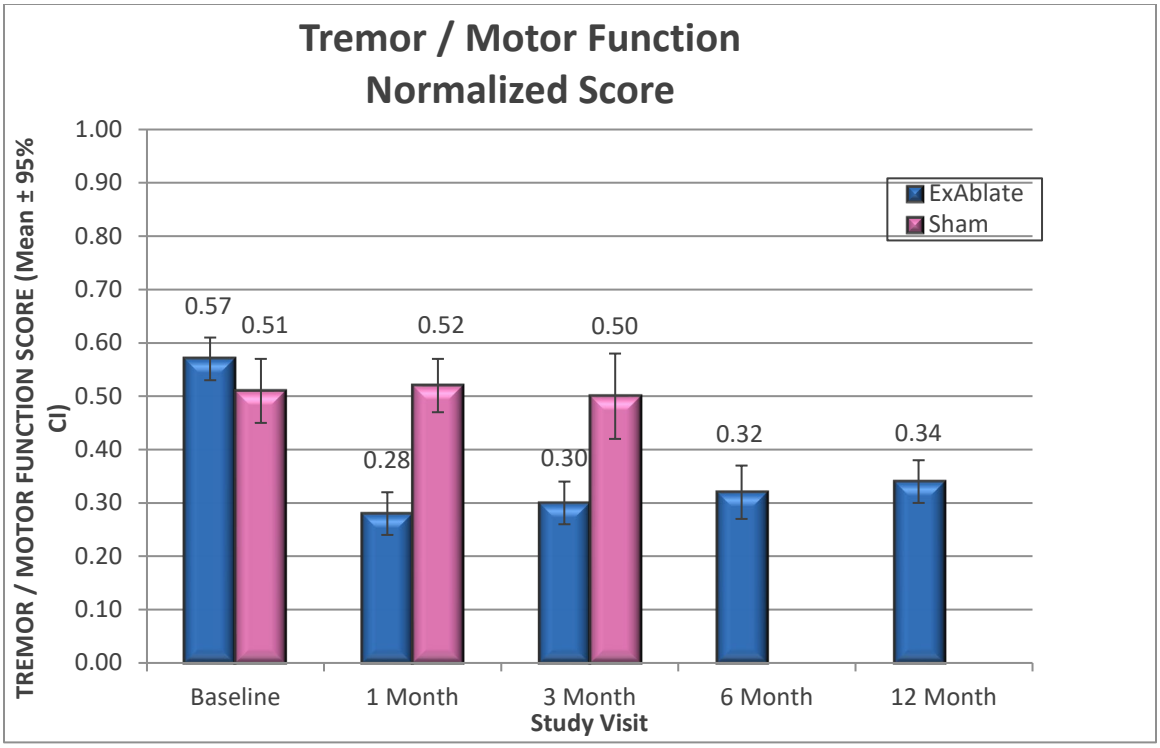

Figure 3 where the actual score is normalized by the maximum score of 32 or 28 depending on the treated (contra-lateral) Arm.

As discussed above, the PE of this study is a robust measure of Tremor "CRST-A" and Motor Functions "CRST-B" effects that characterize the impact of Essential Tremor on the clinical "disability" level of an ET patient. This PE reflects the average change in the combined "Tremor/Motor Function" of ET subjects.

By contrast, current and past literature as well as FDA PMA approvals often refer only to the "Tremor component of CRST-A" as the primary endpoint that reflects ET patient outcome following treatment with device (e.g. DBS) or medications. To enable a suitable comparison, this study "Posture" component of the CRST-A is presented below.

The percent change from baseline indicates that "Posture" improvement was 71.6%, 64.3%, 62.5%, and 65.5% at Months 1, 3, 6, and 12 respectively (**TABLE 13** and **Figure 4**).

TABLE 13: CRST PART A UPPER EXTREMITY, POSTURE COMPONENT ONLY FOR TREATED ARM BY TREATMENT GROUP BY VISIT THROUGH MONTH 12

CRST PART A POSTURE / VISIT			SCORE VALUES TREATED SIDE		CHANGE FROM BASELINE TREATED SIDE		EXABLATE % CHANGE FROM BASELINE[3]	SHAM % CHANGE FROM BASELINE[3]
			EXABLATE N=56	SHAM N=20	EXABLATE (N=56)	SHAM (N=20)		
Part A - Posture Only	Baseline	Mean	2.13	1.65				
		Lower 95% CI	1.82	1.08				
		Upper 95% CI	2.43	2.22				
	1 Month FU	Mean	0.50	1.55	1.63	0.10	71.6%	13.0% (n=16)
		Lower 95% CI	0.28	1.11	1.33	-0.35	61.3%	-6.09%
		Upper 95% CI	0.72	1.99	1.92	0.55	81.9%	32.4%
	3 Months FU[+]	Mean	0.64	1.85	1.48	-0.20	64.3%	-4.4% (n=17)
		Lower 95% CI	0.39	1.36	1.16	-0.69	52.1%	-27.0%
		Upper 95% CI	0.90	2.34	1.80	0.29	76.5%	18.2%
	6 Months FU	Mean	0.71		1.41		62.5% (n=52)	
		Lower 95% CI	0.44		1.08		50.8%	
		Upper 95% CI	0.99		1.74		74.2%	
	12 Months FU	Mean	0.68		1.45		65.5%	
		Lower 95% CI	0.42		1.14		54.7%	
		Upper 95% CI	0.94		1.76		76.3%	

Notes:

1. Change from Baseline was calculated as Percent Change (Baseline - Visit)
2. Higher Change from Baseline values represent improvement (lower score values are better than higher scores)
3 Calculated from means, not from individual subject scores.
[+]Between groups testing at Month 3 was statistically significant ($p<0.001$).
[++] Within groups testing for Exablate Arm as compared to Baseline was significant at all visits.

Figure 4 below shows the mean score value in the Exablate group compared to the Sham group that showed no improvement.

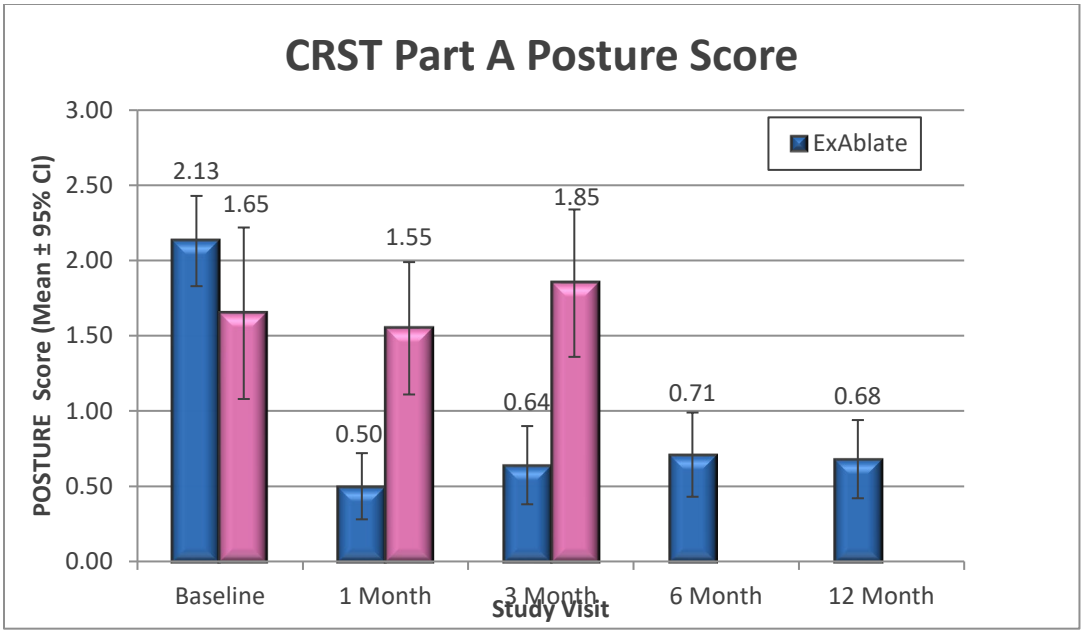

Figure 4: CRST Part a Posture Component Scores over Time and by Treatment Group.
[+]Between groups testing at Month 3 was statistically significant (p<0.001).
[++]Within groups testing for Exablate as compared to baseline was (p<0.001) at all visits.

3.2.2.2.2 CRST Part C Total Score

Overall CRST Part C total score for the percent improvement in functional disabilities was assessed at Month-3 as part of the study endpoints, and through Month-12 follow up. The Part C is another composite score encompassing speaking, eating, drinking, hygiene, dressing, writing, working and activities.

Part C Composite Functional Disabilities improvements from baseline, obtained at the Month 3 follow-up visit, are compared between treatment groups (**TABLE 14**). The Exablate treated group showed significant improvement (63.8%) as compared to the Sham-treated group (1.8%) at Month 3, which was statistically significant (p<0.001).

The Total Part C confirmatory endpoint was successfully met.

As shown in **TABLE 14**, the improvement in the subject overall Functional Disability (CRST Part-C) when compared to baseline was 64%, 62% and 64% at Months 3, 6 and 12, respectively (p<0.001). This improvement was observed across all Functional Disability components for Exablate -treated subjects. However, little/no change to slight worsening was observed in the Sham-treated group for all Functional Disabilities.

TABLE 14: CONFIRMATORY ENDPOINT - CRST PART C OVERALL FUNCTIONAL DISABILITIES SCORE/% CHANGE FROM BASELINE BY TREATMENT GROUP AND BY VISIT (ITT)

SE3	EXABLATE: N=56		SHAM: N=20		BETWEEN GROUPS P-VALUE[+]	WITHIN GROUPS P-VALUE EXABLATE ARM
	CHANGE FROM BASELINE	% CHANGE FROM BASELINE[∫]	CHANGE FROM BASELINE	% CHANGE FROM BASELINE[∫]		
Month 3	10.38	63.8%	0.45	1.8%	P<0.001	P<0.001
Lower 95% CI	8.81	55.3	-0.50	-6.7%		
Upper 95% CI	11.94	72.4%	1.40	11.1%		
Month 6	10.05	61.8%[++]				P<0.001
Lower 95% CI	8.42	64.3%				
Upper 95% CI	11.69	81.8%				
Month 12	10.20	64.0%++				P<0.001
Lower 95% CI	8.66	55.2%				
Upper 95% CI	11.74	72.7%				

[∫]: % change: 100*(Baseline - Follow-up Visit)/Baseline

[+] Difference between treatment groups was statistically significant (p<0.001) (Wilcoxon signed rank test).

[++]% Change from Baseline to Months 3, 6 and 12 was tested and found to be statistically highly significant (p<0.001) for Exablate Arm

Notes:

1. Change from Baseline was calculated as Difference (Baseline - Visit).
2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

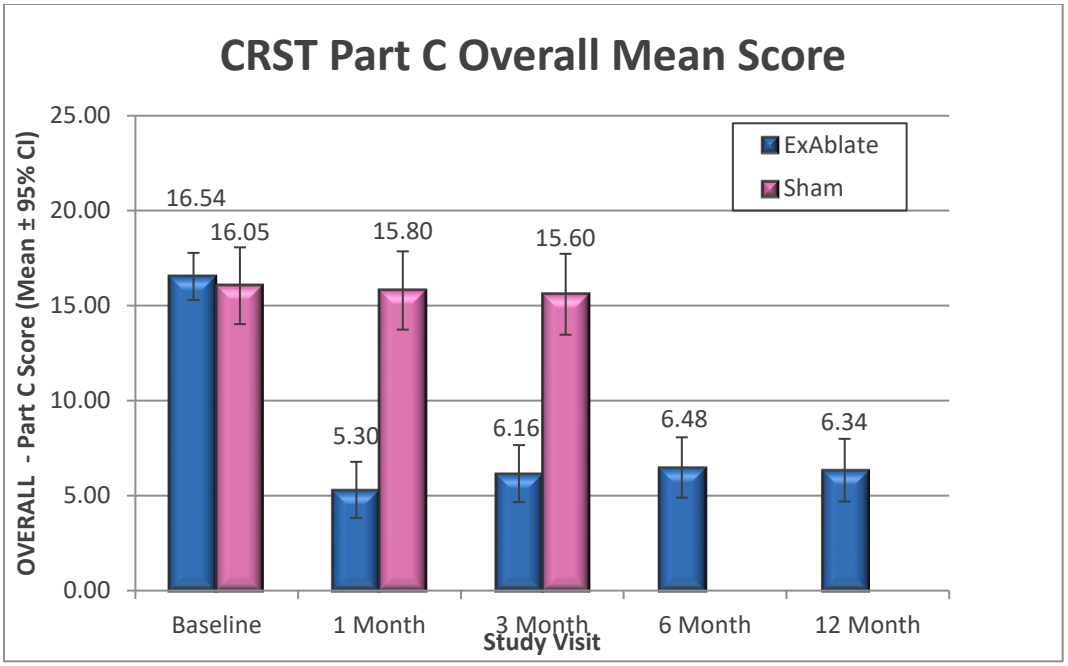

Figure 8.1: The Overall CRST Part C scores through Month-12.
This Part C is a composite of 8-components with a maximum total score of 32.

This Part C is a composite of 8-components: Speaking, Drinking, Eating, Hygiene, Dressing, Writing, Working, and Social Activities. The graphs for all the individual activities are shown in the figures below across time for both treatment groups.

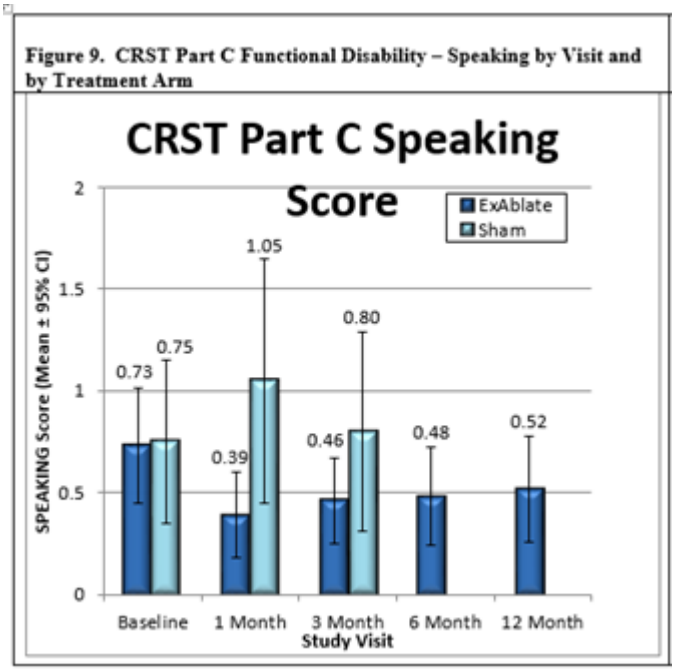

Figure 5. CRST Part C Functional Disability - Speaking by Visit and by Treatment Arm

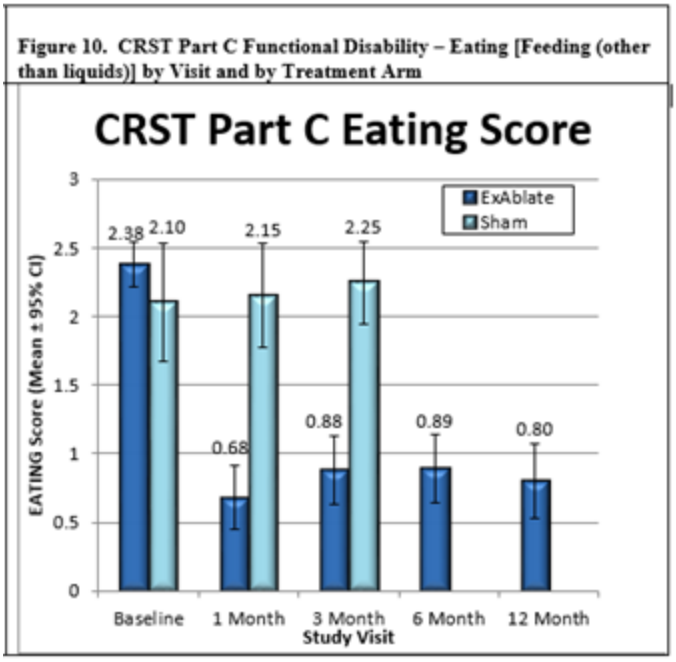

Figure 6. CRST Part C Functional Disability - Eating [Feeding (other than liquids) by Visit and by Treatment Arm]

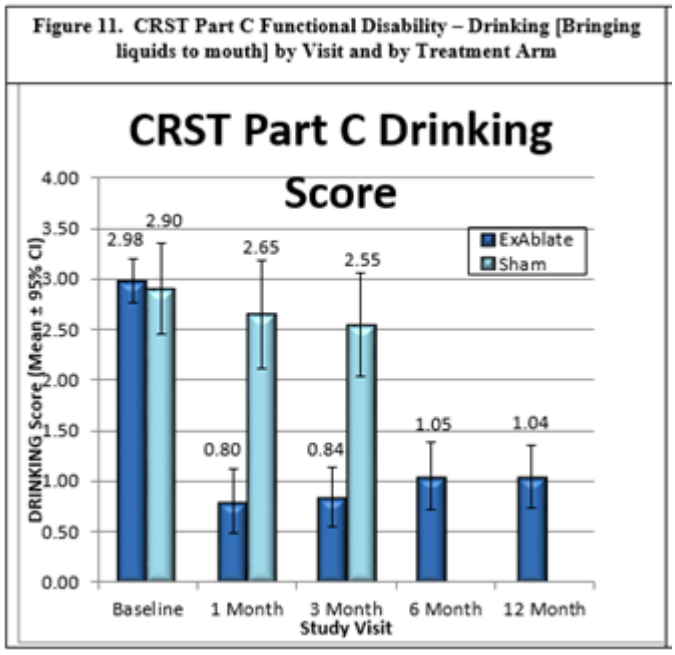

Figure 7. CRST Part C Functional Disability - Drinking [Bringing liquids to mouth] by Visit and Treatment Arm

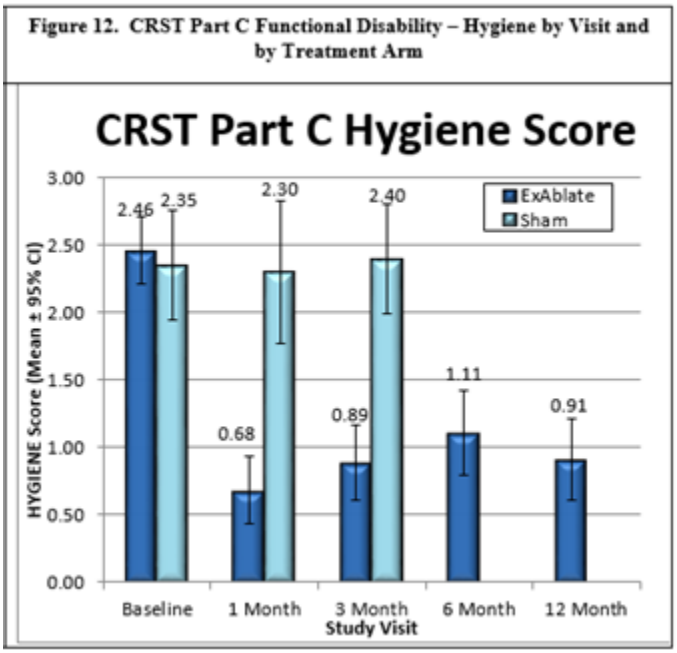

Figure 8. CRST Part C Functional Disability - Hygiene by Visit and by Treatment Arm

Figure 13. CRST Part C Functional Disability – Dressing by Visit and by Treatment Arm

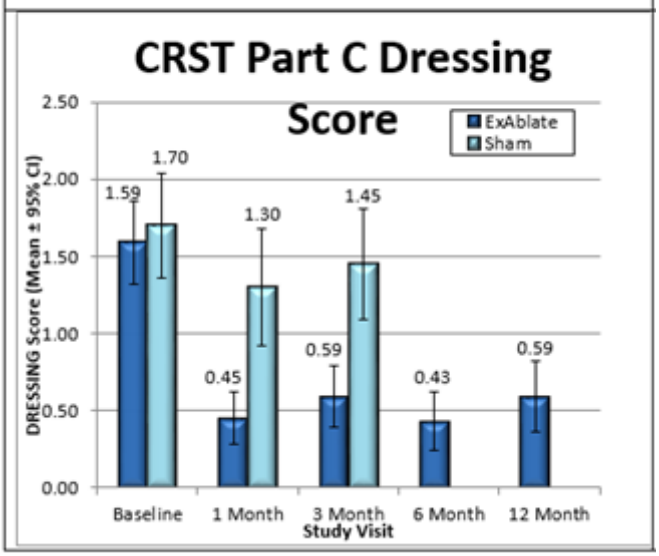

Figure 9. CRST Part C Functional Disability - Dressing by Visit and by Treatment Arm

Figure 14. CRST Part C Functional Disability – Writing by Visit and by Treatment Arm

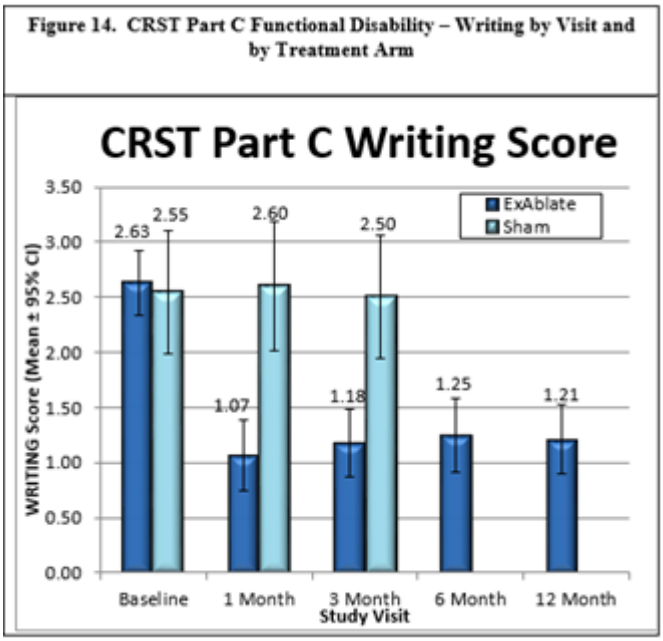

Figure 10. CRST Part C Functional Disability - Writing by Visit and by Treatment Arm

Figure 15. CRST Part C Functional Disability - Working by Visit and by Treatment Arm

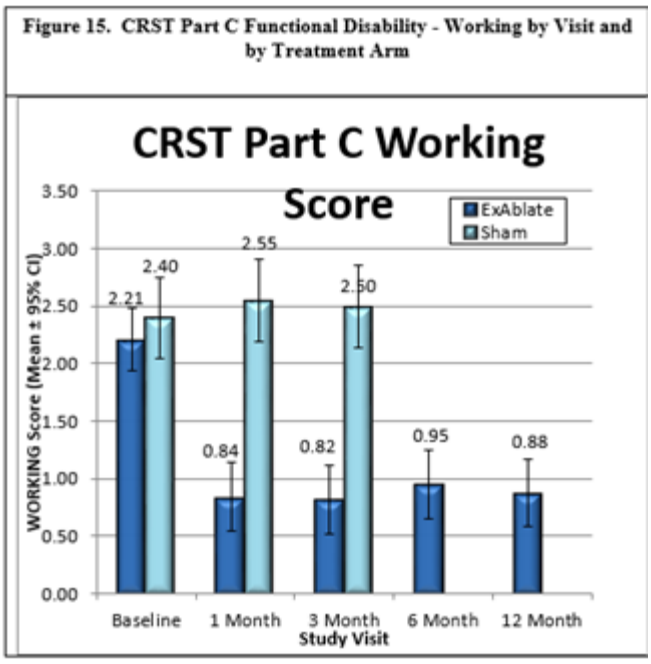

Figure 11. CRST Part C Functional Disability - Working by Visit and by Treatment Arm

Figure 16. CRST Part C Functional Disability – Social Activities by Visit and by Treatment Arm

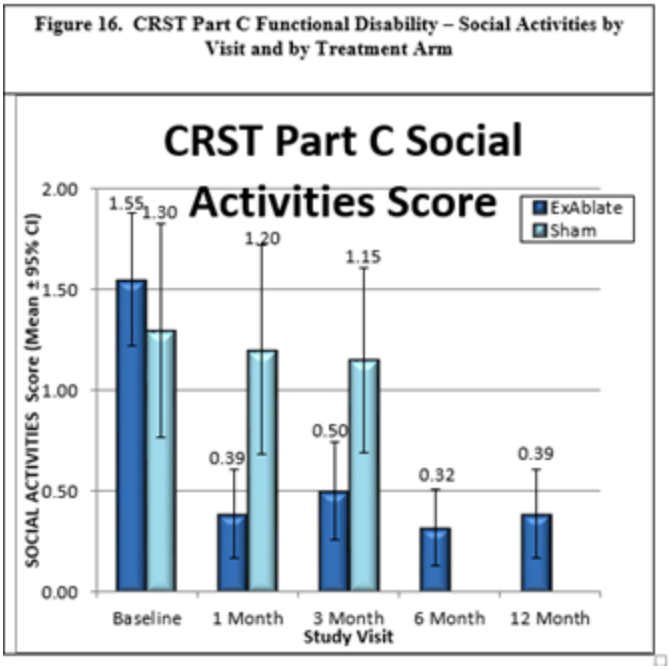

Figure 12. CRST Part C Functional Disability - Social Activities by Visit and by Treatment Arm

3.2.2.2.3 QUEST (Summary of Dimension Score) Baseline to Month 3 – Comparison between Groups – Main Analysis – ITT Population

From the results reported in **TABLE 15**, it may be determined that the result of the QUEST quality of life at the Month 3 time point mimics that of the PE, with a 43.2% improvement in the mean score of dimensions in the Exablate group compared to baseline, and almost no change (5%) for the same measure in the Sham group. This difference between treatment groups was, again, highly significant (p<0.001).

TABLE 15: CONFIRMATORY SECONDARY EFFICACY QUEST SUMMARY OF DIMENSIONS SCORE % CHANGE FROM BASELINE AT MONTH 3 BY TREATMENT GROUP (ITT)

SE1	TREATMENT GROUP				P-VALUE*
	EXABLATE: N=56		SHAM: N=19**		
ITT Mean	23.11	43.2%	41.37	5.0%	<0.001
Lower 95% CI	13.33	34.3%	26.04	-14.9%	
Upper 95% CI	26.11	56.3%	54.22	36.2%	

1. SE1 was calculated as Percent Change ((Baseline - Visit)/Baseline)*100.
2. Higher SE1 values represent improvement
* p-value testing between groups
** One Sham subject did not complete the QUEST at baseline

In summary, the primary endpoint and all confirmatory secondary endpoints were met and were highly statistically significant.

3.2.2.2.4 Summary of Main Efficacy

The efficacy analysis shows a powerful, robust result at Month 3 with the Exablate group experiencing a highly significant improvement in the PE and all secondary confirmatory endpoints, as summarized in **TABLE 15** and **Figure 13.**

TABLE 16. EFFICACY ANALYSIS SUMMARY					
	% OF IMPROVEMENT AT MONTH-3 – ITT			% OF IMPROVEMENT AT MONTH 12 – ITT	
	EXABLATE (N=56)	SHAM (N=20)	P-VALUE BETWEEN GROUPS	EXABLATE (N=56)	P-VALUE VS. BASELINE
Primary Endpoint – Composite Tremor/Motor Function	46.9%	- 0.1%	p< 0.001	39.6%	p< 0.001
..Lower 95% CI	40.3%	-9.6%		34.0%	
Upper 95% CI	53.5%	9.5%		45.3%	
CRST, Part A-Tremor "Posture"	64.3%	- 4.4% (n=17)	p<0.001	65.5 %	p< 0.001
..Lower 95% CI	52.1%	-26.9		54.7 %	
Upper 95% CI	76.5%	18.2		76.3 %	
CRST, Part C	63.8%	1.8%	p< 0.001	64.0%	p< 0.001
..Lower 95% CI	55.3%	-6.7%		55.2%	
Upper 95% CI	72.4%	11.1%		72.7%	
QUEST	43.2%	5.0% (n=19)	p< 0.001	47.1%	p< 0.001
..Lower 95% CI	34.3%	-14.9%		36.5%	
Upper 95% CI	56.3%	36.2%		62.1%	
Note: A negative sign "-" indicates worsening					

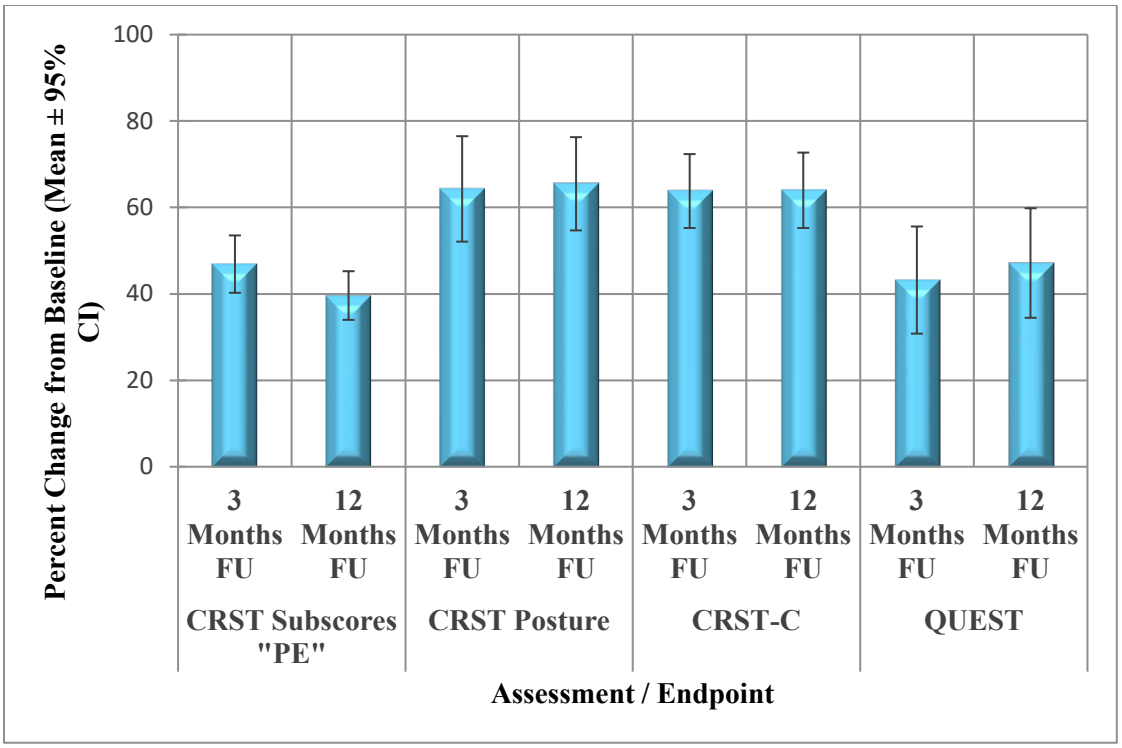

Figure 13. Study Effectiveness Assessment Endpoints; "PE" is the Primary Endpoint

Covariate analysis was performed and indicated that no interactions with any baseline characteristics were present. Similarly, a sensitivity analysis showed that the effect was robust.

3.2.2.2.5 Covariate and Sensitivity Analyses

The Covariate and Sensitivity analyses were performed in this study:

- The data were tested for potentially confounding variables through use of a Covariate analysis. Age, Baseline, CRST score at Baseline, Gender and Center were assessed for all primary and secondary confirmatory analyses. No significant interaction was found on the study results with any of these variables.
- Sensitivity analyses were performed to determine how robust the results were using Best case and Worst case imputation methods. Only 2 subjects in the Exablate dropped out prior to the study endpoint of Month 3. Using both methods, the result by either method had negligible change on the PE values, and did not affect the difference between groups which was still high at $p<0.001$.

3.2.2.2.6 Additional Analyses – CRST Part – B

Figure 14 shows the CRST Part-B total score through Month-12 for both Main Exablate and Sham Arms. This data shows that while sham shows little to no change in their total score, the Exablate Arm shows a mean of approximately 5 points change was achieved at all the visits.

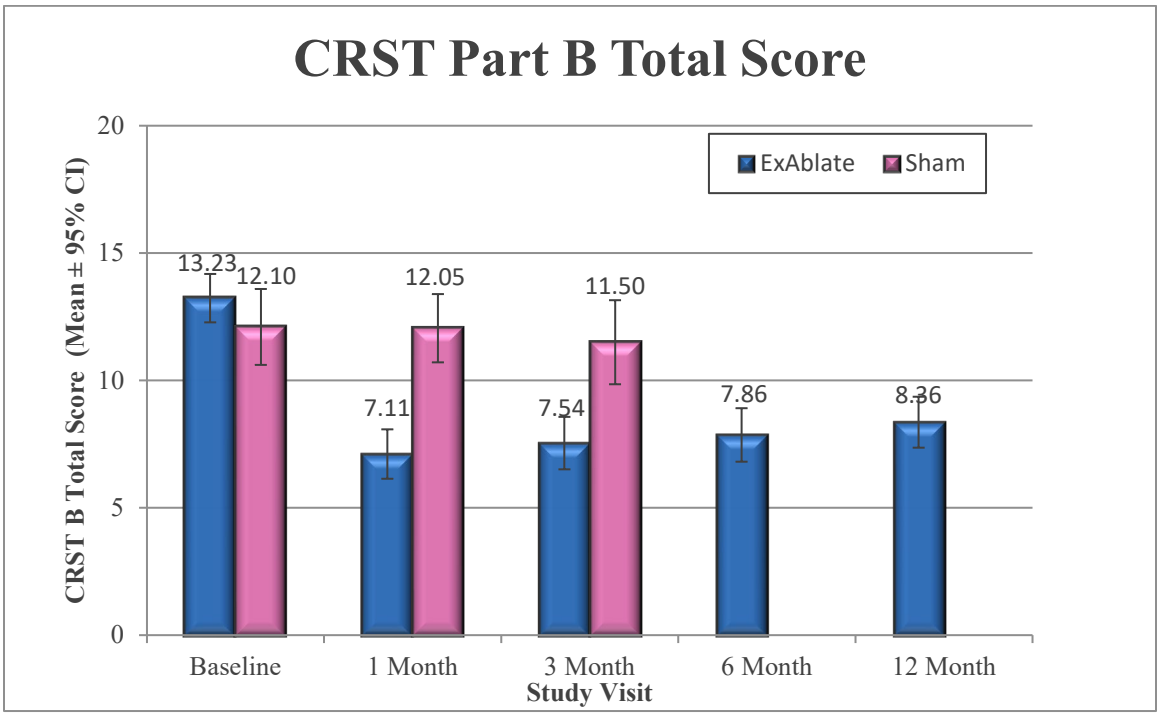

Figure 14. CRST Part-B Total score through Month-12

3.2.2.3 Confirmatory Secondary Endpoints Safety Results

3.2.2.3.1 Subject Disposition & Accountability

The Exablate Crossover arm started with 21 subjects who were fairly evenly distributed across all sites as follows

Similar to the Main Analysis population, the Exablate Crossover Subject videotaping for CRST analyses was performed by the same Core lab as in the Main analysis. The statistical analyses of all the study Crossover endpoints were performed in the same way as those for the main analyses.

Subject disposition in the Crossover arm is presented in **TABLE 17**. As discussed with the Agency, some of these subjects are still in follow-up, but all data available at the time of the PMA submission are presented herein.

TABLE 17. SUBJECT DISPOSITION FOR CROSSOVER SUBJECTS						
CATEGORY	BASELINE	1 WEEK FU	1 MONTH FU	3 MONTHS FU	6 MONTHS FU	12 MONTHS FU
Theoretical[1]	21	21	21	21	21	21
Not Due Yet	0	0	0	0	0	12
Death	0	0	0	0	0	0
Failure[2]	0	0	0	0	0	0
Expected[3]	21	21	21	21	21	9
Actual[4]	21	21	21	21	21	9
Actual %[5]	100%	100%	100%	100%	100%	100%

[1]Theoretical is equal to the number of subjects entered Rescue stage of the study

[2]Failures include any subjects who discontinued study due to non-response to treatment

[3]Expected equals Theoretical minus Death minus Failures

[4] Actual is the number of subjects actually returning for the follow-up visit

[5]Actual % is the number of Actual subjects divided by Expected.

3.2.2.3.2 Subject Disposition & Accountability

Similar to the Main Analysis population, the primary analysis of safety was based upon the collection of AEs during the study as collected by the investigators at each site from the time of the crossover treatment to the Month 12 visit. All AEs were recorded on case report forms and entered into the Crossover Database for proper attribution of relation of events. The Crossover safety profile shows no new events, and further re-affirm the safety profile of the Main population.

TABLE 18 succinctly summarizes the safety profile of the Exablate 4000 as used in unilateral thalamotomy for the Exablate Crossover group. A total of 76 AEs in 20 subjects was reported for the Exablate Crossover group. Most reported AEs (61/76, 80% in 13 subjects) were Mild and Moderate (13/76, 17% in 7 subjects) with one unrelated SAE (1/76, 1% in 1 subjects).

Similar to what was observed in the blinded portion of the study, 22% of AEs were unrelated (17/76, 22%). In addition, 34% of AEs (26/76) were transient and were driven in large part by the physician/patient interaction during the procedure, (i.e., transient - most resolve right after the sonication or same day up to 72 hours post-procedure). During the procedure, the physician is in constant contact with the subject asking how they feel after each sonication. This solicited information helps to drive the treatment. As shown, these events account for 57% of total events.

TABLE 18. OVERALL SUMMARY OF ADVERSE EVENTS BY SEVERITY IN THE EXABLATE CROSSOVER ARM		
SEVERITY	EXABLATE CROSSOVER	
	FREQUENCY: N=76	INCIDENCE: N=21
Mild	61 (80%)	16 (76%)
Moderate	13 (17%)	7 (33%)
Severe	1 (1.5%)	1 (5%)
TOTAL	76 (100%)	19 (90%)

TABLE 19 shows the AEs by time occurrence. The majority of AEs occurred within the first 30 days following the procedure and resolved within 30 days (68 events in 21 Exablate Crossover subjects). In fact, many of them resolved on the same day as treatment or within 1 week of treatment (92/184, 50%). Many AEs were procedure related events (such as those related to the stereotactic frame, the urinary catheter, the IV line, the head shave, claustrophobia within the MR, etc.). A number of events are generally associated with any ablative treatment of the Vim nucleus (thalamotomy- related), such as numbness/tingling of the lip, face, tongue, or index finger/thumb. These events are generally reported as Mild or possibly Moderate.

TABLE 19. STARTING TIME OF OCCURRENCE FOR ADVERSE EVENTS IN THE EXABLATE CROSSOVER ARM		
START WINDOW	EXABLATE	
	FREQUENCY: N=76	INCIDENCE N=21
Within 30 days of procedure	68 (89%)	18 (86%)
31-90 days post-procedure	3 (4%)	2(10%)
>90 days post-procedure	5 (7%)	3 (14%)
TOTAL	76 (100%)	19 (90%)

Most of the events that occurred within the first 30 days of the procedure were events that would occur in relation to the procedure itself, such as headache, nausea/vomiting, numbness/tingling, pin site events, pain and discomfort. Many of these AEs resolved within days of the procedure. The frequency and incidence of AEs that occurred during the Crossover study are presented in **TABLE 20** by severity.

TABLE 20. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS FOR EXABLATE CROSSOVER BY SEVERITY EXABLATE				
BODY SYSTEM	PREFERRED TERM	MILD	MODERATE	SEVERE
		FREQUENCY N (%)	FREQUENCY N (%)	FREQUENCY N (%)
Cardiovascular	Hypertension	1 (1%)	1 (1%)	
	Preventricular Contractions	1 (1%)		
	Sick Sinus Syndrome			1 (1%)
Gastrointestinal	Dry mouth	1 (1%)		
	Dysgeusia	2 (3%)		
	Nausea/Vomiting	3 (4%)	1 (1%)	
General	Fatigue	1 (1%)	1 (1%)	
	Musculoskeletal Weakness	1 (1%)	1 (1%)	
Infections	Flu	1 (1%)		
Musculoskeletal	Musculoskeletal Weakness	2 (3%)		
	Dysmetria	2 (3%)		
	Imbalance	2 (3%)	1 (1%)	
	Unsteady	1 (1%)	1 (1%)	
Nervous	Ataxia	2 (3%)	2 (3%)	
	Cognitive Disturbance	1 (1%)		
	Dizziness	1 (1%)		
	Dysarthria	2 (3%)	1 (1%)	
	Grogginess	1 (1%)		
	Dysmnesia	1 (1%)		
	Hand Tremor (untreated side)	1 (1%)		
	Numbness/Tingling	10 (13%)		
	Paresthesia	2 (3%)		
	Slow Movements	1 (1%)		
Pain/Discomfort	Headache	5 (7%)	2 (3%)	1 (1%)
	Sonication-related head pain	4 (5%)	2 (3%)	

TABLE 20. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS FOR EXABLATE CROSSOVER BY SEVERITY EXABLATE				
BODY SYSTEM	PREFERRED TERM	MILD	MODERATE	SEVERE
		FREQUENCY N (%)	FREQUENCY N (%)	FREQUENCY N (%)
Stereotactic Head Frame	Pin Site Bleeding	1 (1%)		
	Pin Site Edema	1 (1%)		
	Pin Site Pain	4 (5%)		
	Ptosis	1 (1%)		
Vestibular Disorder	Dizziness	3 (4%)		
	Vertigo	1 (1%)		
TOTAL		60	14	2

Transient events are those events that last less than 3 days and resolve completely. A large number of transient events are the physician-solicited events during the procedure which only last a few seconds to less than 1 day. These events are often solicited during sonications and help the physician to locate the desired ablative target. Transience is determined by calculating the duration between the AE's start and stop date.

The device/procedure unrelated events include events such as the IV, 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.

TABLE 21 summarizes the transient and unrelated AEs, which account for 43 of 76 AEs. Events with the highest frequency included headache (7), sonication-related headache (6), and nausea/vomiting (4) and were transient.

TABLE 21. TRANSIENT ADVERSE EVENTS OR ADVERSE EVENTS THAT ARE UNRELATED TO DEVICE/ PROCEDURE OR THALAMOTOMY IN THE EXABLATE CROSSOVER ARM				
RELATION / BODY SYSTEM / AE CODED TERM			EXABLATE CROSSOVER	
			N	
Transient	Gastrointestinal	Nausea/Vomiting	4	5%
	Nervous	Cognitive Disturbance	1	1%
		Dizziness	1	1%
		Numbness/Tingling	2	3%
		Paresthesia	1	1%
	Pain/Discomfort	Headache	7	9%
		Sonication-Related Head Pain	6	8%
	Vestibular Disorder	Dizziness	3	4%
		Vertigo	1	1%
Subtotal Transient			26	34%
Unrelated Events			17	22%
Total Transient and Unrelated			43	57%

Thirty-three of 76 AEs were related to Exablate safety profile and were determined to be either procedure/device related or thalamotomy related (**TABLE 22**). These events lasted longer than 72 hours. The most frequent events include numbness/tingling (8) and ataxia (4).

TABLE 22. FREQUENCY OF ADVERSE EVENTS RELATED TO THE PROCEDURE OR DEVICE OR THALAMOTOMY IN THE EXABLATE CROSSOVER ARM				
RELATION / BODY SYSTEM / AE CODED TERM			EXABLATE CROSSOVER	
			N	%
Procedure-Related	General	Fatigue	2	3%
		Musculoskeletal Weakness	2	3%
	Musculoskeletal	Imbalance	2	3%
		Musculoskeletal Weakness	2	3%
		Unsteady	2	3%
	Nervous	Grogginess	1	1%
	Pain/Discomfort	Headache	1	1%
	Vestibular Disorder	Dizziness	1	1%
Thalamotomy-Related	Gastrointestinal	Dysgeusia	1	1%
	Musculoskeletal	Dysmetria	2	3%
		Imbalance	1	1%
	Nervous	Ataxia	4	5%
		Dysarthria	2	3%
		Numbness/Tingling	8	11%
		Paresthesia	1	1%
		Slow Movements	1	1%
TOTAL			33	43%

Sixteen AEs with onset within 30 days post-procedure, reported by 9 Exablate subjects, were still on-going at the Month 12 follow-up visit (See **TABLE 25**). All of these events are either Mild or Moderate.

TABLE 23. ONGOING ADVERSE EVENTS FROM THE FIRST 30 DAYS IN EXABLATE CROSSOVER ARM			
BODY SYSTEM	PREFERRED TERM	FREQUENCY: N= 76	INCIDENCE: N=21
Gastrointestinal	Dysgeusia	2	2 (10%)
General	Fatigue	2	2 (10%)
Musculoskeletal	Dysmetria	1	1 (5%)
	Imbalance	2	2 (10%)
	Musculoskeletal weakness	1	1 (5%)
Nervous	Dysarthria	1	1 (5%)
	Numbness/tingling	5	3 (14%)
	Slow movements	1	1 (5%)
Stereotactic Frame	Pin Site Pain	1	1 (5%)
TOTAL		16	9 (43%)

Serious Adverse Event
There was one (1) serious event that occurred in the Exablate Crossover group. One subject was diagnosed with sick sinus syndrome 8 months after the Exablate procedure and underwent a medical procedure to have a pacemaker implanted. This was not related to the Exablate procedure.

PHQ-9
No subject at any time during the Crossover study scored 20 or higher on the PHQ-9.

3.2.2.3.3. Primary Efficacy Endpoint Subject Disposition & Accountability

Exablate treatment was unilateral thalamotomy of the *Vim* nucleus of the thalamus contralateral to the target arm with tremor. Crossover treatments were open label after unblinding from the Month 3 visit in the Main Analysis.

Using the same formula for PE calculation (Composite Tremor/Motor Function Percent Change from Baseline), the Exablate Crossover group at Month 3 CRST was calculated as compared to baseline at the Crossover study screening (**TABLE 26**). An analysis of statistical significance as compared to baseline was performed. The Exablate Crossover group experienced a 53.1% improvement at Month 3 in the Composite Tremor/Motor Function Score ($p<0.001$) (**TABLE 26**). This is highly significant showing a treatment response which is slightly better than that of the Main analysis.

TABLE 24. CROSSOVER ARM - PRIMARY ENDPOINT (COMPOSITE TREMOR/MOTOR FUNCTION % IMPROVEMENT): THREE MONTHS POST-TREATMENT ANALYSES			
PECROSSOVER	TREATMENT GROUP EXABLATE CROSSOVER: N =21		P-VALUE*
	MEAN SCORE	% CHANGE	
Mean	0.24	53.1%	<0.001
Lower 95% CI	0.18	43.4%	
Upper 95% CI	0.30	62.8%	
1. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher SPE values represent improvement			

The percent change of improvement of the Composite Tremor/Motor Function score for the Exablate Crossover group is similar to that experienced by the Exablate group in the blinded portion of the study (46.9% Exablate , p<0.01), thus the treatment effect is of a similar magnitude, or slightly better, as in the blinded portion of the study (see **Figure 18**).

3.2.2.3.4. Crossover Analysis Confirmatory Endpoint—CRST Composite Tremor/Motor Function Score Compared to Baseline.

This second confirmatory endpoint is based on CRST, primary endpoint calculation, the Composite Tremor/Motor Function Score at Month 3, 6, and 12**. TABLE 27** and **Figure 15** show all available data shown through Month 12 for the Exablate Crossover group. While not all the subjects have completed the Month-12 follow up visits, the p-value at Month-12 shows high significance (p=0.004).

As shown in **Figure 15**, the percent change from baseline in the CRST Composite Tremor/Motor Function was 50% or greater at each follow-up visit.

TABLE 25. CROSSOVER ANALYSIS - CONFIRMATORY EFFICACY: COMPOSITE TREMOR MOTOR FUNCTION SCORE (PE) IN EXABLATE CROSSOVER ARM AS COMPARED TO BASELINE BY VISIT			
	EXABLATE CROSSOVER N = 21		
	CALCULATED SCORE CHANGE	% CHANGE	P-VALUE*
Month 3	0.24	53.1%	<0.001
Lower 95% CI	0.18	43.4%	
Upper 95% CI	0.30	62.8%	
Month 6	0.26	50.7%	<0.001
Lower 95% CI	0.20	41.8	
Upper 95% CI	0.31	59.6	
Mean 12 (N=16)	0.26	47.0%	<0.001
Lower 95% CI	0.17	30.6	
Upper 95% CI	0.34	63.3	
Notes: 1. SE2 was calculated as Percent Change ({(Baseline - Visit)/Baseline}*100) 2. Higher SE2 values represent improvement 3. Month 12 visits are still on going for patient follow-up. **p-value reflects testing Vs baseline			

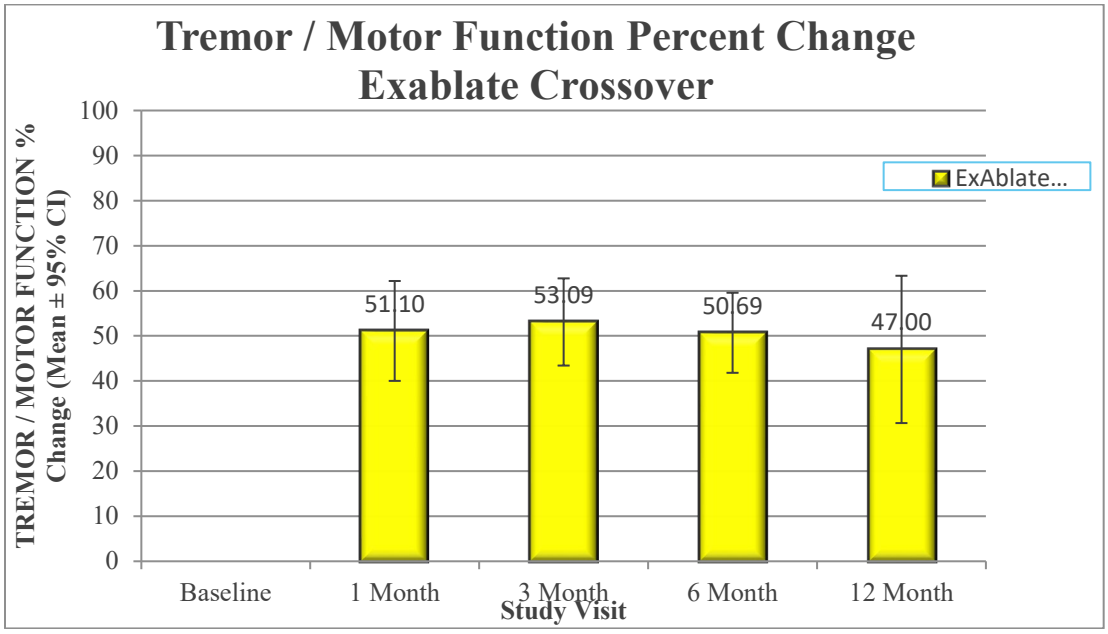

Figure 15: Primary Endpoint (Composite Tremor/Motor Function Score) for the Crossover Arm

The difference from Baseline is highly significant ($p<0.001$ at Months 3 and 6; $p<0.001$ at Month 12 with partial data, n=16). The result here is similar to that observed in the blinded portion of the study for the Exablate group.

Similar to the Main "blinded" populations (Exablate Main Arm and Sham Arm), the total CRST subscores (Part A + Part B) are presented in **Figure 16,** whereas their corresponding normalized subscores are presented in **Figure 17**.

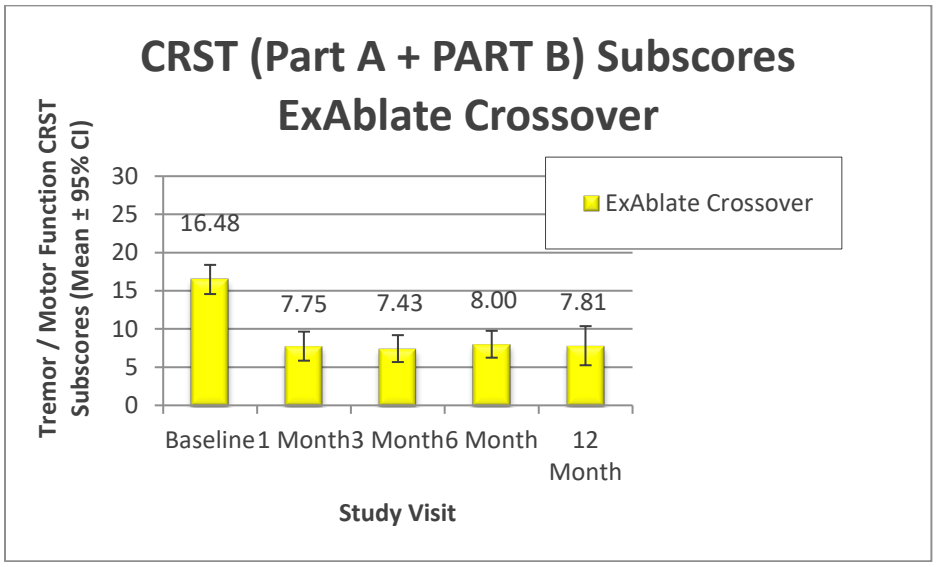

Figure 16: Tremor / Motor Function CRST actual Subscores (Part A + Part B) through Month-12 for the Crossover Arm. Note Month-12 Crossover N=16.

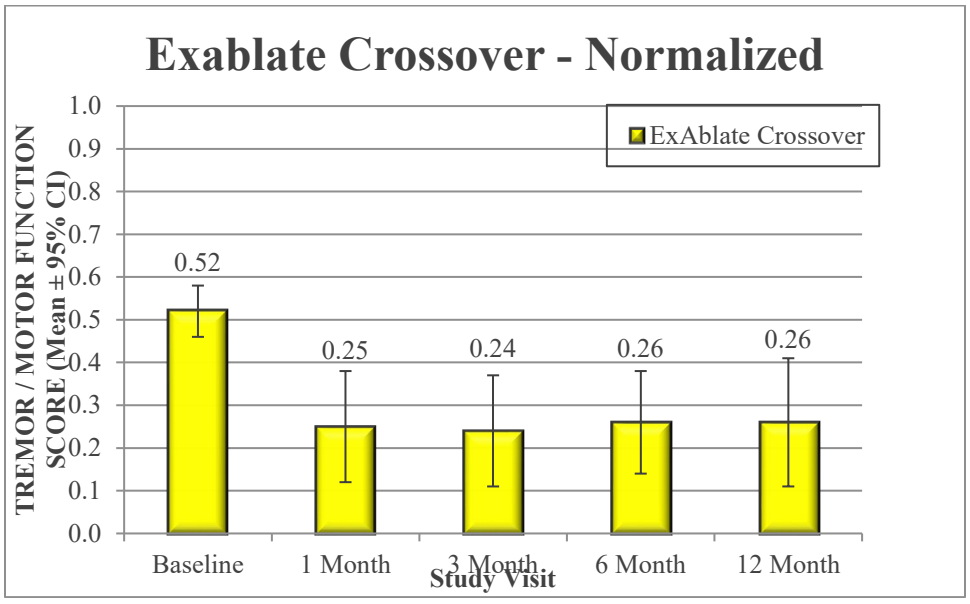

Figure 17: Same data as in Figure 16 where the actual score is normalized by the maximum score of 32 or 28 depending on the treated (contra-lateral) Arm.
Note Month-12 Crossover N=16.

The percent of improvement of CRST Composite Tremor/Motor Function Score for the Exablate Crossover group is similar, or slightly improved, compared to the Exablate group in the Main Analysis (47% Exablate, p<0.001) across all visits (**Figure 18**).

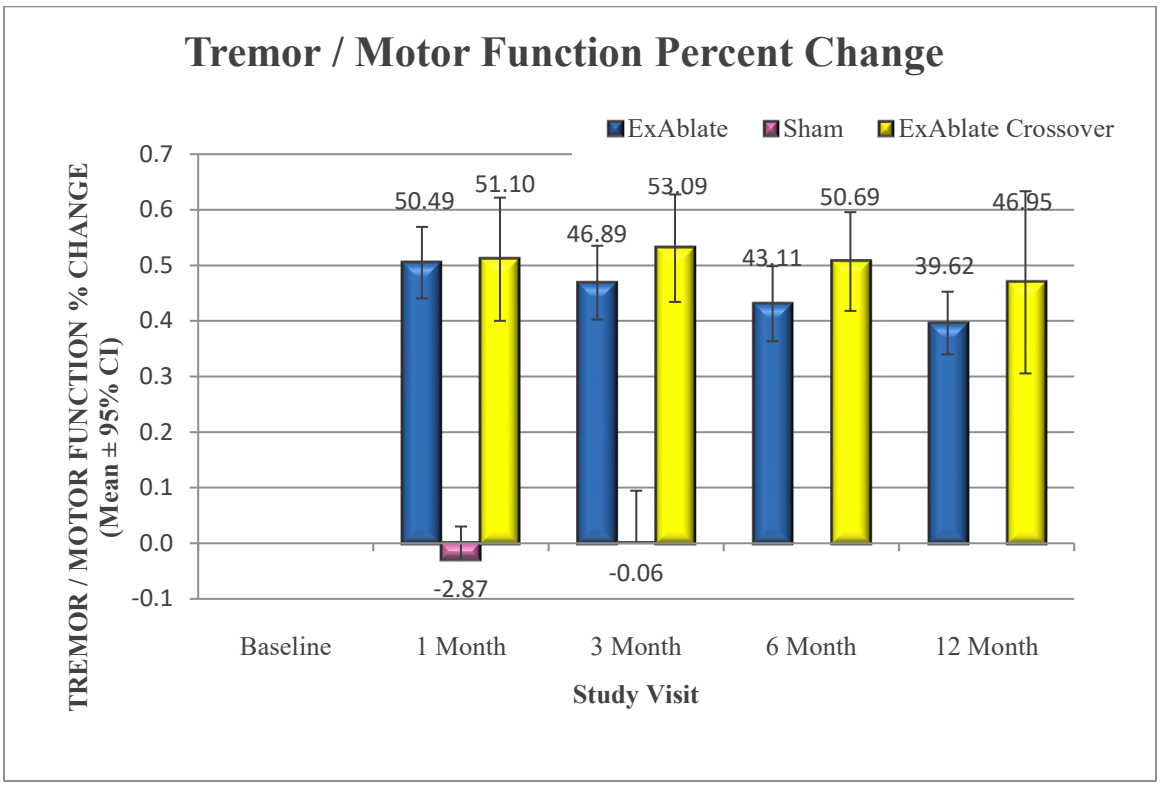

Figure 18: Primary Endpoint (Composite Tremor/Motor Function Score) for the 3 Study Arms: Main, Sham, and Crossover Arms.

The total CRST subscores (Part A + Part B) of the 3-study Arms are presented in **Figure 19**.

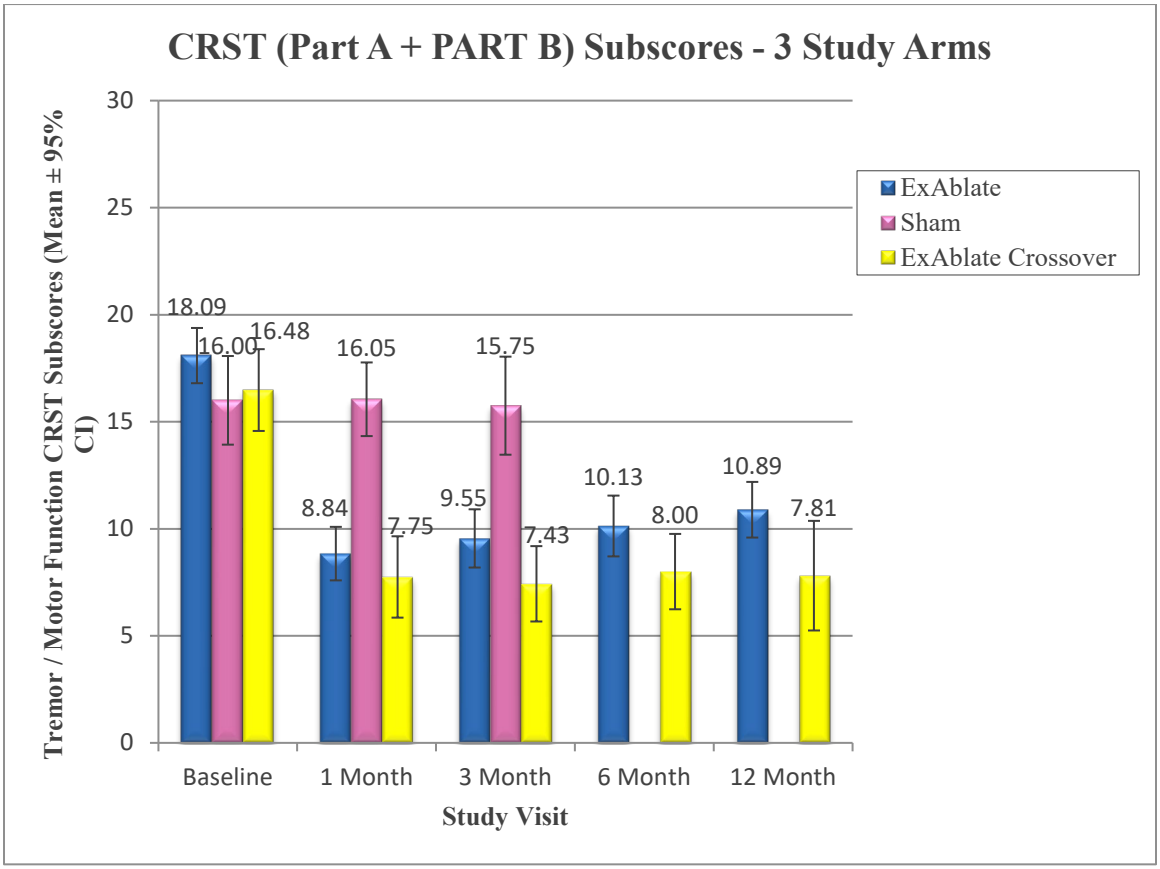

Figure 19: Tremor / Motor Function CRST actual subscore (Part A + Part B) through Month-12 for Exablate Main Arm, Sham and Crossover Arms. Note: Month-12 Crossover N=7

3.2.2.3.5. CRST, Part A Posture Component

As was done for the Main Analysis and as a means for comparison to literature, using the single component of CRST, Posture pulled from the Composite Tremor/Motor Function Score, the mean CRST Part-A Posture score was calculated and is presented in **TABLE 26**.

As can be seen in **TABLE 26** below, an improvement in contralateral or treated arm tremor (CRST-Part A, Posture) of 56.4% at Month 3, 56.8% at Month 6, and 46.4% at Month 12 (at Month 12, N = 16) with a highly significant p-values of <0.001 at Month-3 and 6, and of 0.004 at Month-12.

TABLE 26. CRST PART A POSTURE FOR TREATED ARM BY TREATMENT GROUP BY VISIT THROUGH MONTH 3 – EXABLATE CROSSOVER ARM				
		CRST POSTURE CALCULATED SCORES[1]	CHANGE FROM BASELINE[2]	PERCENT CHANGE FROM BASELINE
Baseline	Mean	1.71		
	Lower 95% CI	1.17		
	Upper 95% CI	2.26		
	N	21		
1 Month FU	Mean	0.45	1.15	54.2%
	Lower 95% CI	0.06	0.66	32.0%
	Upper 95% CI	0.84	1.64	76.4%
	N	20	20	20
3 Months FU	Mean	0.43	1.29	56.4%
	Lower 95% CI	0.12.	0.78	36.6%
	Upper 95% CI	0.74	1.79	76.1%
	N	21	21	21
Month 6	Mean	0.43	1.29	56.8%
	Lower 95% CI	0.12.	0.81	36.3%
	Upper 95% CI	0.74	1.77	77.2%
	N	21	21	21
Month 12	Mean	0.56	0.94	46.4%
	Lower 95% CI	0.09	0.28	22.3%
	Upper 95% CI	1.04	1.60	70.5%
	N	16	16	16

Notes:

1. Change from Baseline was calculated as Difference (Baseline - Visit)
2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores))

Similar to the primary endpoint, the "Posture" CRST outcome for the Exablate Crossover group is favorable and similar to what was seen in the Main Analysis Exablate group (**Figure 20** below).

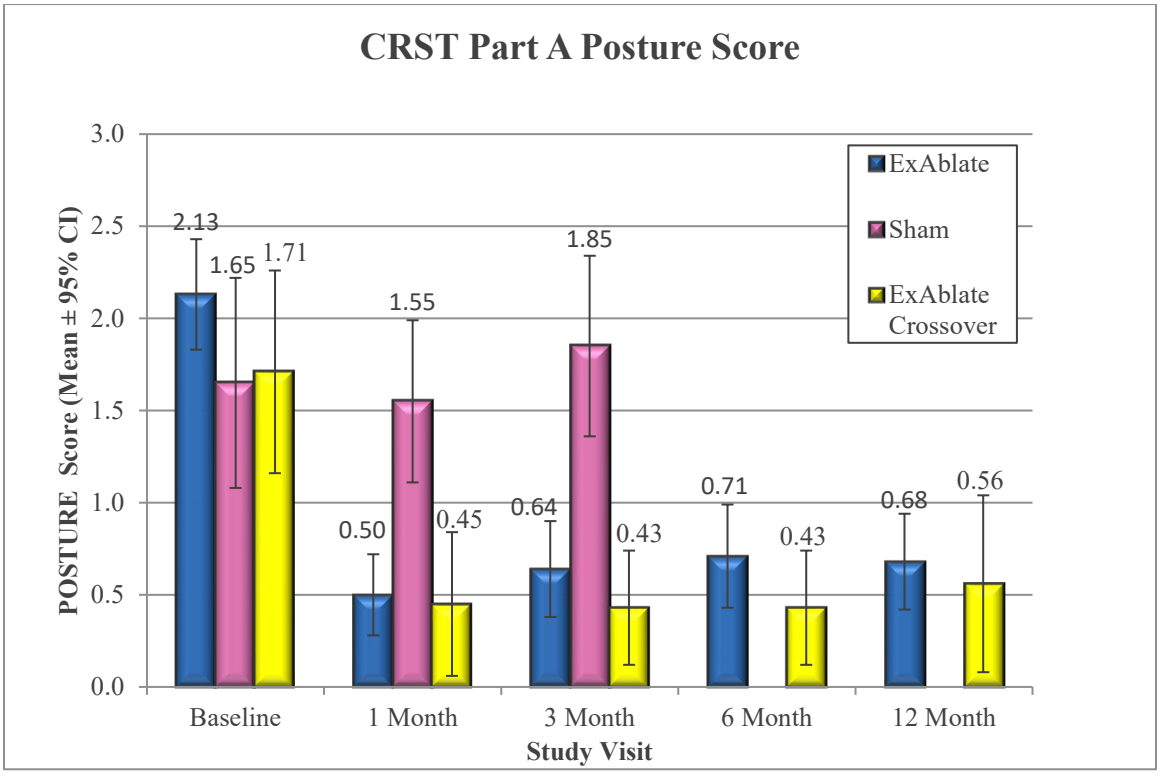

Figure 20: Primary Endpoint (Composite Tremor/Motor Function Score) for the 3 Study Arms: Main, Sham, and Crossover Arms

3.2.2.3.6. CRST Overall Part C Comparison to Baseline

The Overall Part C percent change from baseline scores are presented below in **TABLE 27**. The analysis presents all available data. At all scheduled visits, a high percentage of improvement in the functional activities of daily living was observed: 74.6% at Month 3, 72.1% at Month 6, and 68.9 (for data collected up to February 22, 2016) at Month 12. This level of improved functionality was highly significant ($p<0.001$).

TABLE 27. CROSSOVER STAGE, CONFIRMATORY SECONDARY EFFICACY: CRST TOTAL PART-C FUNCTIONAL DISABILITIES TOTAL SCORE - PERCENT IMPROVEMENT FROM BASELINE BY VISIT			
VISIT /SE3$_{CROSSOVER}$	MEAN SCORE	% CHANGE FROM BASELINE	P-VALUE
3 Months FU Mean N=21	4.29	74.6%	<0.001
Lower 95% CI	1.00	66.2%	
Upper 95% CI	7.00	82.9%	
6 Months FU Mean N=21	4.62	72.1%	<0.001
Lower 95% CI	2.00	62.4%	
Upper 95% CI	6.00	81.8%	
12 Months FU Mean N=18	5.17	68.9	<0.001
Lower 95% CI	0.00	55.0	
Upper 95% CI	9.00	82.9	
1. % Change from Baseline for CRST Total part C score was calculated as Percent Change ({(Baseline - Visit)/Baseline}*100) 2. Higher % Change from Baseline for CRST Total part C score values represent improvement			

The result for the Exablate Crossover group compares favorably with that of the Main Analysis, where the Exablate group experienced mean improvement in activities of daily living of 63.8% at Month 3 (p<0.001). The Exablate Crossover group was able to reproduce, and improve upon, that outcome (74.6%; p<0.001).

3.2.2.3.7. QUEST Endpoint Analyses compared to Baseline

QUEST - Quality of Life, overall score was calculated for the Exablate Crossover group in the same way as it was done for the Main Analysis population. The percent improvement in QUEST Summary of Dimensions at Month 3 for the Exablate Crossover group was 59.2 % (p<0.001) (**TABLE 28** below).

TABLE 28. CROSSOVER QUEST ANALYSIS - IMPROVEMENT FROM BASELINE AT 3 MONTHS POST-TREATMENT			
SE1CROSSOVER	TREATMENT GROUP EXABLATE CROSSOVER		P-VALUE*
Mean	19.20	59.2%	<0.001
Lower 95% CI	3.54	38.16	
Upper 95% CI	30.28	94.94	
2. QUEST Summary of Dimensions was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 3. Higher QUEST Summary of Dimension values represent improvement * p-value testing compared to Baseline			

The percent of improvement in QUEST for the Exablate Crossover group further validates the QUEST treatment outcome experienced by the Exablate group in the Main Analysis at Month 3 (43.2%).

3.2.2.3.8. Additional Analyses – CRST Part-B Total Score

Figure 21 shows the CRST Part-B total score through Month-12 for all three study Arms: Main Exablate, Sham, and Crossover Arms. This data shows that while sham shows little to no change in their total score, the Exablate main Arm shows a mean of approximately 5 points change was achieved at all the visits. Further improvement is shown by the Crossover Arm where approximately a mean of 6-points is achieved at all visits.

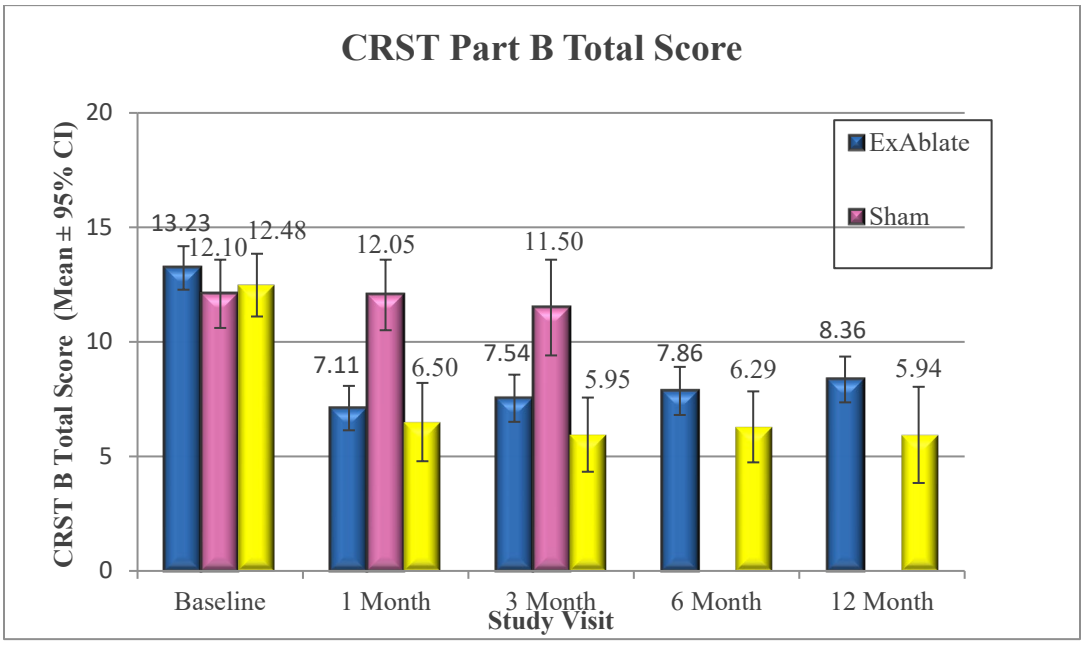

Figure 21: CRST Part B total Score through Month-12 for all 3-Study Arms: Exablate, Sham, and Crossover Arms

3.3 Conclusions Drawn from the Studies

3.3.1 Study Safety Conclusions

Overall, the summary of safety demonstrated that no Severe or Life-threatening events related to device or procedure occurred and no worsening depression occurred during the course of the study. A total of 184 AEs were reported in this study for the Exablate group (3.3 AEs per Exablate subject).

There were 53 AEs that were transient (resolved within 72 hours) and another 57 that were unrelated to Exablate. Of the remaining 74 AEs, the events with the highest frequency were numbness/tingling (22; 12%), imbalance (10; 5%), unsteady (4; 2%), and gait disturbance (4, 2%). These events are usually coincident with thalamotomy as reported in the literature.

Events that were related to the use of the stereotactic frame pins included the following: bruising (1 Mild event in Exablate group); numbness/tingling (1 Mild event in Exablate group; 1 Mild event and 1 Moderate event in Sham group); facial edema (1 Moderate event in Exablate group); eyelid ptosis (2 Mild event in Exablate group); pin site edema (1 Mild event in Exablate group; 1 Mild event and 1 Moderate event in Sham group), pin site abrasion (2 Mild events in Exablate group), pin site bleeding (1 Moderate event in Sham group), and pin site pain (7 Mild events and 1 Moderate event in Exablate group; 4 Mild events in Sham group).

Events categorized as procedure-related (e.g., fatigue, weakness, headache, and sonication-related head pain) lasting longer than 3 days. Of the 210 AEs, 99.5% were categorized as Mild or Moderate and many resolved within 3 months.

While 183 out 184 of the Exablate arm events were either Mild or Moderate (See **Table 5**), 8 events (8/184 = 4%) began at >30 days post-procedure and 14 events (14/184 = 8%) began more than 90 days post procedure (See **Table 8**). All of these events were single occurrence events and deemed Unrelated, with the most significant including transient ischemic attack (TIA) 6 weeks post-procedure, peripheral vision change, bradycardia, etc.

Of these 184 events recorded in this study, 42 events (42/184 = 23%) were recorded as on-going. The events occurring at a frequency greater than 3% were persistent mild or moderate numbness/tingling (12 events, 7%) and imbalance (6 events, 3%). Overall, the study shows a very favorable safety profile.

One Moderate event was deemed to become serious at Month 3 when the subject reported that the numbness/tingling in their hand impaired their ability to hold a pencil/write at work. The safety profile of the Exablate Crossover group mirrored that of the Exablate group in the Main Analysis.

The transient and unrelated events occurred at a similar frequency, as well as the procedure and thalamotomy events and the on-going events. In the Exablate Crossover group, 76 AEs were reported. There was 1 serious AE that occurred in the Exablate Crossover group. The subject was diagnosed with sick sinus syndrome 8 months after the Exablate procedure and underwent a

medical procedure to have a pacemaker implanted. This AE was not related to the Exablate procedure.

There were no unanticipated adverse device events reported, for the either the Exablate group or the Sham group, during the pivotal study

3.3.2 Study Efficacy Conclusions

The results of the present analysis provide reasonable assurance of efficacy and meet the pre-specified criteria for success. The Exablate group demonstrated a 46.9% improvement in the Composite Tremor/Motor Function score compared to baseline ($p<0.001$), while the Sham group demonstrated no improvement by Month 3. Furthermore, the study showed an improvement of approximately 64% in the tremor "Posture" score of the Exablate group, whereas the Sham group experienced a worsening of 4%.

When looking at the secondary endpoints, the Exablate treatment performed significantly better ($p<0.001$) on all 3 secondary confirmatory endpoints.

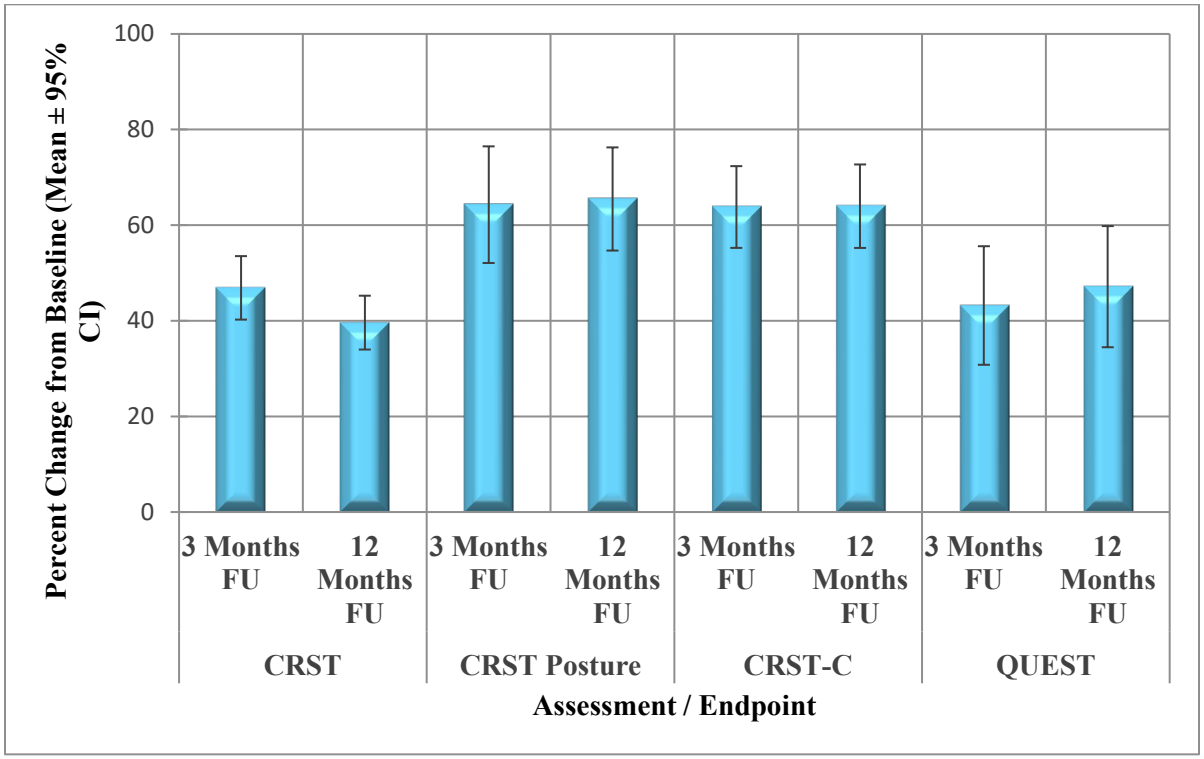

Figure 22: Summary of Study Effectiveness Assessment Endpoints

It is noted that by the Month 3 time point, 5 Exablate subjects who received sonications did not continue in the Exablate group. Two subjects withdrew after the Month 1 follow-up visit due to reasons unrelated to study participation. Three subjects withdrew from the study after the Month 3 follow-up visit due to: 1) one subject had DBA alternative treatment; 2) the other 2 subjects

withdrew due to personal reasons unrelated to the study. Finally, 2 Exablate subjects were moved to the Crossover study.

3.3.3 Study Overall Conclusions

The data from the pivotal clinical study support 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 idiopathic ET with medication-refractory tremor, the Exablate Neuro treatment is a reasonable alternative to existing treatments. The result from the pivotal study demonstrates that it is efficacious, and the safety profile is reasonable and does not cause any increased for this population who are at high risk due to the treatment location.

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

CHAPTER 4: CLINICAL STUDY EXABLATE 1.5T HEAD COIL "PMA P150038/S02"

4.1 Investigational Objectives

The purpose of this study report is to show equivalence of the safety profile and efficacy of Exablate Neuro 1.5T MRgFUS with dedicated head coil to Exablate Neuro 3T MRgFUS and its ability to cause thermal ablation of a designated area in the brain of patients suffering from medication-refractory ET. For all subjects, a unilateral thermal lesion was created in the *ventralis intermedius* (*Vim*) nucleus of the thalamus. Herein, the following data measures of the Exablate 1.5T cohort are shown alongside the Exablate cohorts of the pivotal study:

- Treated (contralateral) upper limb **CRST** applicable subscores of Part A and Part B
- CRST Part-C (subscales)
- Quality of life (as measured by QUEST) measures
- Safety profile

Because the primary endpoint analyses of the PMA (P150038) study was performed at Month-3 post-treatment, the outcomes of the 1.5T Exablate Neuro study are also presented up to Month-3 post-treatment. It should be noted that the PMA effectiveness data of both Exablate Pivotal and Exablate Crossover cohorts are presented through Month 12.

4.2 Study Design

This was a prospective, multi-center clinical trial. The protocol was identical to the ET002CA (IDE G120246/S07) protocol which was implemented in Japan across multiple centers during PMDA review of the ET002 pivotal study. The study population was medication-refractory ET patients who failed ET medications.

4.2.1 Clinical Report Sample Size

The report sample size includes the first 10 subjects treated using the Exablate Neuro system with its 1.5 Tesla MR Head-Coil in a 1.5-T MR Scanner. The following table (**TABLE 29**) provides information regarding the enrollment status at each of the participating centers. Osaka enrolled 8 subjects (80%) and Ohnishi enrolled 2 subjects (20%).

4.2.2 Selection of Study Population

Subjects met all the below inclusion/exclusion criteria as determined by two movement disorders specialists.

4.2.2.1 Inclusion criteria

1. Men and women age 22 years or older
2. Subjects who are able and willing to give consent and able to attend all study visits
3. A diagnosis of ET as confirmed from clinical history and examination by a neurologist or neurosurgeon specialized in movement disorder
4. Have had an inadequate response to one or two oral doses of medication, per local standards. An inadequate medication trial is defined as a therapeutic dose of each medication and poor response to drug, or the development of side effects as the medication dose is titrated.
5. Following the 1-month medication stability period, subject must be on stable medication for tremor. The 1-Month stability period visit will be 1-month post consent date
6. Vim nucleus of thalamus can be target by the ExAblate device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
7. Able to communicate sensations during the ExAblate treatment
8. Postural or intention tremor severity score of greater than or equal to 2 in the dominant hand/arm as measured by the CRST rating scale while stable on medication.
9. May have bilateral appendicular tremor
10. Significant disability due to Essential tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])
11. Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
12. Subjects on stable antidepressant medications for at least 3 months may be enrolled into this study (i.e., no change in medication drug or dosage for 3 months).

4.2.2.2 Exclusion Criteria

1. Subjects with unstable cardiac status including:
   - Unstable angina pectoris on medication
   - Subjects with documented myocardial infarction within six months of protocol entry

- Significant congestive heart failure defined with ejection fraction <40
- Subjects with unstable ventricular arrhythmias
- Subjects with atrial arrhythmias that are not rate-controlled

2. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within a 12-month period:
   - Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
   - Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use).
   - Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct).
   - Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).
3. Severe hypertension (diastolic BP > 100 on medication)
4. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
5. Known intolerance or allergies to the MRI contrast agent (e.g., Gadolinium or Magnevist) including advanced kidney disease
6. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m^2 (or per local standards should that be more restrictive) and/or who is on dialysis;
7. History of abnormal bleeding and/or coagulopathy
8. Receiving anticoagulant (e.g., warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
9. Active or suspected acute or chronic uncontrolled infection
10. History of immunocompromise including those who are HIV positive.
11. History of intracranial hemorrhage
12. Cerebrovascular disease (multiple CVA or CVA within 6 months)
13. Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).

14. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment. (can be up to 4 hrs of total table time.)
15. Are participating or have participated in another clinical trial in the last 30 days
16. Significant claustrophobia that cannot be managed with mild medication.
17. Subjects unable to communicate with the investigator and staff.
18. Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
19. Anyone suspected to have the diagnosis of idiopathic Parkinson's disease. Anyone with the presence of parkinsonian features including bradykinesia, rigidity, or postural instability will be excluded. Subjects who exhibit only mild resting tremor, but no other symptoms or signs of PD may be included.
20. Presence of significant cognitive impairment as determined with a score ≤ 24 on the Mini Mental Status Examination (MMSE)
21. Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
22. Subjects with a history of seizures within the past year
23. Subjects with presence or history of psychosis will be excluded. Subjects with significant or active mood disorders including depression will be excluded. For the purpose of this study, we consider a significant mood disorder to include any subject who:
    - Scores ≥ 20 on the PHQ-9 questionnaire
    - Is currently under the care of a psychiatrist
    - Is currently participating in cognitive-behavioral therapy
    - Has been hospitalized for the treatment of a psychiatric illness within 12 months
    - Has ever received transcranial magnetic stimulation
    - Has ever received electroconvulsive therapy
24. Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimeter, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
25. Subjects with brain tumors
26. Any illness that in the investigator's opinion preclude participation in this study.
27. Pregnancy or lactation.
28. Legal incapacity or limited legal capacity.

29. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
30. Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
31. Subjects who have an Overall Skull Density Ratio of 0.3 (±0.05) or less as calculated from the screening CT.
    - It should be noted that for those candidates whose SDR ratio score is within the standard deviation, full technical assessment should be performed and reviewed by study investigator with the support of the sponsor.

4.2.3 Study Conduct

All local and universal Good Clinical Practices were followed during the conduct of this study under Institutional Review Board oversight. A qualified investigator oversaw all activities, and INSIGHTEC monitored the ongoing study activities and data entry on a routine basis per Insightec SOP's.

4.2.4 Pre-Treatment Data Collection and Procedures

Subjects provided demographic and baseline information to determine eligibility status. Subjects were assessed for tremor severity based on CRST measurements performed by the local site neurologist according to a standardized methodology. The Part C and activities of daily living questionnaire that was conducted by the local site neurologist based upon patient interview. Subjects were asked to complete a QUEST quality of life assessment. All measures were taken at Baseline and at each scheduled monthly time point. Comparisons of the post-treatment assessments were compared back to the Baseline condition as a measure of overall improvement.

4.2.5 Study Treatment

The Exablate Neuro system was designed and manufactured to be compatible with either the 3T or 1.5T MR scanners. Insightec developed a dedicated 1.5T MR Head Coil that is intended to enhance the Signal-to-Noise ratio of the 1.5T MR scanner images to be comparable to those of the 3T scanner. Using the dedicated head coil with the 1.5T MR provides comparable imaging, but in no way changes the delivery of energy delivered by the Exablate workstation.

In this study, subjects were treated in the same manner and using the same software version as subjects in the pivotal study except that the treatment was performed with the 1.5T Exablate system using its dedicated MR Head Coil.

4.2.6 Study Follow-up

Subjects were discharged at Day 1 and safety was checked at Week 1. All safety and efficacy assessments were performed at Months 1 and 3 using the same assessments as collected in the

pivotal study and following the same method of statistical analysis as performed for the pivotal according to the Statistical Analysis Plan.

4.3 Study Endpoints

The primary endpoint for the study utilized 8 components of the CRST (Part A + B) which measures the treated arm tremor in 3 conditions (rest, posture, action/intention) as well as the ability to perform five daily tasks. Efficacy for Essential Tremor was assessed for each treated ET patient at each time point. Baseline was compared to the post-treatment interval at Months 3 for each subject. These data were reported in 3 ways:

1. As a normalized value where the sums were divided by the maximum possible score,
2. Using the actual calculated score sums, and
3. Calculations based on percent change from Baseline. All values are reported as a mean for each reporting method across the cohort.

In addition, a single CRST Part A component for the upper extremity for 'posture' tremor was compared as an individual measure in a similar fashion using just the score value and % Change from Baseline.

The CRST Part C is a measure of how well the patient performs activities of daily living without accommodations to their tremor. It encompasses the following areas: Speaking, Eating, Drinking, Hygiene, Dressing, Writing, Working, and Social Activities. The composite score of these activities was calculated at each time point and compared back to Baseline and % Change from Baseline was also calculated.

A third measure of efficacy, a Quality of Life (patient-reported measure covering Communication, Work and Finances, Hobbies and Leisure, Physical and Psychosocial domains), was also collected using the validated QUEST assessment questionnaire and was analyzed as change from Baseline and Percent Change from Baseline.

The safety profile included all adverse events collected for all 10 subjects. These events were evaluated and compared to the types and frequency of events that were observed in the PMA Exablate cohort.

4.4 Results

4.4.1 Demographics

The baseline and demographic characteristics (See **TABLE 29**) of the patients showed no major differences between the pivotal study population and the Exablate 1.5T cohort with the exceptions being subjects in the Exablate 1.5T population were 100% Japanese and had a BMI roughly 17% less than the Exablate Pivotal cohort. Neither of these differences has an effect on the thalamotomy procedure or outcome.

TABLE 29. BASELINE AND DEMOGRAPHIC INFORMATION BY TREATMENT COHORT			
DEMOGRAPHIC CHARACTERISTICS		Treatment Cohort	
		EXABLATE PIVOTAL N=56	EXABLATE 1.5T N=10
Age [Years]	Mean	70.8	70.2
BMI [kg/m²]	Mean	26.9	22.39
Height [cm]	Mean	171.9	163.9
Weight [kg]	Mean	79.6	59.9
Gender	Male	37 (66%)	8 (80%)
	Female	19 (34%)	2 (20%)
Race	Caucasian	41 (73%)	0
	Black	0	0
	Asian	14 (25%)	10 (100%)
	Hispanic	0	0
	Other	1 (2%)	0
Family History of ET	Yes	39 (70%)	8 (80%)
	No	17 (30%)	2 (20%)
Average Years History of ET	Mean	13.9	11.2
Skull Density Ratio	Mean	0.6	0.46
Baseline CRST PE score	Mean	0.57	0.61
Baseline QUEST	Mean	42.55	31.06
Baseline Part C CRST	Mean	16.3	16.0

4.4.2 CRST (Part A + Part B) Normalized Tremor Motor Function

The primary efficacy analysis of the Pivotal cohort evaluated the Month 3 post-treatment improvement compared to Baseline in the treated (contralateral) upper extremity CRST sub-score (Part A and B). At Baseline, the normalized Tremor/Motor Function score was 0.61. By Month 3, the score had improved to 0.23.

This compares favorably with the Exablate Pivotal cohort (0.57 at Baseline; 0.30 at Month 3). The Exablate 1.5T cohort showed equivalent improvements in the Tremor/Motor Function Normalized Score as shown in **Figure 23**.

It should be noted the following graphs of the primary and secondary endpoints below also include 6 and 12 Month pivotal study data to provide a likely expectation for Exablate 1.5T MR cohort.

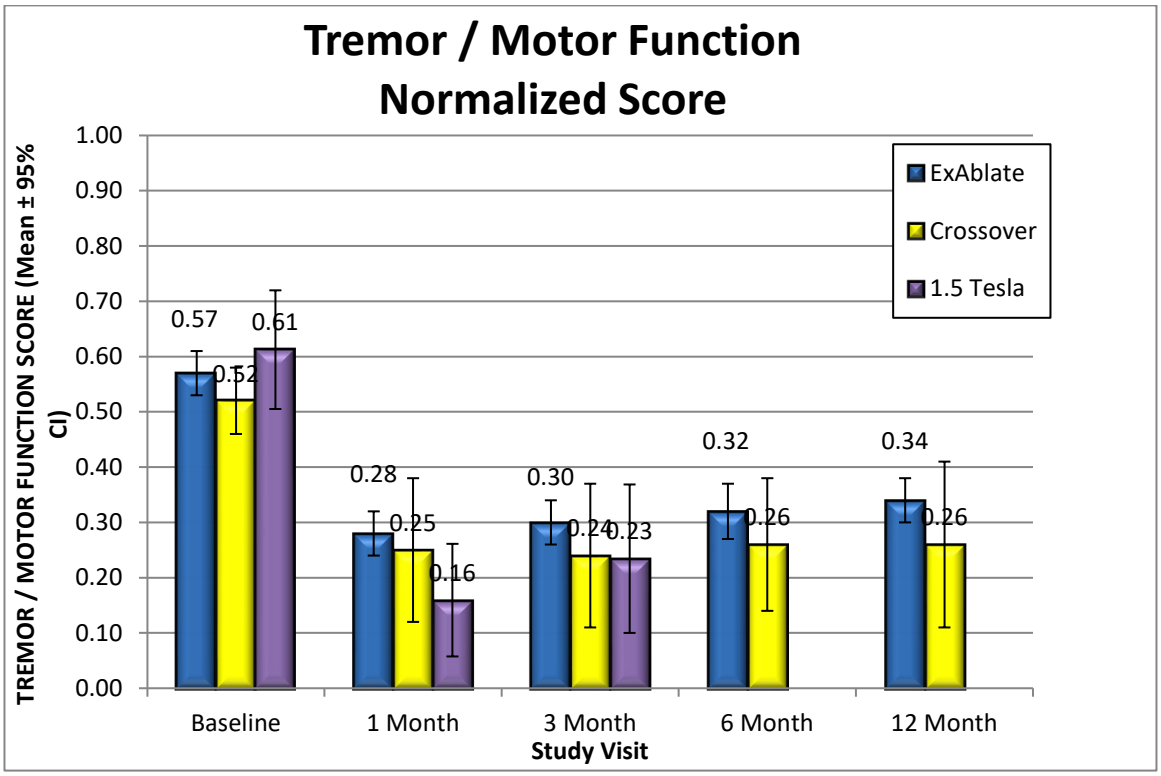

Figure 23: The actual score is normalized by the maximum score of 32 or 28 depending on the treated (contra-lateral) Arm

4.4.3 CRST (Part A + Part B) Actual Value Tremor / Motor Function

In the following **Figure 24** the actual values of the tremor/motor function subscores of Parts-(A+B) are displayed. The Baseline value was 19.6 which improved to 7.5 by Month 3. This compares favorably to Exablate Pivotal (18.6 at Baseline; 9.55 at Month 3). At the Month-3 post-treatment, equivalent improvements in clinical outcomes were observed between the pivotal cohorts and the Exablate 1.5T cohort.

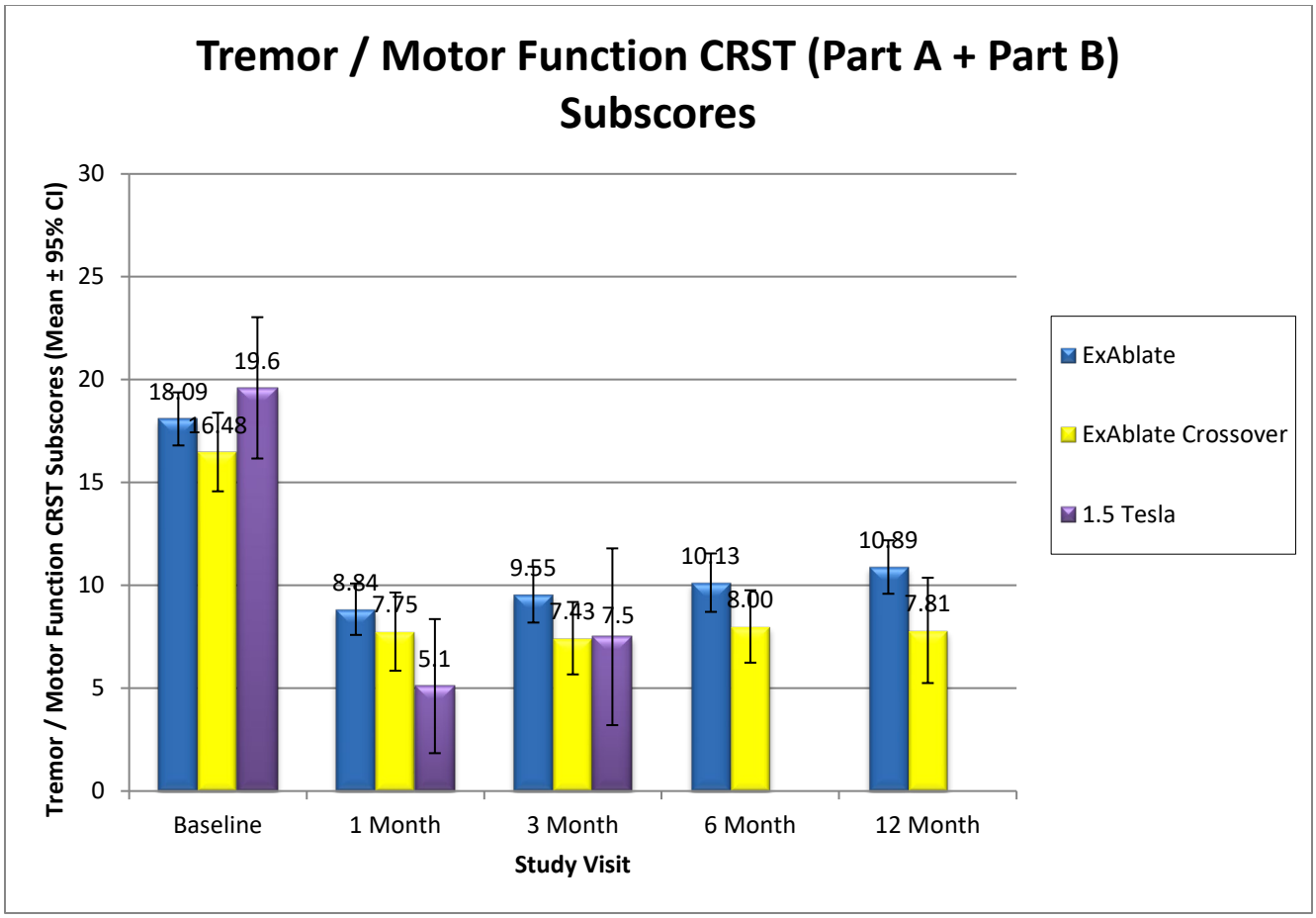

Figure 24: Tremor / Motor Function CRST actual Subscore (Part A + Part B)

4.4.4 Percent Tremor / Motor Function

Percent Change from Baseline of the primary endpoint Parts-(A + B) was also calculated. By Month 3 post-treatment, the Exablate 1.5T cohort demonstrated a 75.3% improvement compared to the Exablate Pivotal cohort demonstrated a 46.9% improvement compared to Baseline (see **Figure 25**). It should be noted the Exablate Cross-over cohort reflected a mean improvement of 53%.

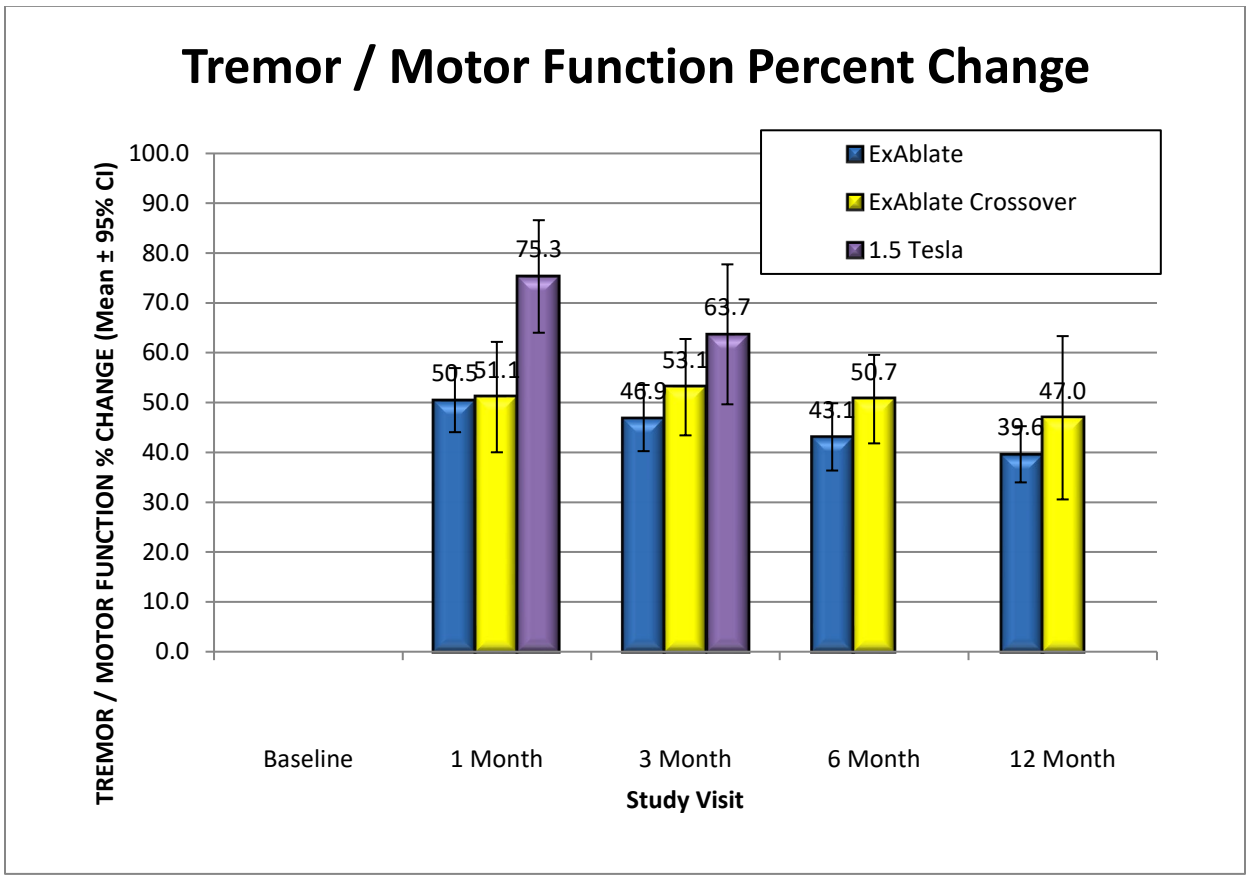

Figure 25: Tremor / Motor Function Percent of Change

4.4.5 CRST Part A Posture Upper Extremity Only

The Part A Posture component is an important single indicator of tremor for ET subjects. For this reason, the Part A was evaluated as a lone measure. **Figure 26** shows the actual postural component score values across all three cohorts.

The 1.5T Exablate cohort improved from 2.70 at Baseline to 0.70 at Month 3. The Exablate Treatment cohort improved from 2.13 at Baseline to 0.64 at Month 3. Similarly, the Exablate Crossover cohort improved from 1.71 at Baseline to 0.43 at Month 3. At Month 3, the Percent Change from Baseline was 73.3% for the Exablate 1.5%, 64.3% for the Exablate Treatment cohort, and 56.4% for the Exablate Crossover cohort (**TABLE 30**).

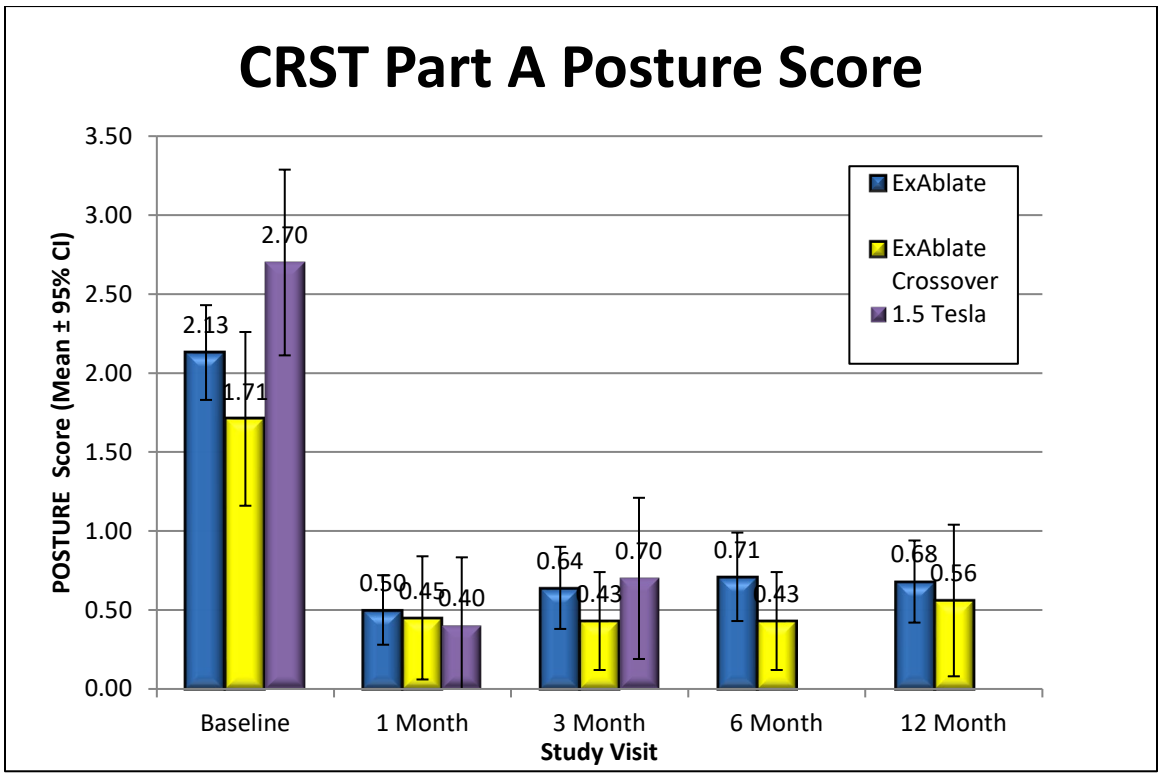

Figure 26: CRST Part A Posture Component Scores over Time and by Treatment Cohort

TABLE 30. CRST PART A (UPPER EXTREMITY, POSTURE COMPONENT ONLY FOR TREATED ARM BY TREATMENT COHORT BY VISIT)

SE3	EXABLATE N=56		CROSSOVER N=21		EXABLATE 1.5T N=10	
	Change from Baseline	% Change from Baseline[ʃ]	Change from Baseline	% Change from Baseline[ʃ]	Change from Baseline	% Change from Baseline
Month 3	1.48	64.3%	1.29	56.4%	1.82	73.3%
Lower 95% CI	1.16	52.1%	0.78	36.6%	1.24	52.6%
Upper 95% CI	1.8	76.5%	1.79	76.1%	2.4	94.1%
Month 6	1.41	62.5% (n=52)	1.29	56.8%		
Lower 95% CI	1.08	50.8%	0.81	36.3%		
Upper 95% CI	1.74	74.2%	1.77	77.2%		
Month 12	1.45	65.5%	0.94	46.4%		
Lower 95% CI	1.14	54.7%	0.28	22.3%		
Upper 95% CI	1.76	76.3%	1.60	70.5%		

[ʃ]: % Change: 100*(Baseline - Follow-up Visit)/Baseline

[+] Difference between treatment cohorts was statistically significant (P<0.001) (Wilcoxon signed rank test).

[++]% Change from Baseline to Months 3, 6 and 12 was tested and found to be statistically highly significant (P<0.001) for ExAblate Arm

Notes:
1. Change from Baseline was calculated as Difference (Baseline - Visit).
2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores)

4.4.6 CRST Part C Total Score

In addition to the primary endpoint and Part A, the overall CRST Part C total score for the percent improvement in functional disabilities was assessed at Month-3 as part of the study endpoints.

The Part C is another composite score encompassing speaking, eating, drinking, hygiene, dressing, writing, working and activities. The Exablate 1.5T cohort improved from 16.00 at Baseline to 4.70 at Month 3. The Exablate Treatment cohort improved from 16.54 at Baseline to 6.16 at Month 3 while the Exablate Crossover cohort improved from 16.0 to 4.29 at Month 3 (**Figure 27**).

The Mean Percent Change from Baseline was 72.9% in the 1.5T cohort, 63.8% in the Exablate Treatment cohort, and 74.9% in the Exablate Crossover cohort (**TABLE 31**). The Exablate 1.5T results were once again similar to the pivotal and crossover cohorts.

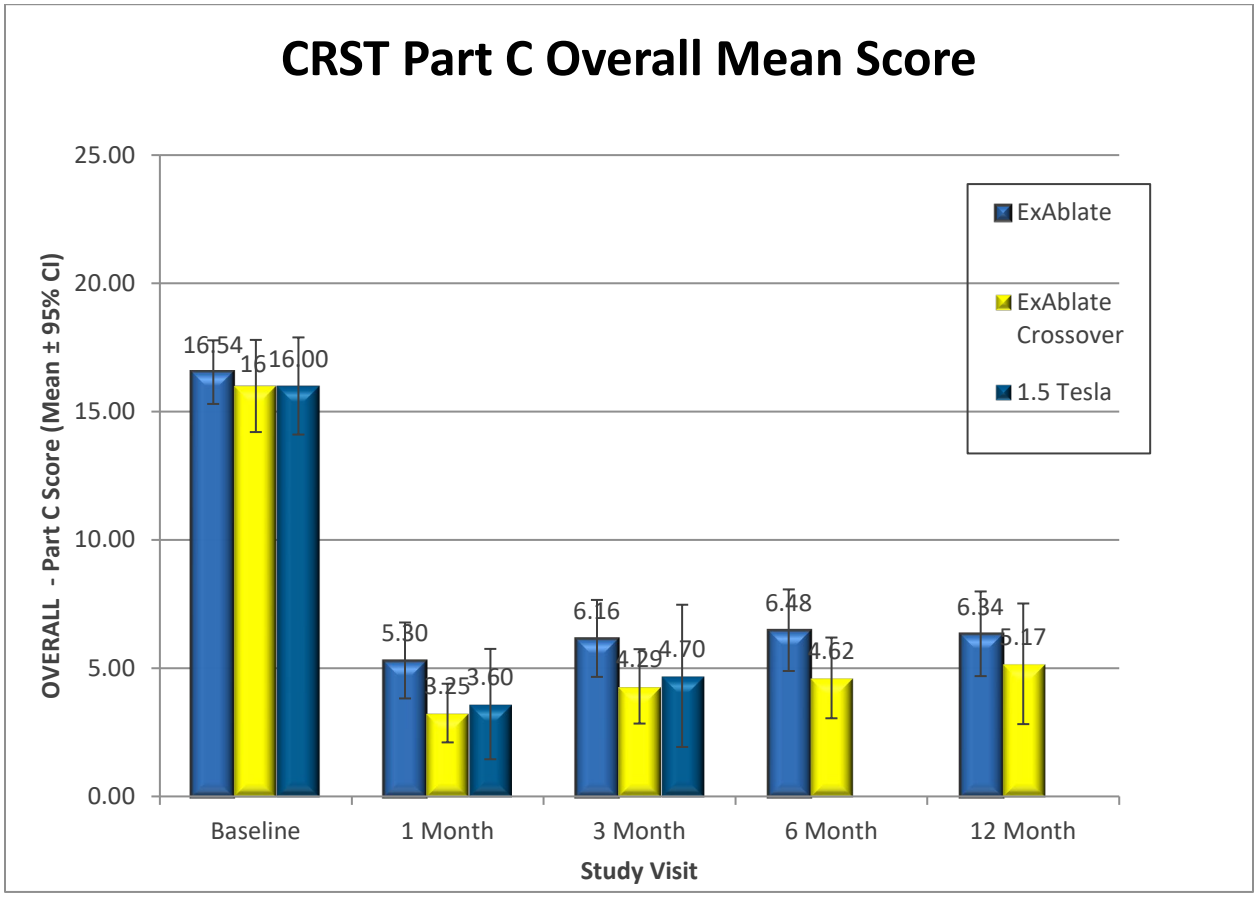

Figure 27: the Overall CRST Part-C scores through Month-12.
This Part-C is a composite of 8-components with a maximum total score of 32

TABLE 31. CONFIRMATORY ENDPOINT - CRST PART C OVERALL FUNCTIONAL DISABILITIES SCORE /% CHANGE FROM BASELINE BY TREATMENT COHORT AND BY VISIT (ITT)

	EXABLATE N=56		CROSSOVER N=21		EXABLATE 1.5T N=10	
SE3	Change from Baseline	% Change from Baseline[∫]	Change from Baseline	% Change from Baseline[∫]	Change from Baseline	% Change from Baseline
Month 3	10.38	63.8%	4.29	74.6%	11.30	72.9%
Lower 95% CI	8.81	55.3	1.00	66.2%	9.32	59.6%
Upper 95% CI	11.94	72.4%	7.00	82.9%	13.28	85.2%
Month 6	10.05	61.8%[++]	4.62	72.1%		
Lower 95% CI	8.42	64.3%	2.00	62.4%		
Upper 95% CI	11.69	81.8%	6.00	81.8%		
Month 12	10.20	64.0%++	5.17 (N=18)	68.9%		
Lower 95% CI	8.66	55.2%	0.00	55.0%		
Upper 95% CI	11.74	72.7%	9.00	82.9%		

[∫]: % change: 100*(Baseline - Follow-up Visit)/Baseline

[+] Difference between treatment cohorts was statistically significant (p<0.001) (Wilcoxon signed rank test).

[++]% Change from Baseline to Months 3, 6 and 12 was tested and found to be statistically highly significant (p<0.001) for Exablate Arm

Notes:

1. Change from Baseline was calculated as Difference (Baseline - Visit).
2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

4.4.7 QUEST – Quality of Life

Quality of Life scores at the Month-3 were also equivalent between Exablate treatment cohort and 1.5T treatment cohort. This QUEST Patient Reported Outcome (PRO) was completed by the patients and was meant to confirm the measured reduction in tremor with an improvement in daily physical and social activities.

TABLE 32 shows improvement in the mean scores of the Summary of Dimension in the Exablate 1.5 Tesla cohort was 73.3%, 43.2% in the Exablate Treatment cohort, and 59.2% in the Crossover cohort.

TABLE 32. CONFIRMATORY SECONDARY EFFICACY QUEST SUMMARY OF DIMENSIONS SCORE % CHANGE FROM BASELINE AT MONTH 3 BY TREATMENT COHORT (ITT)

SE1	TREATMENT COHORT					
	EXABLATE N=56		CROSSOVER N=21		EXABLATE 1.5T N=10	
ITT Mean	23.11	43.2%	19.20	59.2%	21.58	73.3%
..Lower 95% CI	13.33	34.3%	3.54	38.16	14.23	60.77%
Upper 95% CI	26.11	56.3%	30.28	94.94	28.94	85.86%

1. SE1 was calculated as Percent Change ((Baseline - Visit)/Baseline)*100.

2. Higher SE1 values represent improvement

4.4.8 Summary of Results

Using the measure of Percent Change from Baseline to Month 3 for all variables, **TABLE 33** and **Figure 28** show that there is equivalent improvement in all 4 efficacy measures across the Exablate treated cohorts. It is believed that as more experience is gained with the therapy, that the results show a slightly improved outcome due to a learning curve in performing thalamotomy.

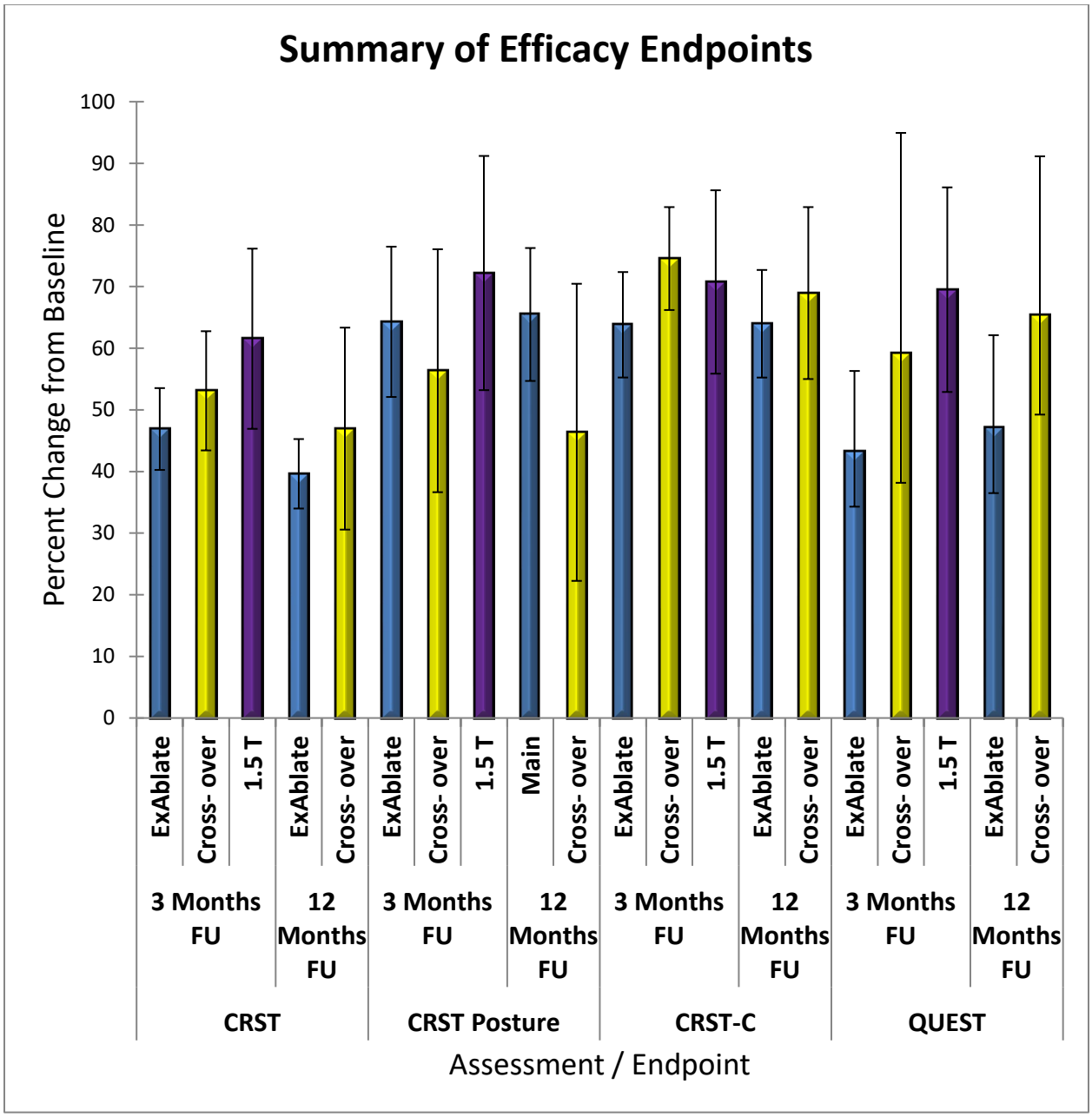

Figure 28: Study Efficacy Assessment Endpoints

TABLE 33. SUMMARY OF MAJOR EFFICACY ENDPOINTS (PRIMARY & SECONDARY ENDPOINTS)			
	EXABLATE N=56	CROSSOVER N=21	EXABLATE 1.5T N=10
Primary Endpoint – Composite Tremor/Motor Function	46.9%	53.1%	63.7%
CRST, Part A Tremor "Posture"	64.3%	56.6%	73.3%
CRST, Part C	63.8%	74.6%	72.9%
QUEST Summary of Dimensions	43.2%	59.2%	73.3%

4.4.9 Safety Assessment

The primary analysis of safety was based upon the collection of adverse events during the study as collected by the investigators at each site. Similar to the Exablate cohort, an average of 2.3 events per subject (min 0, max 4) was recorded in the Exablate 1.5T MR cohort. An average of 2.8 events per subject (min 0, max 12 events) was recorded in the Exablate cohort. Three subjects in the Exablate 1.5T MR cohort had no adverse events reported, and eight subjects in the Exablate cohort had no adverse events. As shown in **TABLE 34**, most events were Mild or Moderate in Exablate 1.5T MR cohort (14/15, 93%). This was consistent with Exablate cohort where 98% (183/184) were Mild/Moderate events:

TABLE 34. NUMBER OF ALL ADVERSE EVENTS BY SEVERITY AND TREATMENT COHORT				
SEVERITY	EXABLATE PIVOTAL		EXABLATE 1.5T	
	Frequency N=184	Incidence N=56	Frequency N=15	Incidence N=10
Mild	137 (74%)	46 (82%)	10 (67%)	7 (70%)
Moderate	46 (25%)	28 (50%)	4 (27%)	2 (20%)
Severe	1 (1%)	1 (2%)	1 (7%)	1 (1%)
Life	0	0 (0%)	0 (0%)	0 (0%)
TOTAL	184 (100%)	49 (88%)	15 (100%)	7 (70%)

TABLE 35 below shows all the events that occurred by severity and treatment cohort as well as by coded term and body system. In this study, there were no Serious or Life-threatening events, or new or unexpected events. The overall safety profile is no different from what was reported in the PMA study.

TABLE 35. FREQUENCY OF ADVERSE EVENTS BY TREATMENT COHORT AND SEVERITY							
		EXABLATE (N EVENTS = 184; # PTS = 56)			EXABLATE 1.5T (N EVENTS = 15; # PTS = 10)		
BODY SYSTEM	PREFERRED TERM	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular	Bradycardia	1 (0.5%)	1 (0.5%)	0	0	0	0
	Hypertension	1 (0.5%)	4 (2%)	0	0	0	0
	Hypotension	0	1 (0.5%)	0	0	0	0
	TIA	0	0	1 (0.5%)	0	0	0
ENT	Tinnitus	3 (2%)	0	0	0	0	0
Eye	Vision problems	1 (0.5%)	0	0	0	0	0
	Watering Eyes	1 (0.5%)	0	0	0	0	0
Gastrointestinal	Dysphagia	1 (0.5%)	0	0	0	0	0
	Increased salivation	1 (0.5%)	0	0	0	0	0
	Nausea/Vomiting	6 (3%)	7 (4%)	0	0	2 (13%)	0
General	Fatigue	2 (1%)	0	0	0	0	0
	Generalized Weakness	0	1 (0.5%)	0	0	0	0
	Impatience	1 (0.5%)	0	0	0	0	0
	Restlessness	1 (0.5%)	0	0	0	0	0
Infection	Common Cold	1 (0.5%)	0	0	0	0	0
	Ear Infection	0	1 (0.5%)	0	0	0	0
	Herpes zoster	0	0	0	1 (7%)	0	0
Musculoskeletal	Gait Disturbance	2 (1 %)	2 (1%)	0	1 (7%)	0	0
	Dysergia	1 (0.5%)	1 (0.5%)	0	0	0	0

TABLE 35. FREQUENCY OF ADVERSE EVENTS BY TREATMENT COHORT AND SEVERITY							
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS = 184; # PTS = 56)			EXABLATE 1.5T (N EVENTS = 15; # PTS = 10)		
		MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Imbalance	7 (4%)	3 (2%)	0		0	0
	Musculoskeletal Weakness	1 (0.5%)	1 (0.5%)	0	0	0	0
	Other Musculoskeletal Pain	0	1 (0.5%)	0	0	0	0
	Positional Pain	5 (3%)	0	0	1 (7%)	0	0
	Unsteady	5 (3%)	1 (0.5%)	0	0	0	0
Nervous	Anxiety	1 (0.5%)	0	0	0	0	0
	Ataxia	6 (3%)	1 (0.5%)	0	0	0	0
	Dizziness	0	1 (0.5%)	0	0	0	0
	Dysesthesia	1 (0.5%)	0	0	0	0	0
	Dysgeusia	3 (2%)	0	0	0	0	0
	Dysgnosia	2 (1%)	0	0	0	0	0
	Dysmetria	2 (1%)	0	0	0	0	0
	Involuntary Movements-UE	1 (0.5%)	0	0	0	0	0
	Memory Deterioration	1 (0.5%)	0	0	0	0	0
	Numbness/Tingling	24 (13%)	3 (2%)	0	0	0	0
	Slurred speech	1 (0.5%)	0	0	1 (7%)	0	0
	Paresthesia	1 (0.5%)	0	0	0	0	0
	Somnolence	1 (0.5%)	0	0	0	0	0
Pain/Discomfort	Ankle pain	0	1 (0.5%)	0	0	0	0

TABLE 35. FREQUENCY OF ADVERSE EVENTS BY TREATMENT COHORT AND SEVERITY							
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS = 184; # PTS = 56)			EXABLATE 1.5T (N EVENTS = 15; # PTS = 10)		
		MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Foot pain	0	1 (0.5%)	0	0	0	0
	Headache	10 (5%)	5 (3%)	0	0	1 (7%)	0
	Sonication-related Head pain	7 (4%)	7 (4%)	0	3 (20%)	1 (7%)	1 (7%)
Respiratory	Hiccups	1 (0.5%)	0	0	0	0	0
Skin	Bruising	1 (0.5%)	0	0	0	0	0
	Skin Rash	1 (0.5%)	0	0	0	0	0
Stereotactic Frame	Eyelid Ptosis	2 (1%)	0	0	0	0	0
	Facial edema	0	1 (0.5%)	0	0	0	0
	Numbness/Tingling	1 (0.5%)	0	0	0	0	0
	Bruising – Stereotactic Frame	1 (0.5%)	0	0	0	0	0
	Pin Site Edema	1 (0.5%)	0	0	1 (7%)		0
	Pin Site Abrasion	2 (1%)	0	0	0	0	0
	Pin site bleeding	0	0	0	0		0
	Pin site pain	7 (4%)	1 (0.5%)	0	1 (7%)	0	0
Urinary	Catheter Irritation	1 (0.5%)	0	0	0	0	0
	Urinary Urgency	1 (0.5%)	0	0	0	0	0
	BHP	0	1 (0.5%)	0	0	0	0
Vestibular Disorder	Vertigo	2 (1%)	0	0	0	0	0
	Dizziness	11 (6%)	0	0	1 (7%)	0	0

TABLE 35. FREQUENCY OF ADVERSE EVENTS BY TREATMENT COHORT AND SEVERITY							
BODY SYSTEM	PREFERRED TERM	EXABLATE (N EVENTS = 184; # PTS = 56)			EXABLATE 1.5T (N EVENTS = 15; # PTS = 10)		
		MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Paroxysmal Vertigo Episodes	1 (0.5%)	0	0	0	0	0
Vision	Vision change	1 (0.5%)	0	0	0	0	0
TOTAL		137 (74%)	46 (25%)	1 (0.5%)	10 (67%)	4 (27%)	1 (7%)

As reported in the PMA, in accordance with the DSMB and following their review, the events were categorized as follows:

- TRANSIENT Events: Transient events are those events that last seconds to less than 72 hours and resolve completely. These events are often solicited during sonications and help the physician to locate the desired ablative target.
- Events UNRELATED to Exablate: These 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.

Out of the 15 1.5T MR events, there are 9 events that were categorized as Transient and four events that are Unrelated. **TABLE 36** summarizes the transient and unrelated events. **TABLE 37** summarizes the procedure, device and thalamotomy-related events.

TABLE 36. FREQUENCY OF EXABLATE ADVERSE EVENTS CATEGORIZED AS TRANSIENT OR UNRELATED TO EXABLATE						
Relation / Body System / AE Coded Term			EXABLATE PIVOTAL N =184		EXABLATE 1.5T N =15	
			N	%	N	%
Transient Events	Gastrointestinal	Nausea/Vomiting	12	7%	2	13%
	Nervous	Anxiety	1	0.5%	0	0%
		Dysgnosia	1	0.5%	0	0%
		Dysgeusia	1	0.5%	0	0%
		Numbness/Tingling	4	2%	0	0%
	Pain/Discomfort	Headache	10	5%	2	13%
		Sonication-Related Head Pain	13	7%	4	27%
	Vestibular Disorder	Dizziness	9	5%	1	7%
		Vertigo	2	1%	0	0%
Transient Subtotal			53	29%	9	60%
Unrelated Events	Cardiovascular	Bradycardia	2	1%	0	0%
		Hypertension	5	3%	0	0%
		Hypotension	1	0.5%	0	0%
		TIA	1	0.5%	0	0%
	Eye	Vision Problem	2	1%	0	0%
		Watering Eyes	1	0.5%	0	0%
	Gastrointestinal	Increased Salivation/Drooling	1	0.5%	0	0%
		Nausea/Vomiting	1	0.5%	0	0%
	General	Impatience	1	0.5%	0	0%
		Restlessness	1	0.5%	0	0%
	Infection	Common Cold	1	0.5%	0	0%
		Ear Infection	1	0.5%	0	0%
		Herpes Zoster	0	0%	1	7%
	Musculoskeletal	Other Musculoskeletal Pain	1	0.5%	0	0%
		Positional Pain	5	2.7%	1	7%
		Unsteady	2	1.1%	0	0%
	Nervous	Anxiety	1	0.5%	0	0%
		Dizziness	1	0.5%	0	0%
		Dysgeusia	1	0.5%	0	0%
		Involuntary Movements - UE	1	0.5%	0	0%

TABLE 36. FREQUENCY OF EXABLATE ADVERSE EVENTS CATEGORIZED AS TRANSIENT OR UNRELATED TO EXABLATE						
Relation / Body System / AE Coded Term			EXABLATE PIVOTAL N =184		EXABLATE 1.5T N =15	
			N	%	N	%
		Memory Deterioration	1	0.5%	0	0%
		Somnolence	1	0.5%	0	0%
	Pain/Discomfort	Ankle pain	1	0.5%	0	0%
		Foot pain	1	0.5%	0	0%
	Respiratory	Hiccups	1	0.5%	0	0%
	Skin	Bruising	1	0.5%	0	0%
		Skin Rash	1	0.5%	0	0%
	Stereotactic Frame	Bruising - Stereotactic Frame	1	0.5%	0	0%
		Eyelid Ptosis	2	1.1%	0	0%
		Facial edema	1	0.5%	1	7%
		Numbness/Tingling	1	0.5%	0	0%
		Pin Site Abrasion	2	1.1%	0	0%
		Pin site bleeding	0	0.0%	0	0%
		Pin Site Edema	1	0.5%	0	0%
		Pin Site Pain	8	4.3%	1	7%
	Urinary	Catheter Irritation	1	0.5%	0	0%
		Urinary Urgency	1	0.5%	0	0%
	Urogenital	Benign Prostate Hypertrophy	1	0.5%	0	0%
	Vestibular Disorder	Paroxysmal vertigo episodes	1	0.5%	0	0%
SUBTOTAL UNRELATED			57	31%	4	27%
TOTAL			110	60%	13	87%

TABLE 37 presents the remaining events. These were categorized as procedure-related (lasting longer than 72 hours) or are related to the device/thalamotomy. Of the events that resolved, resolution generally was within 1 week to 3 months.

TABLE 37. FREQUENCY OF ADVERSE EVENTS CATEGORIZED AS RELATED TO THE PROCEDURE OR TO DEVICE/THALAMOTOMY BY TREATMENT COHORT						
Relation/Body System, AE Coded Term			ExAblate Pivotal N=184		ExAblate 1.5T N=15	
			N	%	N	%
Procedure-related	ENT	Tinnitus	3	2%	0	0%
	Gastrointestinal	Dysphagia	1	0.5%	0	0%
	General	Fatigue	2	1%	0	0%
		Generalized Weakness	1	0.5%	0	0%
	Musculoskeletal	Imbalance	0	0%	0	0%
	Nervous	Dysgnosia	1	0.5%	0	0%
		Numbness/ Tingling	1	0.5%	0	0%
	Pain/Discomfort	Headache	5	3%	0	0%
		Sonication-Related Head Pain	1	0.5%	0	0%
	Vestibular Disorder	Dizziness	1	0.5%	0	0%
Procedure Related Subtotal			16	9%	0	0%
Thalamotomy related	Musculoskeletal	Dysergia	2	1%	0	0%
		Gait Disturbance	4	2%	1	7%
		Imbalance	10	5%	0	0%
		Musculoskeletal Weakness	2	1.1%	0	0%
		Unsteady	4	2.2%	0	0%
	Nervous	Ataxia	7	3.8%	0	0%
		Dysesthesia	1	0.5%	0	0%
		Dysgeusia	1	0.5%	0	0%
		Dysmetria	2	1.1%	0	0%
		Numbness/ Tingling	22	12%	0	0%
		Paresthesia	1	0.5%	0	0%
		Slurred Speech	1	0.5%	1	7%
	Vestibular disorder	Dizziness	1	0.5%	0	0%
Subtotal Thalamotomy related			58	32%	2	13%
TOTAL			74	100%	2	13%

In summary, no major differences were observed between the pivotal trial data set and 1.5T MRI patient data set.

4.5 Discussion and Overall Conclusion

The data from this clinical study support the reasonable assurance of safety and effectiveness of this 1.5T MR Head Coil in conjunction with the Exablate Neuro when used in accordance with the indications for use. The result from this clinical study demonstrates that it is efficacious, and the safety profile is reasonable and does not cause any increased for this population who are at high risk due to the treatment location.

In conclusion, the treatment benefits of the Exablate Neuro when used in 1.5T MR scanner with its corresponding 1.5T MR Head coil for the target population outweigh the risks when used in accordance with the directions for use.

CHAPTER 5: SUMMARY OF LONG TERM FOLLOW-UP CLINICAL STUDY – 5 YEARS FOLLOW-UP

5.1. STUDY PURPOSE AND DESIGN

This chapter presents the results of the annual visits Year 2 through Year 5 of long-term follow up of subjects treated for their Essential Tremor (ET).

After Exablate-treated subjects completed the 12-month visit of the original pivotal study (see Chapter 3 for study design and pivotal study results), they continued into a long-term follow-up study with annual assessments out to Year 5. After the IDE (G120246) closed, subjects entered the Post Approval Study (PAS) for follow-up at whatever visit was due. Annual follow-up was continuous from the time of treatment to the 5-year visit.

5.1.1. OBJECTIVES

The objective of this study was to follow, observationally, IDE # G120246 Exablate-treated subjects for Essential Tremor for safety and effectiveness from Year 2 to Year 5 in compliance with the post approval conditions under PMA P150038.

Safety: To evaluate long-term incidence and severity of adverse events/serious adverse events (AE/SAEs) associated with Exablate Neuro treatment in medication-refractory ET.

Effectiveness: To collect long term effectiveness of tremor control (CRST-Clinical Rating Scale for Tremor) and quality of life in Essential Tremor (QUEST) of the Exablate Neuro treated subjects.

No hypothesis testing was proposed. Results are presented as summary statistics, e.g., percent, mean, standard deviation and 95% confidence intervals of percent change from Baseline (prior to treatment in the pivotal study/Chapter 3).

5.1.2. SUBJECT POPULATION, ELIGIBILITY CRITERIA

All subjects that were Exablate-treated in the original pivotal study (“Main” blinded Exablate arm (ET002) and Crossover arm (ET002C) under IDE # G120246) were consented to participate in the PAS long-term follow-up study. There is no comparator group for long-term follow-up. These subjects had medication-refractory Essential Tremor confirmed by medical history and examination by a neurologist or neurosurgeon that specialized in movement disorders. They were refractory to trials of at least two ET medications, one of which was a first line therapy of either propranolol or primidone.

Seventy subjects (i.e., 51 in the Exablate test arm and 19 treated in the Crossover arm) completed the 12 Month visit in the pivotal study (Chapter 3) and consented to participate in

this long-term PAS. All subjects in this long-term follow-up received a unilateral thalamotomy for Essential Tremor in the pivotal trial. Subject participation in study visits through five years is presented below (**Figure 1**).

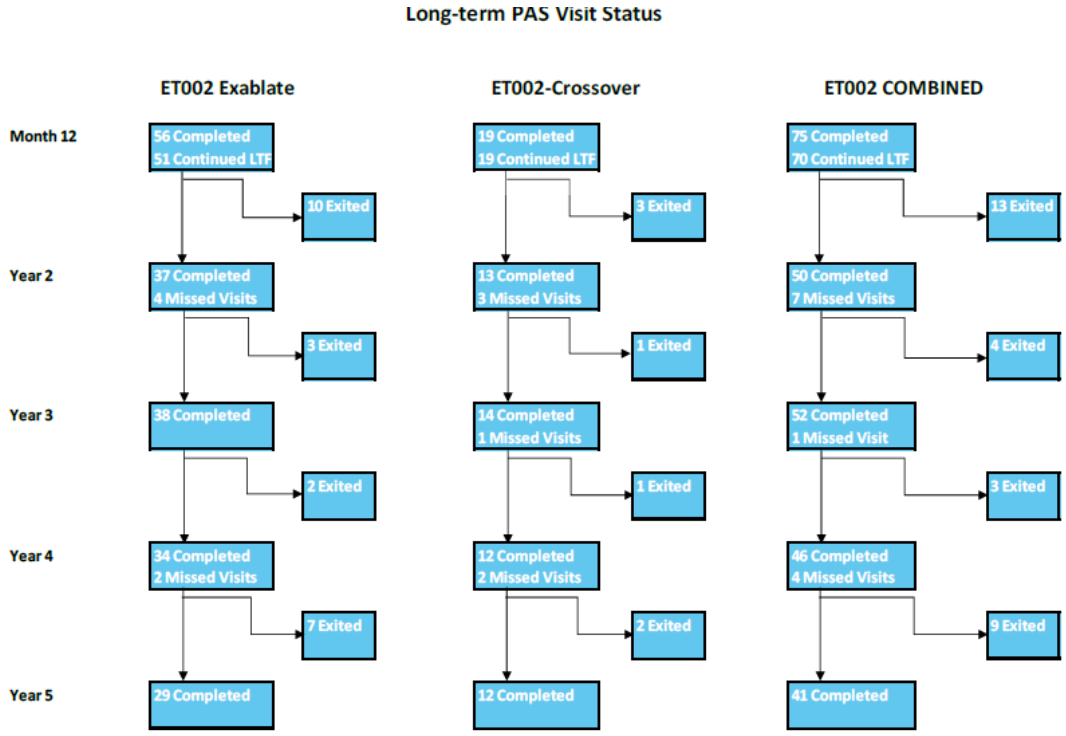

Figure 1. Subject participation in study visits through five years follow up in the PAS. Continued Long-Term Follow-Up (LTF): Subjects enrolled following the Month 12 visit. Completed: Subjects completing the visit. Missed Visit: Subjects missed the visit but continuing in study. Exited: Subjects exiting the study

Characteristics of the subjects continuing to the 2 Year visit in the PAS are presented in the following table. The population had an average age of 71 years, was predominantly white and male. The left- brain side had been treated to relieve ET symptoms of their right arm.

SUBJECT CHARACTERISTICS				
Characteristics		ET002*	ET002C*	Combined
Age (years)	Mean	70.8	71.0	70.9
	Std	9.07	6.69	8.41
	Total (n)	41	16	57
Race (n)	White	29	14	43
	Asian	11	2	13
	Other	1	0	1
	Total (n)	41	16	57
Gender (n)	Male	29	13	42
	Female	12	3	15
	Total	41	16	57
Brain side treated (n)	Left	38	12	50
	Right	3	4	7
	Total	41	16	57

*ET002 is the Exablate-treated study arm subjects and ET002C is the Crossover arm subjects from the PAS starting at Year 2.

5.1.3. Study Follow Up

All participating subjects were consented at baseline for 5 years. Subjects are seen for follow-up at year 2, year 3, year 4 and year 5. Subjects are evaluated for general health, efficacy measurements as well as for device/procedure related AEs that occurred during the follow-up period. **TABLE 38** below includes the summary of the long-term study visit schedule and procedures.

TABLE 38. SUMMARY OF STUDY SCHEDULE EVALUATIONS				
	YEAR 2	YEAR 3	YEAR 4	YEAR 5
PHYSICAL EXAM	X	X	X	X
CRST	X	X	X	X
QUEST	X	X	X	X
ADVERSE EVENTS	X	X	X	X
EXIT FORM	X	X	X	X

5.1.4 Study Endpoints

5.1.4.1 Safety Endpoint

The primary safety outcome is to provide an evaluation of the incidence and severity of device / treatment related complications from the treatment day visit to all study follow ups through Year 5. Resolution of ongoing events was assessed at each visit as well as any new events that occurred since the last visit.

5.1.4.2 Effectiveness Endpoint

The long-term CRST and QUEST score for each subject at each long-term visit is compared to their own baseline assessment prior to treatment. Change from the original baseline before treatment is calculated at each visit for each patient and for each outcome used in the study. The % change from baseline for each patient is then averaged across all subjects for assessing the mean value and mean % change from baseline for each of the following outcomes which is assessed annually at years 2, 3, 4, and 5:

1. Tremor Motor Function using the Clinical Rating Scale for Tremors (CRST) Parts A + B
2. Upper Extremity Posture using the CRST Part A
3. Functional Disability using the CRST Part C
4. Quality of life using the Questionnaire for Essential Tremor (QUEST)

5.1.5 Analysis Population

5.1.5.1 Study Sample Size

There was no statistical consideration or sample size for this study. All Exablate treated subjects who were treated in the pivotal study were included in this long-term follow-up study, starting at the next scheduled study visit date.

5.1.5.2 Study Analysis Population

The following analysis populations were used to evaluate study results:

Exablate Population

The “Exablate” population includes all subjects from the pivotal study with at least one sonication in either the Exablate or the sham arm for whom there exist valid baseline measurement and at least one post-baseline measurement on the efficacy data. All subjects were unblinded to treatment assignment as of their Month 3 visit.

Crossover Population

The “Crossover” population includes only the pivotal study subjects who elected to receive the Exablate sonication after being unblinded following completion of the 3- month study visit. The long-term follow-up visit schedule was established from the time of the Exablate procedure. This population was treated with an unblinded Exablate procedure after being informed of their

treatment assignment in the "Main" analysis, and they elected to undergo an Exablate treatment.

Combined Population

All subjects in each of the Exablate and Crossover populations completed the same treatment procedure and visit schedule; therefore a "Combined" population was also evaluated. This population includes all subjects from the Exablate and Crossover populations. All visits for all subjects in this combined population were unblinded.

5.1.6 Study Subject Accountability

During the pivotal study, 76 subjects received treatment (i.e., Exablate or sham), of which 74 (97.4%) completed follow-up through the primary endpoint (3-month). Two Exablate subjects who withdrew prior to the 3-month follow-up visit did so for reasons unrelated to their participation in the study. All 20 sham subjects completed the primary endpoint visit. The full subject accountability for the pivotal study is found in **Chapter 3**. Fifty-one (51) Exablate subjects completed their 12-month follow-up visit and continued in the long-term follow-up study.

At the 3-month follow-up visit, sham subjects were given the option of crossing over to the Exablate treatment if they still met the enrollment criteria. Of the 20 sham subjects, 19 became crossover subjects. In addition, 2 non-responding Exablate subjects were placed in the crossover group and re-treated with Exablate. Of the sham Crossover subjects, all 19 completed their 12-month follow up visit and continued in the long-term follow-up study (see Chapter 3 of this document for more details). Thus, a combined seventy subjects completed the 12 Month visit and continued to the 2 Year visit (**Figure 1** above, **Table 39**).

All attempts were made to follow subjects enrolled in the long-term follow-up study to 5 years of follow-up, including the implementation of remote visits during the COVID-19 pandemic and subject accountability is presented below in Tables 3 and 4. The final years of follow-up occurred during the COVID-19 pandemic when physician offices were closed to routine visits and travel was very difficult for subjects who lived far away. Despite these conditions and the long duration of follow-up, approximately 60% of all subjects were evaluated through 5 years. A total of 29 subjects withdrew from the study. Three subjects could not be found to schedule follow-up visits, 5 subjects had alternative treatments, such as deep brain stimulation (DBS), 2 subjects could not be treated effectively due to skull shape or skull density, and 19 subjects were unable to travel due to difficulties relating to travel restrictions and/or the COVID-19 pandemic or chose not to continue in the study for personal reasons.

Subject accountability is shown on the next page.

TABLE 39. PATIENT DISPOSITION BY ANALYSIS GROUP AND SCHEDULED VISIT												
CATEGORY	YEAR 2 FU			YEAR 3 FU			YEAR 4 FU			YEAR 5 FU		
	EXABLATE	CROSSOVER	COMBINED	EXABLATE	CROSSOVER	COMBINED	EXABLATE	CROSSOVER	COMBINED	EXABLATE	CROSSOVER	COMBINED
Theoretical	51	19	70	51	19	70	51	19	70	51	19	70
Exited	10	3	13	3	1	4	2	1	3	7	2	9
Expected	41	16	57	38	15	53	36	14	50	29	12	41
Missed Visit	4	3	7	0	1	1	2	2	4	0	0	0
Actual	37	13	50	38	14	52	34	12	46	29	12	41
Actual/Expected%	90%	81%	88%	100%	93%	98%	94%	86%	92%	100%	100%	100%
Actual/(Theoretical – Deaths)	73%	68%	71%	75%	74%	74%	67%	63%	66%	57%	63%	59%

TABLE 40: PATIENT EXIT BY REASON

CATEGORY	YEAR 2 FU			YEAR 3 FU			YEAR 4 FU			YEAR 5 FU		
	EXABLATE	CROSSOVER	COMBINED	EXABLATE	CROSSOVER	COMBINED	EXABALTE	CROSSOVER	COMBINED	EXABLATE	CROSSOVER	COMBINED
Lost to follow-up	2	0	2	0	0	0	1	0	1	0	0	0
Alternative treatment received	2	0	2	1	0	1	0	1	1	1	0	1
Treatment failure	2	0	2	0	0	0	0	0	0	0	0	0
Other –not related to study	4	3	7	2	1	3	1	0	1	6	2	8
Total	10	3	13	3	1	4	2	1	3	7	2	9

Lost to follow up: site was unable to contact subject (3 subjects).

- 43203, 11204, 307216

Alternative treatment: subject had a follow-up treatment such as DBS (5 subjects).

- 107205, 111201, 111210, 111212, 307203

Treatment failure: subject did not receive an effective treatment due to skull shape or skull density (2 subjects).

- 106214, 107210

Other- personal or health reasons specified by subject as unrelated, travel burden/restrictions and COVID-19 pandemic (19 subjects).

- 43201
- 43212
- 106206
- 106217
- 106223
- 106224
- 106228
- 106229
- 107202
- 107208
- 107214
- 107215
- 107218
- 111205
- 111208
- 111211
- 307204
- 307211
- 315204

5.2 Study Results

5.2.1 Safety Results

There have been no new device or procedure related adverse events reported between years 1 and 5. As reported in Chapter 3, the device or procedure related adverse events began within 30 days of the procedure and these events were followed up to 5 years. Adverse events that were unresolved at the Year 5 visit are shown in **Tables 41a-41b and Table 42**.

- In Table 41a (pivotal Exablate cohort), six (6) adverse events in 4 subjects resolved with longer follow-up. Twenty-one (21) mild and moderate adverse events in 14 subjects remained

through 5 years follow-up. Thirteen (13 of the 21) events occurred in subjects that exited the study during the long-term period of the study and outcome (resolution or ongoing) could not be ascertained. Eight (8) events were known to be ongoing in subjects at completion of the year 5 visit. Most of these events (13/21 = 62%) were mild in nature whereas the remaining were moderate.

- In Table 41b (Crossover cohort), three (3) events in 3 subjects resolved with longer follow-up. Ten (10) mild and moderate adverse events in 6 subjects remained through 5 years follow-up. Two (2 of the 10) events occurred in subjects that exited the study and outcome (resolution or ongoing) could not be ascertained. The remaining eight (8) events were known to be ongoing at completion of the year 5 visit.
- In Table 42 (Combined cohorts), nine (9) events in 7 subjects resolved with longer follow-up. Thirty-one (31) mild and moderate adverse events in 20 subjects remained through 5 years follow-up. Fifteen (15 of the 31) events occurred in subjects that exited the study and outcome (resolution or ongoing) could not be ascertained. The remaining sixteen (16 of the 31) events were known to be ongoing at completion of the year 5 visit.

In the safety tables below, all adverse events were reported by frequency of event as well as by the incidence, e.g., the number of subjects reporting such events. Severity reporting is based on frequency or number of events recorded in each category. In some instances, events could not be assessed when subjects withdrew from the study. These events are called censored and are noted as the last known knowledge of the event by time point.

Table 41a. Thalamotomy or Procedure Related Adverse Events Unresolved at Year 5 Completion in Exablate-treated Pivotal Arm.

Body system	Preferred Term	Frequency (Events)	Incidence (Subjects) N=56	Severity		Events Resolved #Subj/#days	Exited Before 5YR (Events)	Completed 5YR (Events)
				Mild	Moderate			
ONGOING AT STUDY 5YR COMPLETION								
Carryover from PMA		35	21					
# Events resolved before Month 12*		5	4					
# Events not procedure or thalamotomy related**		3	2					
Adverse Events Ongoing from Month 12		27	18	19	8	0	21	
Musculoskeletal	Gait disturbance	2	2	1	1	0	1	1
	Imbalance	5	5	3	2	0	3	2
	Musculoskeletal weakness	1	1	0	1	0	0	1
Nervous	Unsteady	2	2	1	1	0	1	1
	Dysgeusia	2	1	2	0	0	2	0
	Dysmetria	1	1	1	0	0	1	0
	Numbness/tingling	7	5	4	3	0	5	2
Pain/Discomfort	Sonication-related head pain	1	1	1	0	0	0	1
TOTAL		**21**	**14**	**13**	**8**	0	**13**	**8**
RESOLVED AT STUDY 5YR COMPLETION								
Musculoskeletal	Dysergia	1	1	1	0	1/570 days	1	0
	Imbalance	1	1	1	0	1/UNK	0	1
Nervous	Numbness/tingling	4	3	4	0	1/507 days 1/666 days 1/370 days 1/UNK	0 0 0 0	1 1 1 1
TOTAL		**6**	**4**	**6**	**0**	**6**	**1**	**5**

*Events resolved within 12 months: 106226 numbness/tingling , < 365 days; 107214 dizziness, 350 days; 307217 oral dysesthesia, 95 days; 111221 hip pain, 79 days; 111221 dysergia , 14 days.

** Events not procedure or thalamotomy related removed from table: skin rash, urinary urgency, and benign prostate hypertrophy.

Table 41b. Thalamotomy or Procedure Related Adverse Events Unresolved at Year 5 Completion in Exablate-treated Crossover Arm								
Body system	Preferred term	Frequency (Events)	Incidence (Subjects) N=21	Severity		Events Resolved #Subj/#days	Exited Before 5YR (Events)	Completed 5YR (Events)
				Mild	Moderate			
ONGOING AT STUDY 5YR COMPLETION								
Adverse events ongoing at Month 12		13	9	11	2	0	13	
Musculoskeletal	Imbalance	1	1	0	1	0	0	1
	Musculoskeletal weakness	1	1	1	0	0	0	1
Nervous	Dysgeusia	1	1	1	0	0	1	0
	Dysmetria	1	1	1	0	0	0	1
	Numbness/tingling	5	3	5	0	0	1	4
	Slow movements	1	1	1	0	0	0	1
TOTAL		**10**	**6**	**9**	**1**	0	**2**	**8**
RESOLVED AT STUDY 5YR COMPLETION								
General	Fatigue	1	1	1	0	1/2188	1	0
Musculoskeletal	Imbalance	1	1	1	0	1/735	1	0
Nervous	Dysarthria	1	1	0	1	1/801	1	0
TOTAL		**3**	**3**	**2**	**1**	**3**	**3**	**0**

Table 42. Thalamotomy or Procedure Related Adverse Events Unresolved at Year 5 Completion in Exablate-treated ET002 & ET002C COMBINED.								
Body System	Preferred term	Frequency (Events)	Incidence (Subjects) N=75	Severity		Events Resolved	Exited Before 5YR (Events)	Completed 5YR (Events)
				Mild	Moderate	Subj /#days		
ONGOING AT STUDY 5YR COMPLETION								
Adverse events ongoing at Month 12		40	27	30	10	0	4 0	
Musculoskeletal	Gait disturbance	2	2	1	1	0	1	1
	Imbalance	6	6	3	3	0	3	3
	Musculoskeletal weakness	2	2	1	1	0	0	2
Nervous	Dysgeusia	3	2	3	0	0	3	0
	Dysmetria	2	2	2	0	0	1	1
	Numbness/tingling	12	8	9	3		6	6
	Slow movements	1	1	1	0	0	0	1
	Unsteady	2	2	1	1	0	1	1
Pain/Dis-comfort	Sonication-related head pain	1	1	1	0	0	0	1
TOTAL		**31**	**20**	**22**	**9**	0	**15**	**1 6**
RESOLVED AT STUDY 5YR COMPLETION								
General	Fatigue	1	1	1	0	1/2188	1	0
Musculo-skeletal	Dysergia	1	1	1	0	1/570 days	1	0
	Imbalance	2	2	2	0	1/UNK	1	0
						1/735	1	0
Nervous	Numbness/tingling	4	3	4	0	1/507 days	0	1
						1/ 666 days	0	1
						1/370 days	0	1
						1/UNK	0	1
	Dysarthria	1	1	0	1	1/801	1	0
TOTAL		**9**	**7**	**8**	**1**	**9**	**4**	**5**

The long-term follow-up safety profile shows that no new device/procedure related adverse events presented during long-term follow-up.

5.2.2 Effectiveness Results

The summary statistics presenting the effectiveness outcomes are the same as those used in the original PMA (P150038) as defined in the statistical plan. Mean, standard deviation and 95% confidence intervals of the percent change from baseline in the CRST and QUEST are presented for three analysis populations described above annually for year 2 through year 5 outcomes.

The CRST was administered annually, and outcomes were scored by the site neurologist/neurosurgeon. The QUEST is a patient completed quality of life assessment.

The effectiveness outcomes are presented in **Figures 32a-32c** and **Table 43**. **Figures 32a-32c** include the pivotal trial (see **Chapter 3**) clinical outcomes for comparison.

Figure 32a presents the Tremor/Motor response from Baseline through the Year 5 follow-up.

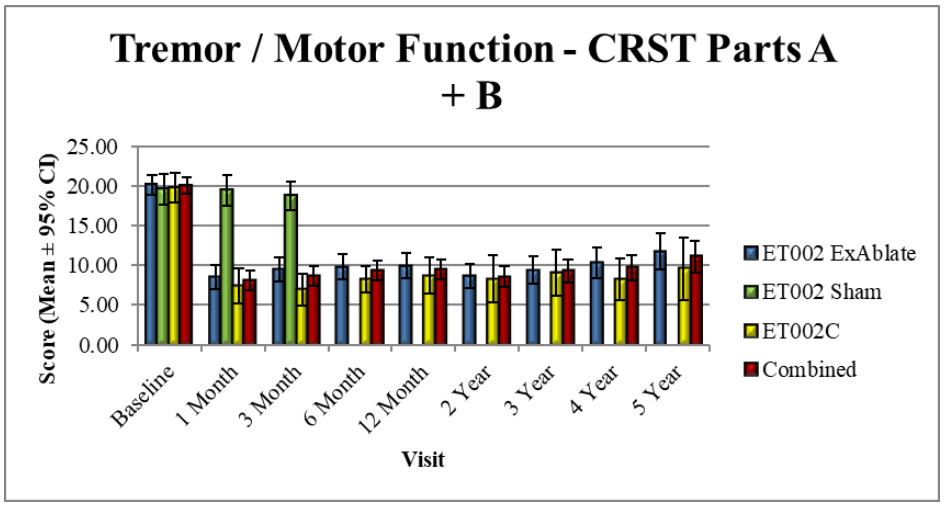

Figure 32a. Tremor/Motor Function Scores for Part A Treated Upper Arm Tremor plus Part B Function.

The CRST Posture score (the posture component of the CRST Part A treated arm) outcomes were similar to that of the Tremor/Motor scores. Posture change from baseline is presented below in Figure 32b.

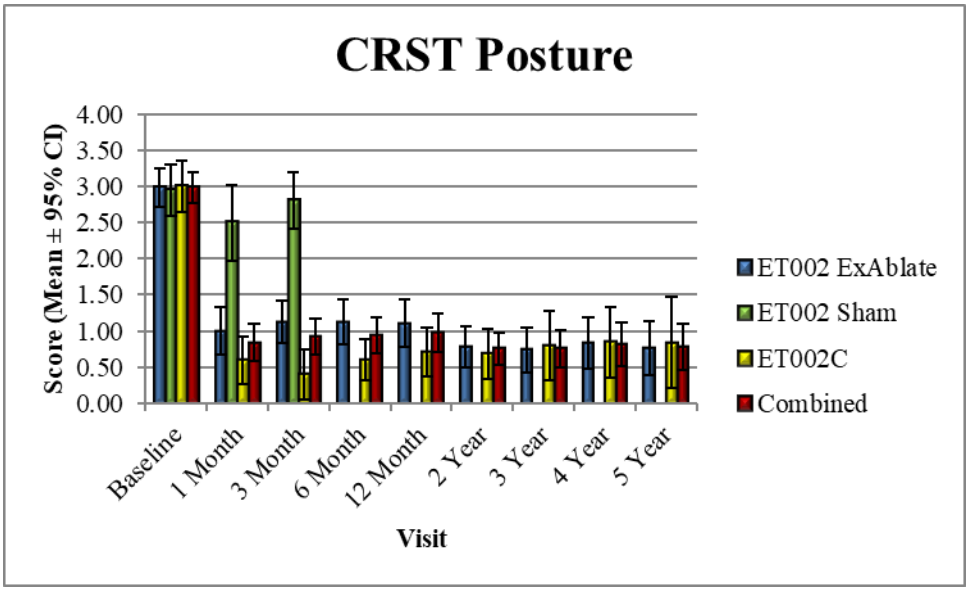

Figure 32b. CRST Posture Component of the Treated Upper Arm by Cohort and by Study Visit

The CRST Part C Activities of Daily Living Scores is shown in Figure 32c.

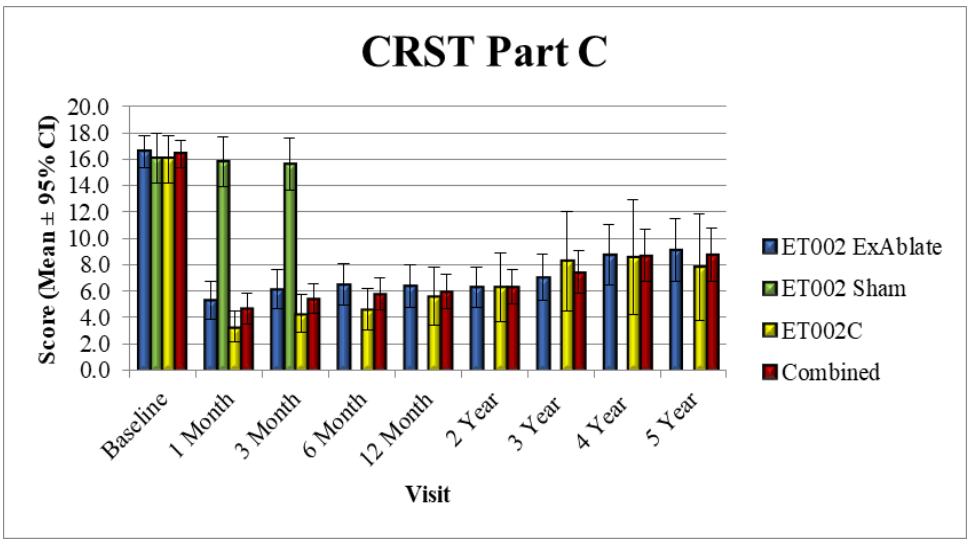

Figure 32c. CRST Part C Activities of Daily Living

The effectiveness result was sustained over time based on available patient data, as summarized in **Table 43** and Figures **33a-33d**.

TABLE 43: EFFECTIVENESS ANALYSIS SUMMARY					
MEASURE	VISIT		ANALYSIS POPULATION		
			EXABLATE	CROSSOVER	COMBINED
Composite Tremor/Motor Function (Percent Change from Baseline)	Year 2 FU	Mean (%)	55.94	56.19	56.01
		Std	23.15	31.93	25.61
		Lower 95% CI	48.86	40.54	49.36
		Upper 95% CI	63.03	71.84	62.66
		N	41	16	57
	Year 3 FU	Mean (%)	52.58	53.51	52.85
		Std	22.20	28.12	23.74
		Lower 95% CI	45.53	39.28	46.46
		Upper 95% CI	59.64	67.74	59.24
		N	38	15	53
	Year 4 FU	Mean (%)	46.75	55.50	49.20
		Std	27.66	25.25	27.04
		Lower 95% CI	37.71	42.48	41.704441
		Upper 95% CI	55.79	68.72	56.7056.7
		N	36	14	50
	Year 5 FU	Mean (%)	37.51	50.18	41.22
		Std	30.87	31.26	31.14
		Lower 95% CI	26.28	32.49	31.69
		Upper 95% CI	48.75	67.87	50.75
		N	29	12	41
CRST, Part A (Percent Change from Baseline)	Year 2 FU	Mean (%)	73.78	78.65	75.15
		Std	28.11	20.63	26.14
		Lower 95% CI	65.18	68.54	68.36
		Upper 95% CI	82.38	88.75	81.93
		N	41	16	57
	Year 3 FU	Mean (%)	76.75	76.11	76.57
		Std	29.14	28.67	28.73
		Lower 95% CI	67.49	61.60	68.84
		Upper 95% CI	86.02	90.62	84.31
		N	38	15	53
		Mean (%)	71.99	71.43	71.83
		Std	37.28	28.63	34.79

TABLE 43: EFFECTIVENESS ANALYSIS SUMMARY					
MEASURE	VISIT		ANALYSIS POPULATION		
			EXABLATE	CROSSOVER	COMBINED
	Year 4 FU	Lower 95% CI	59.81	56.43	62.19
		Upper 95% CI	84.17	86.42	81.48
		N	36	14	50
	Year 5 FU	Mean (%)	72.99	75.69	73.78
		Std	34.33	31.67	33.21
		Lower 95% CI	60.49	57.77	63.62
		Upper 95% CI	85.48	93.62	83.94
			29	12	41
CRST, Part C (Percent Change from Baseline)	Year 2 FU	Mean (%)	62.09	61.85	62.02
		Std	27.78	29.50	28.00
		Lower 95% CI	53.59	47.39	54.75
		Upper 95% CI	70.59	76.30	69.29
		N	41	16	57
	Year 3 FU	Mean (%)	58.68	51.03	56.51
		Std	26.95	38.66	30.52
		Lower 95% CI	50.11	31.47	48.30
		Upper 95% CI	67.25	70.60	64.73
		N	38	15	53
	Year 4	Mean (%)	47.48	449.48	48.04
		Std	37.93	41.78	38.62
		Lower 95% CI	35.09	27.60	37.34
		Upper 95% CI	59.87	71.37	58.74
		N	36	14	50
	Year 5	Mean (%)	43.38	51.35	45.71
		Std	34.67	40.01	35.99
		Lower 95% CI	30.76	28.71	34.70
		Upper 95% CI	56.00	73.98	56.73
		N	29	12	41
	Year 2 FU	Mean (%)	48.54	49.24	48.74
		Std	36.37	37.15	36.25
		Lower 95% CI	37.41	31.04	39.33
		Upper 95% CI	59.67	67.45	58.15
		N	41	16	57

TABLE 43: EFFECTIVENESS ANALYSIS SUMMARY					
MEASURE	VISIT		ANALYSIS POPULATION		
			EXABLATE	CROSSOVER	COMBINED
QUEST (Percent Change from Baseline)	Year 3	Mean (%)	40.95	24.26	36.22
		Std	48.25	85.65	60.74
		Lower 95% CI	25.60	-19.08	19.87
		Upper 95% CI	56.29	67.61	52.58
		N	38	15	53
	Year 4	Mean (%)	36.89	21.68	32.63
		Std	36.58	89.04	55.74
		Lower 95% CI	24.94	-24.96	17.18
		Upper 95% CI	48.84	68.32	48.08
		N	36	14	50
	Year 5	Mean (%)	31.22	16.55	26.92
		Std	36.62	89.66	56.53
		Lower 95% CI	17.89	-34.18	9.62
		Upper 95% CI	44.55	67.28	44.23
		N	29	12	41

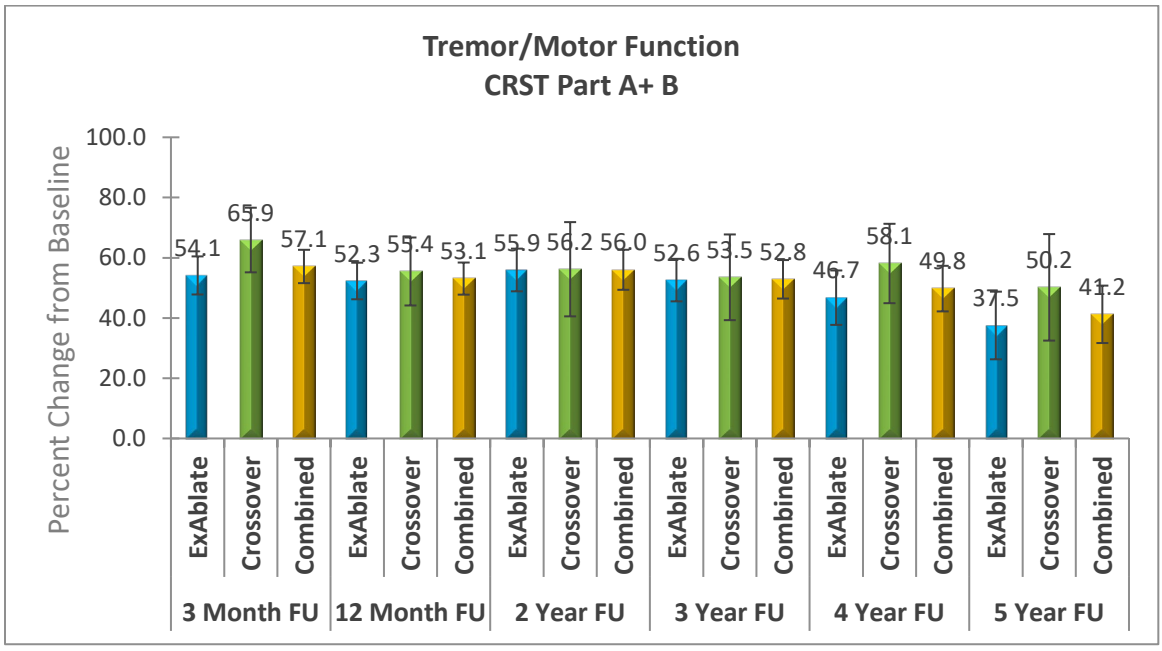

Figure 33a: Tremor / motor function percent of change from baseline over time

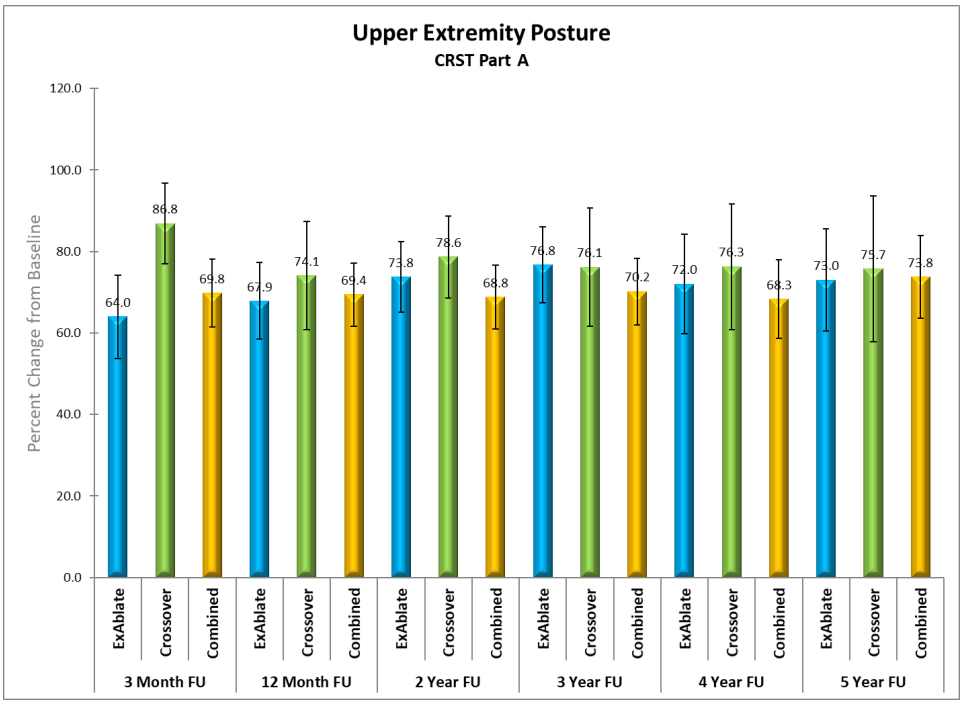

Figure 33b: Upper extremity posture percent of change from baseline over time

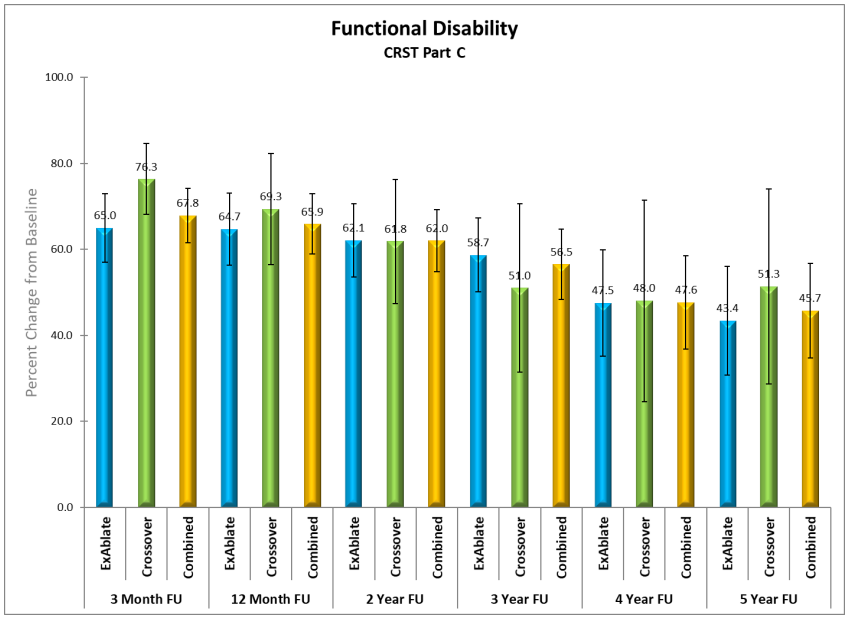

Figure 33c: Functional disability percent of change from baseline over time

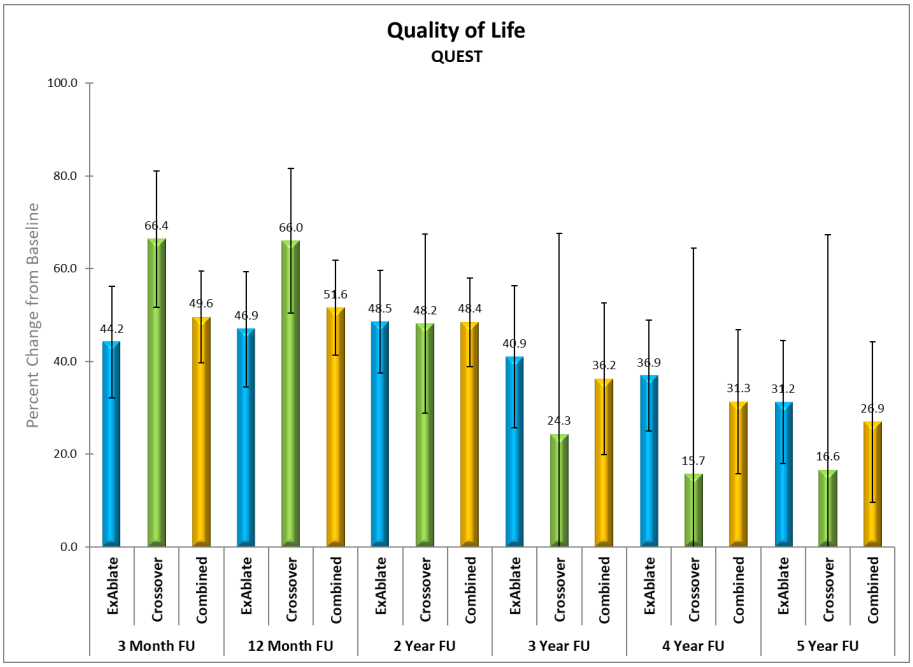

Figure 33d: Quality of life (QUEST) percent of change from baseline over time

To evaluate the impact of early withdrawal on the results, we performed an analysis comparing the CRST Tremor Motor ("TM") responses of subjects that completed the Year 5 follow-up (Completers) vs. those that did not complete Year 5 follow-up (Non-completers). The relative

magnitudes of outcomes for Non-completers was dispersed among those for Completers. Overall, these results show that Non- completers achieved results comparable to those of Completers and there was not a trend of Non- completers disproportionately exiting the study due to poor Tremor Motor outcomes.

To evaluate the impact of adverse events ongoing at Year 2 through Year 5 on study outcomes, events were grouped by ambulatory events (gait disturbance, imbalance, unsteady), other (primarily numbness/tingling), or no ongoing AEs related to the device or procedure. It should be noted that ALL AEs are either mild or moderate (see Chapter 3 for more details). The Non-completers were scattered throughout the entire sample and the magnitudes of the percent change scores of the Non-completers were dispersed among those for the Completers without regard to AE type or absence. Non-completers achieved outcomes comparable to Completers and there was no trend of Non-completers disproportionately exiting due to presence of significant AEs.

5.3 Conclusions Drawn from The Study

For this population of patients suffering from idiopathic ET with medication-refractory tremor, the Exablate Neuro treatment is a reasonable alternative to existing treatments. The result from the pivotal study demonstrated that the treatment is efficacious, and the safety profile is reasonable and does not cause any increased risk due to the treatment location. Similarly, the data from the 5-years long-term follow-up results continues to support the reasonable assurance of continued favorable safety and effectiveness profiles of this device when used in accordance with the indications for use.

The main strength of this PAS is the 5-year follow-up duration. With respect to effectiveness, the duration of tremor/motor function, posture and activities of daily living remained sustainable through year 5 based on the available data.

Regarding safety, no new adverse events were observed during long-term follow-up that were related to the device, procedure or thalamotomy. Furthermore, some of the unresolved events at the end of Month 12 continued to resolve with time.

With respect to weaknesses of the study, long-term follow-up of the primary cohort was performed without a comparator; however, a Sham group comparator for a period of 5 years is not possible. In this study, the Sham group was allowed to Crossover and receive an Exablate procedure after their Month 3 follow-up visit in an open label fashion. The effect in the long-term outcome seems durable through 5 years, however, in view that 40% of the subjects were lost to follow up during the 5 years, the full impact on the risks/benefits assessments may not be known.

In addition, the study was performed as a unilateral procedure and was performed on the subjects' tremor dominant arm. While some patients might benefit from bilateral treatment, clinically meaningful improvements were observed in the unilateral side that permitted subjects to have improvement in their long-term activities of daily living.

CHAPTER 6: SUMMARY OF CLINICAL STUDY – TREMOR DOMINANT PARKINSON'S DISEASE

6.1. Study Design

Exablate Thalamotomy for Essential Tremor was approved by FDA in 2015 as an effective treatment. Tremor Dominant Parkinson's Disease (TDPD) has been reported to be effectively treated using a thalamotomy (Anderson *et al*, Parkinson's Disease, 2017). A small cohort of TDPD subjects was evaluated using the same Exablate thalamotomy technique to demonstrate that Exablate thalamotomy techniques can produce similar tremor motor improvement in the TDPD population.

The study that forms the basis of this expanded indication in TDPD patients was a prospective, multi-center, randomized, sham-control, double-blinded clinical trial. Subjects with idiopathic TDPD with medication-refractory tremor who were at least 30 years old were recruited into the study. Both the subject and the movement disorder specialist measuring the PD assessment were blinded to the treatment assignment until after Month 3. Randomization was based on a 2:1 ratio. Qualified subjects were randomized at a 2:1 ratio to either active Exablate treatment arm or Sham control (with sonication energy disabled). At the Month 3 visit, Sham subjects were permitted to Crossover to an active Exablate treatment. All subjects were followed to Month 12 following an Exablate treatment. The study design used here was the same as was used in the pivotal trial for Exablate thalamotomy to treat Essential Tremor.

Two sites participated in this TDPD patient cohort study. One site enrolled 25 subjects and a second site joined the study late and enrolled 2 subjects.

6.1.1 Eligibility Criteria

The Screening criteria used for this TDPD cohort are similar to the ET pivotal trial but modified for selection of the TDPD cohort.

For this study, ALL Inclusion and Exclusion criteria were reviewed by the Principal Investigator and by a separate investigator of the medical team who was a neurologist, neuroradiologist, or neurotherapist. Two members of the medical team agreed on all aspects of the Inclusion/Exclusion criteria listed below for each subject.

6.1.1.1 Inclusion Criteria

1. Men and women, age 30 years and older
2. Subjects who are able and willing to give informed consent and able to attend all study visits through 3 Months
3. Subjects with a diagnosis of idiopathic PD as confirmed from clinical history and examination by a movement disorder neurologist at the site

4. All subjects included in this study will have a TD/PIGD ratio ≥ 1.5 in the *medicated* [ON] state as calculated from the UPDRS formula as described by Jankovic, *et. al*., [6]

Tremor score from UPDRS		Posture/Gait of UPDRS	
Part II, #16		Part II, #13	
Part III, #20:	FLC	Part II, #14	
	RH	Part II, #15	
	LH	Part III, #29	
	RF		
	LF		
Part III, #21:,	RH	Part III, #30	
	LH		
Mean tremor score = x/8		Mean Posture/Gait score = x/5	
Tremor score ( )/ Posture Gait score ( ) = ( )			
Note: Ratios for TD/PIGD that are greater than or equal to 1.5 are defined as TDPD. PIGD includes those with a ratio of less than or equal to 1.0. Scores of greater than 1.0 and less than 1.5 are considered a mixed subtype.			

5. Subject demonstrates a resting tremor severity score of greater than or equal to 3 in the hand/arm as measured by the medicated (*ON*) UPDRS question #20 or a postural/action tremor greater than or equal to a 2 for question #21.
6. Subject exhibits a significant disability from their PD tremor despite medical treatment. A significant disability is defined as a PD tremor with at least a score of 3 on #16 of the medicated (*ON*) UPDRS or as identified by a score of 2 or more on any item in Part C of the CRST.
7. 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 at the site
8. Subjects should be on a stable dose of all PD medications for 30 days prior to study entry.
9. The thalamus must be apparent on MRI such that targeting of the Vim nucleus can be performed indirectly by measurement from a line connecting the anterior and posterior commissures of the brain.

- Subject is able to communicate sensations during the Exablate Transcranial procedure.

6.1.1.2 Exclusion criteria

1. Subjects with unstable cardiac status including:
   - Unstable angina pectoris on medication
   - Subjects with documented myocardial infarction within six months of protocol entry
   - Significant congestive heart failure defined with ejection fraction < 40
   - Subjects with unstable ventricular arrhythmias
   - Subjects with atrial arrhythmias that are not rate-controlled
2. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within the preceding 12-month period:
   - Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
   - Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
   - Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
   - Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).
3. Severe hypertension (diastolic BP > 100 on medication)
4. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
5. Known intolerance or allergies to the MRI contrast agent (e.g., Gadolinium or Magnevist) including advanced kidney disease or severely impaired renal function (estimated glomerular filtration rate < 45ml/min/1.73 m^2) or receiving dialysis.
6. Significant claustrophobia that cannot be managed with mild medication.
7. Current medical condition resulting in abnormal bleeding and/or coagulopathy
8. Receiving anticoagulant (e.g., warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
9. Subjects with risk factors for intraoperative or postoperative bleeding as indicated by: platelet count less than 100,000 per cubic millimeter, a documented clinical coagulopathy, or INR coagulation studies exceeding the institution's laboratory standard

10. History of intracranial hemorrhage
11. History of multiple strokes, or a stroke within past 6 months
12. Subject who weigh more than the upper weight limit the MR scanner table
13. Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment.
14. Are participating or have participated in another clinical trial in the last 30 days
15. Subjects unable to communicate with the investigator and staff.
16. Presence of central neurodegenerative disease, including but not limited to Parkinson-plus syndromes, suspected on neurological examination. These include multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and Alzheimer's disease.
17. Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications.
18. Presence of significant cognitive impairment as determined with a score ≤ 21 on the Montreal Cognitive Assessment (MoCA).
19. Unstable psychiatric disease, defined as active uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation. Subjects with stable, chronic anxiety or depressive disorders may be included provided their medications have been stable for at least 60 days prior to study entry and if deemed appropriately managed by the site neuropsychologist
20. Subjects with significant depression as determined following a comprehensive assessment by a neuropsychologist. Significant depression is being defined quantitatively as a score of greater than 14 on the Beck Depression Inventory.
21. Legal incapacity or limited legal capacity as determined by the neuropsychologist
22. Subjects with a history of seizures within the past year
23. Subjects with brain tumors
24. Subjects with intracranial aneurysms requiring treatment or arterial venous malformations (AVMs) requiring treatment.
25. Any illness that in the investigator's opinion preclude participation in this study.
26. Pregnancy or lactation.
27. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
28. Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening CT.[1]

[1] Exclusion added to protocol amendment 1.

The Schedule of Events is shown in **TABLE 40**.

TABLE 40. SCHEDULE OF EVENTS

Procedures	Screening	Baseline	Day 0	Day 1	Day 7 (±3 days)	Month 1 (±7 days)	Month 3 (±14days)ə	Month 6- Telephone (± 3 weeks)	Month 12 (±1 Month)
Written Consent	X								
Eligibility Consensus	X								
Demographics, Medical History	X								
CT Scan	X								
Labs*	X								
Concomitant meds;	X	X	X	X	X	X	X	X	X
PD Meds - Levodopa equivalents (mg)	X	X	X	X	X	X	X	X	X
MRI	X		X	X	β	X	β		X
General Physical Exam	X		X	X			X		X
Neurological Exam	X		X	X	X	X	X		X
Tremor rating scale (CRST)	X	X				X	X		X
QUEST	X	X				X	X		X
Full UPDRS parts I-IV		X					X		X
UPDRS part-III	X***	X				X	X***		X***
Neuropsychological Assessment**	X						X		X
Quality of Life (PDQ-39)		X					X		X
Randomization			X						
Exablate procedure forms			X						
Adverse Events			X	X	X	X	X	X	X

* includes blood draw for PT, PTT, CBC, platelets, creatinine; urine - Beta-hCG for women for screening; **full battery of neuropsychological testing as defined in **Appendix C**. ***UPDRS III is not required to be performed separately as it is part of the full UPDRS Parts I–IV. Note: CRST and UPDRS assessment should be performed by a blinded assessor at Baseline and follow-up through Month 3. ɘSham subjects may opt to crossover to Exablate at Month 3.

β: See MR Table Schedule

6.1.4 Study Endpoints

Analysis of all TDPD cohort study endpoints was performed using the same statistical techniques as in the Exablate Essential Tremor pivotal trial.

Safety Endpoint

The safety of the Exablate was determined by an evaluation of the incidence and severity of device-related adverse events and serious adverse events from treatment day through the Month 12 post-treatment time point.

Primary Effectiveness Endpoint

The Primary Effectiveness (PE) was evaluated using a validated, tremor rating scale: the Clinical Rating Scale for Tremors (CRST) for ET subjects, based upon subjects in whom unilateral Exablate lesioning is attempted (i.e., Intent-to-Treat analysis; "ITT"). The specific study hypothesis was as follows:

- Primary effectiveness was evaluated using validated scores: on medication Upper Limb tremor score (32-point maximum) from the 8 items of Parts A & B of the CRST based upon TDPD subjects where unilateral Exablate Neuro thalamotomy was attempted (i.e., Intent-to-Treat analysis). This is the same endpoint used in the ET P150038 study.

PE =% Improvement=(〖CRST〗_[contralateral, Baseline] - 〖CRST〗_[contralateral, 3 month FU])/〖CRST〗_[contralateral,Baseline] x 100

Where the CRST score implemented for this study is the average of 8 components, combining the 3-components of the tremor CRST Part-A with the 5-components of the Motor Functions of the CRST Part-B from the treated side of the body:

〖CRST〗_[Contralateral] = (PART_(_A) + PART_B)/(Max_Score)

- **Part A** = Rest + **Posture** + Action/Intention
- **Part B** = **all** 5 motor functions:

Writing + Drawing A (large spiral) + Drawing B (small spiral) + Drawing C (straight lines) + Pouring (transfer of water between 2 glasses).

The primary efficacy endpoint in this study is referred to hereinafter as the "Composite Tremor/Motor Function Score".

Hence, this PE characterizes the impact of Essential Tremor on the "clinical disability" level of an ET patient. The robustness of this matrix parameter is further enhanced by the fact that it undergoes a normalization procedure allowing a true comparison between patients. Hence, this combined **"Composite Tremor/Motor Function"** score, i.e., study PE, is a robust measure of the impact of Essential Tremor in the subject's life [1].

Secondary Effectiveness Endpoint

The secondary endpoints are the same as those presented in the ET P150038. Secondary endpoints of the study included comparison of Baseline to Month 3 and Month 12 assessments for the following:

- CRST upper extremity score (CRST Part A + Part B)
- CRST posture score (from CRST Part A)
- Level of disability measure from using the CRST Part C total score
- Quality of Life assessment with Quality of Life in ET questionnaire (QUEST)

The outcomes from this TDPD study are compared with those of the ET P150038 study.

6.1.5 Study Analysis Population

The data analysis in this report involves three analysis populations **TABLE 41**:

- Safety Analysis Population - which includes all randomized subjects with at least one sonication (Exablate or Sham) in the main stage of the study.
- Intent-to-Treat (ITT) – which includes all Safety subjects for whom there exists a valid baseline measurement and at least one post-baseline measurement on the primary efficacy data.
- Crossover – which includes all subjects who received at least one sonication in the Crossover stage of the study. Because the sample size of the crossover was small, only safety data is presented in this clinical report.

TABLE 41. NUMBER OF SUBJECTS IN EACH OF THE ANALYSIS SETS BY TREATMENT GROUP

Analysis Set	Exablate	Sham	Crossover
Safety Analysis (N=27)	20	7	6
Intent-To-Treat (ITT) Efficacy Analysis (N=27)	20	7	NA
Crossover (N= 6)*	NA	NA	6
*Of the 7 Sham treated subjects, one elected not to receive crossover Exablate treatment.			

6.1.6. Study Subject Accountability

Fifty-three subjects were recruited for this trial. Out of these subjects, 19 were screen failures (**TABLE 42, Figure 29**) and an additional seven declined to participate prior to randomization. The remaining 27 subjects were randomized and treated accordingly.

Patient accountability for this study is presented in **TABLE 42**. Recruitment included screening of 53 subjects to arrive at a total of 27 eligible study participants (N=20 Active Exablate; N=7 Sham control). The study's actual random ratio became 3:1because the study was stopped early as the number of active subjects was reached at an earlier timepoint.

The table below shows the patient disposition through the 12-month study visit. All the Exablate and Sham Control subjects (27/27, 100%) completed the blinded portion of the study (through 3 months) that serves as the basis for the TDPD cohort study primary endpoint analysis.

TABLE 42. PATIENT DISPOSITION BY TREATMENT GROUP AND SCHEDULED VISIT								
Category	Baseline		1 Month FU		3 Months FU		6 Months FU	12 Months FU
	Exablate	Sham	Exablate	Sham	Exablate	Sham	Exablate	Exablate
Recruited	53							
SF 1[1]	19							
Discontinued for Reasons Other than SF (not yet randomized)	7							
Randomized[2]	20	7						
Discontinued for Reasons Other than SF (after randomization)	0	0	0	0	0	0	0	0
Theoretical[3]	20	7	20	7	20	7	20	20
Death	0	0	0	0	0	0	0	0
Failure[4]	0	0	0	0	0	0	2	3
Exited – Other Reasons[5]	0	0	0	0	0	0	1	3
Expected[6]	20	7	20	7	20	7	17	14
Actual[7]	20	7	20	7	20	7	16	14
Actual %[8]	100%	100%	100%	100%	100%	100%	94%	100%

1 - SF 1 – Those subjects Recruited, but not meeting enrollment criteria

2 - Randomized equals those Recruited minus SF 1 minus Discontinued for Reasons Other than SF (not yet randomized)

3 - Theoretical is equal to the number of subjects Recruited minus SF 1 minus Discontinued for Reasons Other than SF. Therefore, theoretical is equal to the number of subjects eligible to receive treatment in either group

4 - Failures include any subjects (Exablate or Sham) who discontinued the study due to beginning another treatment for their condition *

5 – Exited the Main Analysis for reasons other than Failure[2]

6 – Expected is the number of subjects continuing from the previous visit.

7 – Actual is the number of subjects returning for the follow-up visit

8 - Actual % is the number of Actual subjects divided by Expected

TABLE 42. PATIENT DISPOSITION BY TREATMENT GROUP AND SCHEDULED VISIT								
Category	Baseline		1 Month FU		3 Months FU		6 Months FU	12 Months FU
	Exablate	Sham	Exablate	Sham	Exablate	Sham	Exablate	Exablate
[*:] Subjects 106125 and 106136 exited the study for alternative treatment of DBS following the 3 Month visit. Subject 106143 exited following the 6 Month visit to receive DBS. [2]An additional 3 subjects withdrew from the study for personal reasons unrelated to the study (2 subjects) or by subject's request due to health concerns (unable to travel due to feeding tube placement).								

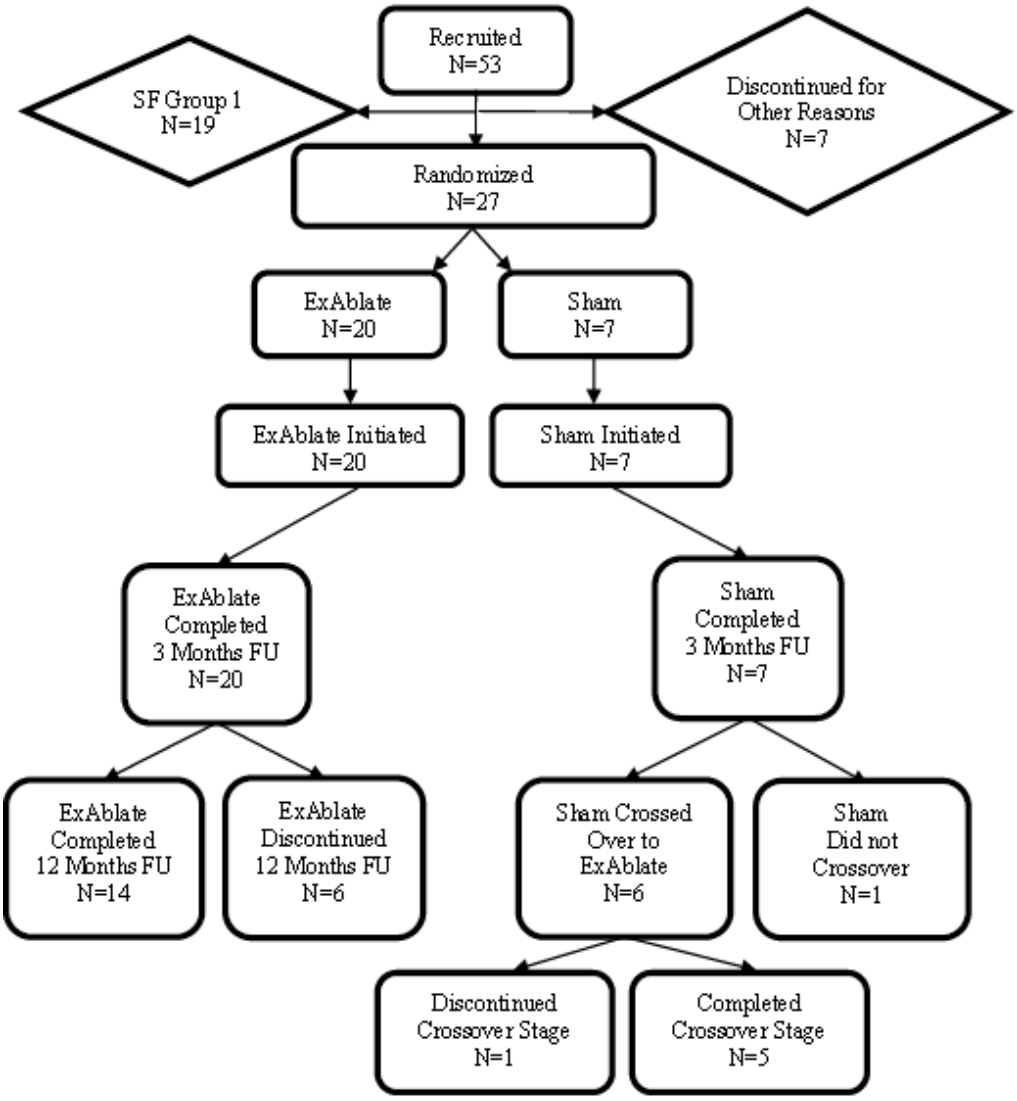

Figure 29. Patient Flowchart

6.1.7. Study Demographics and Baseline Characteristics

Baseline and demographic characteristics of the population are presented in **TABLE 43**. The Exablate and Sham groups were similar at Screening /Baseline in all respects. The Exablate group had a mean age of 68 and the Sham group had a mean age of 63. The study sample consisted predominantly of Caucasian males.

TABLE 43. BASELINE AND DEMOGRAPHIC INFORMATION BY TREATMENT GROUP

Demographic and Baseline Characteristics		**Treatment Group**	
		Exablate N=20	**Sham N=7**
Age [Years]	Mean	67.9	62.9
BMI [kg/m²]	Mean	27.1	24.6
Height [36]	Mean	175.6	180.7
Weight [kg]	Mean	83.3	80.4
Gender	Male	19 (95%)	7 (100%)
	Female	1 (5%)	0 (0%)
Race	Caucasian	18 (90%)	6 (86%)
	Black	2 (10%)	0
	Asian	0	0
	Hispanic	0	0
	Other	0	1 (14.3%)
Baseline CRST [mean (standard deviation)]		19.0 (8.7)	20.1(7.4)
UPDRS question 20 [mean (standard deviation)]		3.7 (1.0)	3.4 (1.5)
UPDRS question 21 [mean (standard deviation)]		3.6 (1.3)	3.6 (1.1)
Years of disease		5.2 (4.1)	6.5 (4.0)

6.2. Study Results

6.2.1. Safety Results

The primary analysis of safety was based upon the collection of adverse events during the study as collected by the investigators at each site from the time of the treatment to the Month 12 visit. All adverse events were recorded on case report forms. An average of 5.0 events per subject (min 2, max 8 events) was recorded in the Exablate group and 1.4 events per subject (min 0, max 3 events) for the Sham-treated subjects. All 20 subjects in the Exablate group had at least 1 adverse event and two subjects in the Sham group had no events.

For this study, a total of 100 events in 20 Exablate-treated subjects was reported; a total of 10 events in 7 subjects were reported for the Sham group who underwent all the procedural preparations including shave, headframe, catheter and "intravenous line." Most Exablate Arm events were Mild (72/100, 72%) and Moderate (23/100, 23%). Five severe events were reported (5/100, 5%). There were no reports of device or procedure-related Severe events or deaths

- Half (50 events, 50% frequency) of the adverse events were transient, i.e., most resolved right after the sonication or the same day up to 3 days post-procedure (see **TABLE 44**).
- Another fifth (21 events, 21% frequency) of events were considered Unrelated to device, thalamotomy, or procedure (see **TABLE 44**).
- The remaining Exablate Arm events 29 (29%) were related to the device, thalamotomy or procedure (see **TABLE 44**).

TABLE 44 succinctly summarizes the safety profile of the Exablate Neuro as used for unilateral thalamotomy as compared to the Sham group. The Exablate group had 95% (95/100) of all the events as Mild/Moderate, 72 events in 19 subjects were Mild, 23 events in 14 subjects were Moderate and 5 events in 4 subjects were severe. In the Sham group, 90% (9/10) of all the events were Mild/Moderate: 3 events in 2 subjects were Mild, 6 events in subjects were Moderate and 1 subject reported an event as severe.

TABLE 44. OVERALL SUMMARY OF SAFETY BETWEEN GROUPS

Severity	**Exablate**		**Sham**	
	Frequency N=100	**Incidence N=20**	**Frequency N=10**	**Incidence N=7**
Mild	72 (72%)	19 (95%)	3 (30%)	2 (29%)
Moderate Thalamotomy-related SAE Unrelated SAE	20 (20%) 1 (1%) 2 (2%)	14 (70%) 1 (5%) 2 (10%)	6 (60%)	4 (57%)

Severe Thalamotomy-related SAE Unrelated SAE	3 (3%) 1 (1%) 1(1%)	2 (10%) 1 (5%) 1 (5%)	0 (0%) 1 (10%)	0 (0%) 1 (14%)
Total	100 (100%)	20 (100%)	10 (100%)	5 (100%)

Of the 100 adverse events, 95% of all events in the Exablate TDPD Cohort were Mild and Moderate.

TABLE 45. SUMMARY OF SAFETY (ADVERSE EVENTS) BETWEEN GROUPS BY SEVERITY				
Severity of SAE	**Exablate**		**Sham**	
	Frequency N=100	**Incidence N=20**	**Frequency N=10**	**Incidence N=7**
Thalamotomy-related	2 (2%)	2 (10%)	0 (0)	0 (0%)
Unrelated	3 (3%)	2 (10%)	1 (10%)	1 (14%)
Total SAEs	5 (5%)	4 (20%)	1 (10%)	1 (14%)

Two subjects experienced Serious Adverse Events:

- One subject experienced ataxia/hemiparesis. They were originally reported separately, but later it was determined that the ataxia was an expression of the hemiparesis. The patient required a walker to assist with walking after discharge. The event resolved in approximately 30 days. MR showed cerebral edema and the lesion trailed off into the internal capsule.
- One subject experienced severe hemiparesis resulting from local cerebral edema and trailing of the lesion toward the internal capsule. Immediately post procedure the patient had no difficulties, but the next day he developed hemiparesis.

Both events were adjudicated by the DSMB and they were noted be a known risk of ablation for thalamotomy.

As a result of these two hemiparesis events and following root cause analysis, all Exablate Physician training since 2013 emphasizes the need for physicians to view the sonications in 2 axes to verify the heat signature of the lesion in 3 dimensions prior to making the final lesion and confirming the shape of the lesion to mitigate these incidents. It should be noted that the Pivotal study under G120246 that lead to PMA approval under PMA P150038 benefited from this enhanced physician training. The Safety profile that is part of the PMA P150038 labeling shows the impact of the training and the resolution of this SAE event.

Unrelated SAEs included one event each of cholecystitis, degenerative knee pain resulting in total knee implant, and worsening depression where the patient discontinued his meds because he felt better and refused them. In the Sham group, one subject had a Transient Ischemic Attack (TIA) two months after the Sham procedure. All these events were adjudicated by the DSMB as Unrelated

The frequency and incidence of all adverse events is presented by treatment group and severity and by body system and coded term in **TABLE 46**.

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
PD Disease Progression	General	Sleep disorder	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysgnosia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)
		Tremor worsened	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PD Disease Progression Subtotal			1 (1%)	1 (5%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)
Procedure Related	General	Fatigue	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Musculoskeletal	Musculoskeletal weakness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysgnosia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Vestibular Disorder	Dizziness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Procedure Related Subtotal			5 (5%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
Thalamotomy Related	Musculoskeletal	Dysmetria	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (%)	0 (0%)	0 (%)	0 (0%)	0 (%)	0 (0%)	0 (0%)	0 (0%)
		Gait disturbance	2 (1%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Hemiparesis	0 (0%)	0 (0%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Imbalance	4 (4%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysmetria	1 (1%)	1 (5%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Ataxia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Numbness/ tingling	7 (7%)	6 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Neurological	Numbness/ tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Unsteady	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamotomy Related Subtotal			18 (18%)	9 (45%)	3 (3%)	2 (10%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
Transient	Cardiovascular	Hypertension	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Syncope	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Dematologic	Sonication related flushing	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Eye	Visual Field Defect	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Gastrointestinal	Nausea/Vomiting	3 (3%)	3 (15%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
	Musculoskeletal	Imbalance	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Positional pain	2 (2%)	2 (10%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Nervous	Imbalance	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Anxiety	0 (0%)	0 (0%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Dysgnosia	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Numbness/ tingling	7 (7%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
	Pain/Discomfort	Headache	5 (5%)	5 (25%)	6 (6%)	6 (30%)	0 (0%)	0 (0%)	2 (%)	2 (29%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Sonication-related scalp pain	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Sonication-related head pain	3 (3%)	2 (10%)	2 (2%)	2 (10%)	1 (11%)	1 (5%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
	Stereotactic Frame	Pin site pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
	Vestibular Disorder	Dizziness	6 (6%)	6 (30%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
Transient Subtotal			33 (33%)	17(85%)	16 (16%)	11 (55%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	3 (30%)	3 (42%)	0 (%)	0 (0%)
Unrelated	Eye	Pigment change in eye	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Vision change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Gastrointestinal	Cholecystitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
		Stomach Pain	0 (0%)	0 (0%)	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	General	Vocal change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Worsening Depression	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Musculoskeletal	Musculoskeletal weakness	2 (2%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other musculoskeletal pain	0 (0%)	0 (0%)	1 (1%)	1 (5%)	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Positional pain	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Cerebellar Infarct	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Dizziness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		TIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)

TABLE 46. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY SEVERITY AND TREATMENT ARM														
Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
	Stereotactic Frame	Facial edema	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Pin site numbness/ tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Pin site pain	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
		Stereotactic frame-Bruising	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
Unrelated Subtotal			15 (15%)	9 (45%)	4 (3%)	4 (20%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	2 (20%)	1(14%)	0 (0%)	0 (0%)

TABLE 47 shows the events in the timeframe of occurrences post-procedure and their durations. Most events occur within the first 30 days following the procedure and resolved within 30 days (63 events in 19 Exablate-treated subjects; 8 events in 4 Sham-treated subjects). In fact, most of them resolved on the same day as treatment or within one week of treatment (65/110, 59%; 58/100, 58% in the Exablate-treated group). Many events are procedure related events (such as those related to the Stereotactic frame, the urinary catheter, the iv line, the head shave, claustrophobia within the MR, etc.), which were experienced by both treatment groups. Events are solicited during the procedure (patient feedback) as the target for ablation is identified with successive sonications (energy experienced only by Exablate group, but feedback was solicited with the Sham group in similar fashion). Several events are generally associated with any ablative treatment of the Vim nucleus (thalamotomy- related), such as numbness/tingling of the lip, face, tongue, or index finger/thumb. These events are generally Mild or possibly Moderate.

TABLE 47. ADVERSE EVENTS ONSET VERSUS ADVERSE EVENT DURATION BY TREATMENT GROUP												
Duration	Exablate[1]						Sham					
	100 events in 20 subjects						10 events in 5 subjects					
	Onset < 30 days		Onset 31-90 days		Onset > 90 days		Onset < 30 days		Onset 31-90 days		Onset > 90 days	
<30 days	63 (63%)	19 (95%)	1 (1%)	1 (5%)	1 (1%)	1 (5%)	8 (80%)	4 (57%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)
31-90 days	6 (6%)	4 (20%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
> 90 days	7 (7%)	4 (20%)	0 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ongoing	14 (14%)	9 (45%)	3 (3%)	2 (10%)	2 (2%)	4 (20%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)
TOTAL	90 (90%)	20 (100%)	4 (4%)	3 (15%)	5 (5%)	3 (15%)	8 (80%)	4 (57%)	2 (20%)	1 (14%)	0 (0%)	0 (0%)

[1]The onset date for one event was unknown.

The safety profile indicates, as expected, that adverse events related to the device, procedure or thalamotomy are observed shortly after the procedure and mostly resolved within 30 days of the procedure.

Summary of Safety.

Overall, the data of this study shows a very favorable safety profile of the Exablate procedure in the TDPD population. Of the 100 adverse events, 95% of all events in the Exablate TDPD Cohort were Mild and Moderate. Of all events in the Exablate TDPD Cohort, 71% were transient and were no longer present 72 hours later. Of the 100 events that occurred, 22 were related to the thalamotomy and 5 were categorized as procedure related. The remaining 78 events were all categorized as Transient, Unrelated or Disease Progression.

Two subjects experienced Thalamotomy-related Serious Adverse Events:

- One subject experienced ataxia/hemiparesis. They were originally reported separately, but later it was determined that the ataxia was an expression of the hemiparesis. The patient required a walker to assist with walking after discharge. The event resolved in approximately 30 days. MR showed cerebral edema and the lesion trailed off into the internal capsule.
- One subject experienced severe hemiparesis resulting from local cerebral edema and trailing of the lesion toward the internal capsule. Immediately post procedure the patient had no difficulties, but the next day he developed hemiparesis.

Both events were adjudicated by the DSMB and they were noted be a known risk of ablation for thalamotomy.

As a result of these two hemiparesis events and following root cause analysis, all Exablate Physician training since 2013 emphasizes the need for physicians to view the sonications in 2 axes to verify the heat signature of the lesion in 3 dimensions prior to making the final lesion and confirming the shape of the lesion to mitigate these incidents. It should be noted that the Pivotal study under G120246 that lead to PMA approval under PMA P150038 benefited from this enhanced physician training. The Safety profile that is part of the PMA P150038 labeling shows the impact of the training related to these two events.

Overall, the safety profile for thalamotomy for ET is the very similar to that for the TDPD population. In comparison to the safety profile of invasive deep brain stimulation procedures, the Exablate safety profile is quite favorable.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Criterion

An Exablate versus Sham treatment comparison of the change from baseline in the upper extremity CRST sub-score (Part A and B) was the primary endpoint in the ET pivotal trial (P150038). This comparison in the present TDPD trial was 51.9% versus 12.7% (p=0.030) for the Exablate and Sham control respectively. The change from baseline results, **TABLE 48** and **Figure 30,** compared very favorably to improvement observed in the ET pivotal trial. In the ET pivotal trial, the 3 Month improvement from baseline was 53.3% versus the Sham of 1.9%.

TABLE 48. DESCRIPTIVE STATISTICS OF PERCENT IMPROVEMENT FROM BASELINE AT THREE MONTHS POST-TREATMENT IN THE TREATED (CONTRALATERAL) UPPER EXTREMITY CRST SUB SCORE BY TREATMENT GROUP (ITT)

	Treatment Group				
Between groups comparison at 3 Months	Exablate N =20		Sham N = 7		p-Value*
	Mean Score	% Change	Mean Score	% Change	
ITT Mean	9.6	51.9%	17.4	12.7%	p = 0.030

1. Wilcoxon rank-sum test was applied for the comparison between groups since the data differed appreciably from normal theory.
2. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100.
3. Higher PE values represent improvement
4. Sham subject 106135 baseline CRST measures taken from screening visit

*p-value reflects testing between groups.

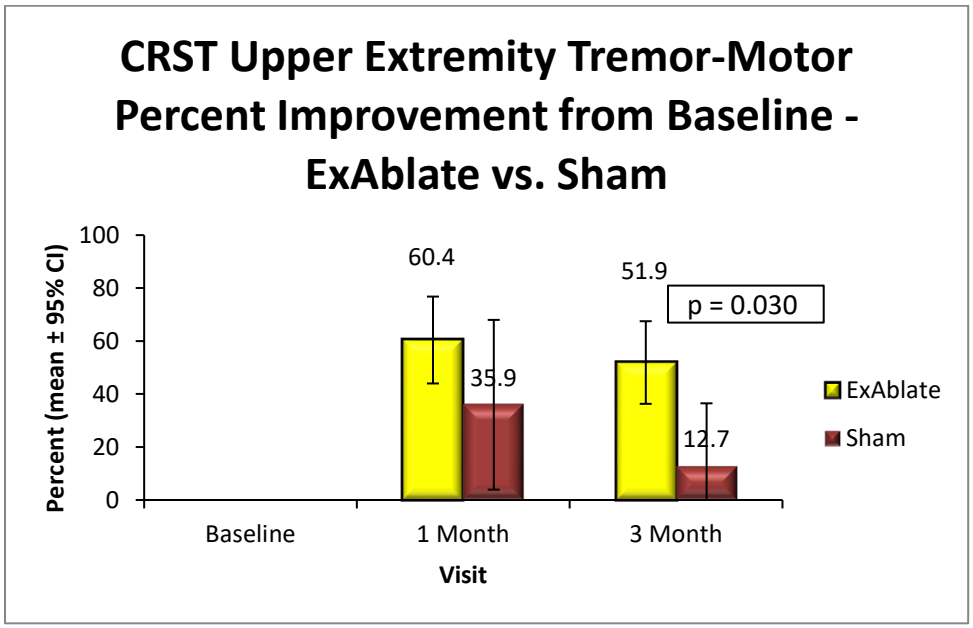

Figure 30. Exablate versus Sham comparison of improvement from Baseline in the CRST upper extremity scores.

Not only was the upper extremity tremor-motor improvement from baseline significant, but it was similar to the outcomes of the ET pivotal trial. Additionally, the improvement in upper-extremity tremor-motor score persisted through the 12 Month visit (see below Error! Reference source not found.**,** Error! Reference source not found.**, TABLE 50.**

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6.3.2 Secondary Efficacy Endpoints

Analysis was conducted on the ITT Analysis Population and is shown in **Error! Reference source not found.** and **Figure 31** below. The Exablate group demonstrated a mean 51.9% improvement from baseline at the 3 Month visit (90 days post Exablate treatment). For illustration, the p-value for change from baseline at the 3 Month visit was $p < 0.001$ based on the Wilcoxon signed-rank test. For comparison to the 51.9% improvement from baseline, the improvement from baseline for the Exablate group in the pivotal trial was 53.3%.

Table 49. Descriptive Statistics of Percent Improvement from Baseline at Three Months Post-Treatment in the Treated (Contralateral) Upper Extremity CRST Sub Score (ITT) for the Exablate Group				
	Treatment Group N = 20			
Within group comparison between baseline and 3 Months	Exablate Baseline	Exablate 3 Months		p-Value*
	Mean Score	Mean Score	% Change	
ITT Mean	19.0	9.6	51.9%	$p < 0.001$

1. Wilcoxon rank-sum test was applied for the comparison between groups since the data differed appreciably from normal theory.

2. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100.

3. Higher PE values represent improvement

4. Sham subject 106135 baseline CRST measures taken from screening visit

*p-value reflects testing between groups.

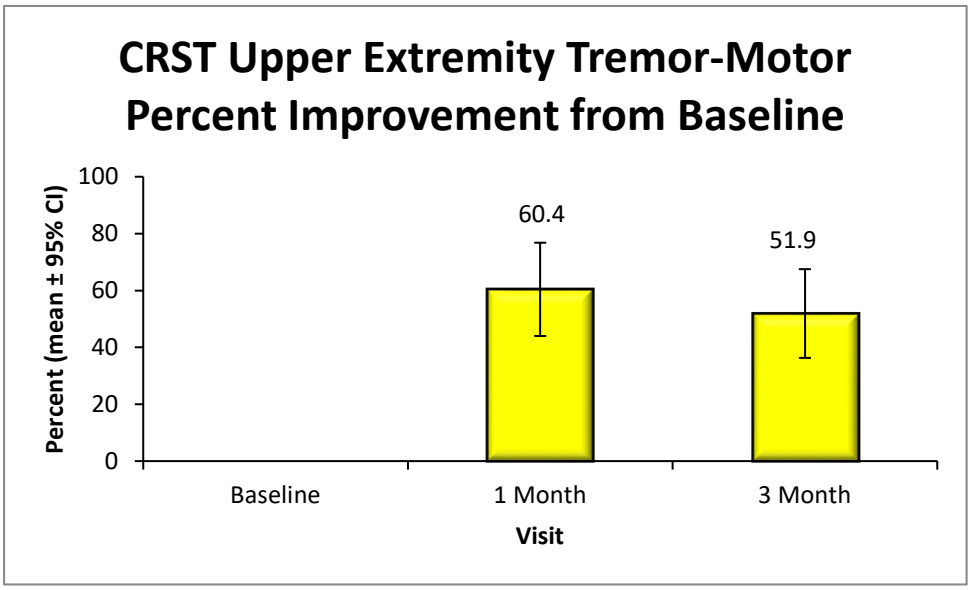


Figure 31. CRST upper extremity tremor-motor improvement from Baseline in the Exablate group.

In addition to the marked clinical improvement from baseline following the Exablate being similar to that demonstrated in the ET trial (51.9% compared to 53.3%), the percent improvement in the Exablate group was also notably greater compared to the Sham Control Group (see below).

6.3.3 CRST Tremor/Motor AB

Figure 32 and **TABLE 50** presents the CRST Part A and Part B summary statistics for the Exablate-treated and Sham Control groups through the 12 Month follow up visit. The percent change from Baseline is illustrated in **Figure 33**. As noted above, the treated-side tremor improved by 51.9% by the 3 Month visit and 45.9% by the 12 Month visit whereas the Sham control group showed improvement of 12.7% by the 3 Month visit. There was a clear trend of improvement from baseline observed in the Exablate-treated group not seen in the Sham group. In fact, the improvement from baseline was very similar to that observed in the ET trial; 51.9% versus 53.3% at 3 Months, and 45.9% versus 54.7% at 12 months for the present trial versus ET pivotal trial respectively (see **Figure 33** and **Figure 34** below).

The mean scores in the Exablate-treated group were 19.0, 8.6, 9.6, and 10.5 at Baseline, 1 Month, 3 Month and 12 Month visits respectively (**TABLE 50** and **Figure 32**). The mean scores in the Sham Control group were 20.1, 13.6, and 17.4 at Baseline, 1 Month and 3 Month visits respectively.

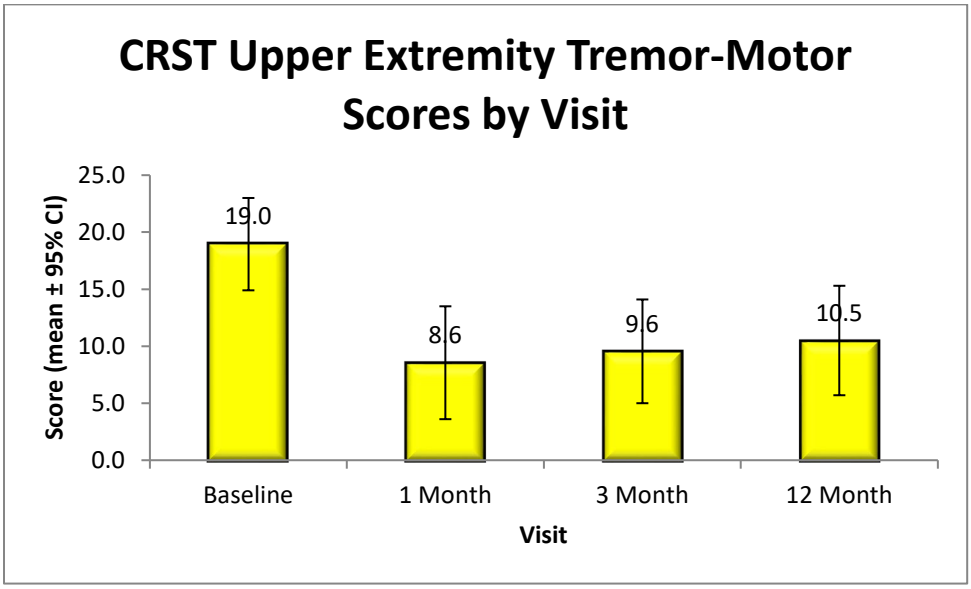


Figure 32. CRST upper extremity tremor-motor scores by visit

TABLE 50. CRST TREMOR-MOTOR SCORES FOR TREATED ARM BY TREATMENT GROUP BY VISIT THROUGH MONTH 12					
Visit / CRST, Part A and B – Tremor-Motor Scores		Observed scores		Percent Change from Baseline	
		Treated Side		Treated Side	
		Exablate	Sham	Exablate	Sham
Baseline	Mean	19.0	20.1	NA	NA
	Std	8.7	7.4	NA	NA
	Median	17.0	23.0	NA	NA
	N	20	7	NA	NA
1 Month FU	Mean	8.6	13.6	60.4	35.9
	Std	10.6	6.4	34.9	34.7
	Median	4.0	15.0	66.1	34.8
	N	20	7	20	7
3 Month FU	Mean	9.6	17.4	51.9	12.7
	Std	9.7	7.8	33.4	25.7
	Median	4.5	17.0	62.2	22.2
	N	20	7	20	7
12 Month FU	Mean	10.5	NA	45.9	NA
	Std	10.2	NA	48.6	NA
	Median	6.0	NA	62.4	NA
	N	20	NA	20	NA

Notes:

1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100).

2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

Figure 33 shows the tremor-motor Change from Baseline for the TDPD trial and **Figure 34** showed the observed scores in the TDPD trial to the scores from the ET trial. At the 3 Month visit the percent improvement was 51.9% compared to 53.3% in the ET pivotal trial. The tremor- motor scores at the 3 Month visits were 9.6 compared to 9.5 for the ET trial and at the 12 Month visits were 10.5 compared to 9.9 for the ET trial.

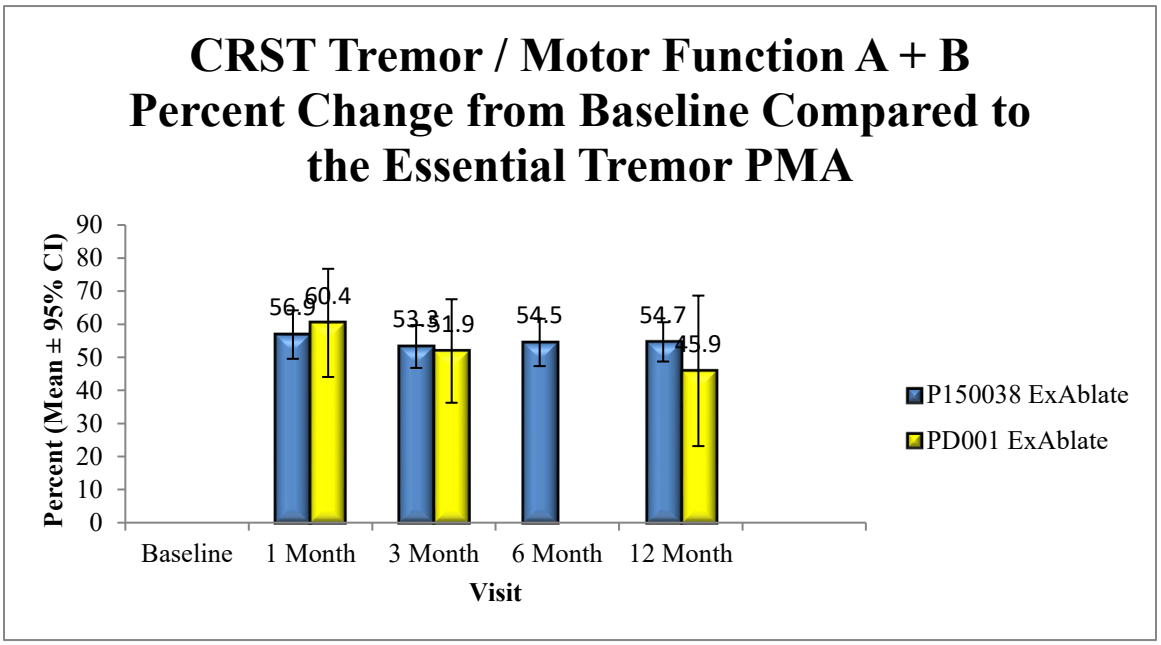


Figure 33. CRST Tremor Motor Function A+B Change from Baseline

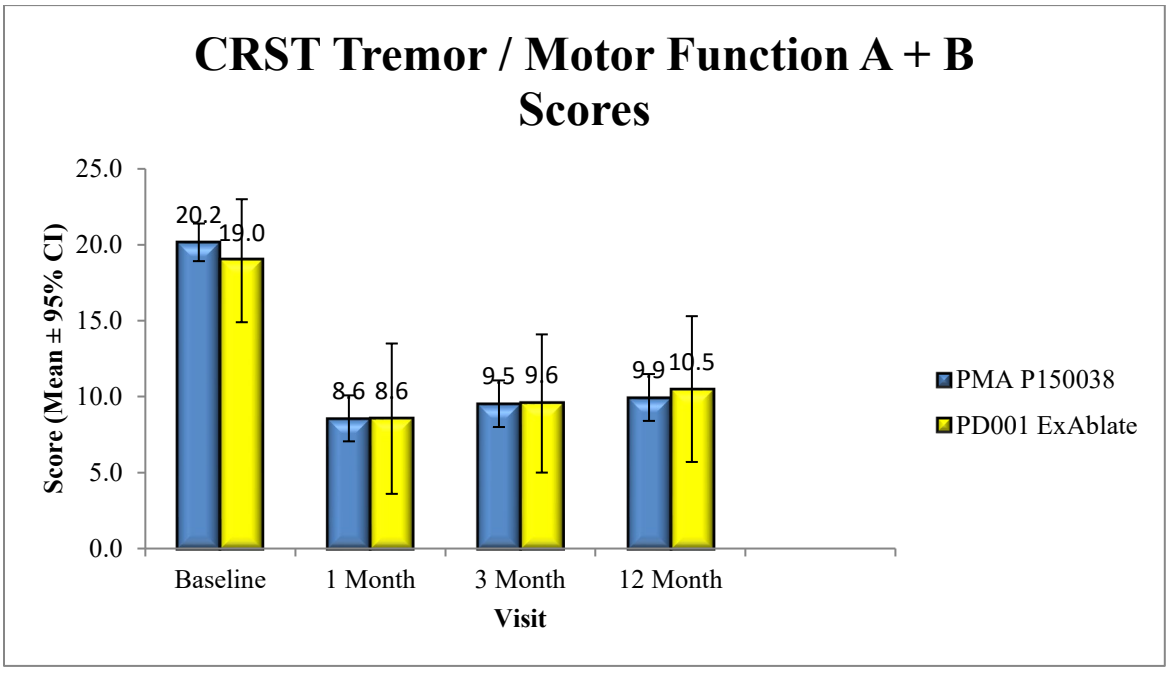


Figure 34. CRST Tremor/Motor Function A+B

6.3.4 CRST Part A Posture and Rest

The Part A Posture component (score of 0-4) is an important single indicator of tremor for ET subjects. For this reason, the Part A was evaluated as a lone measure in the ET Pivotal cohort. For Parkinson's Disease, resting tremor is the cardinal symptom. For the purposes of this measure, we have included the Rest component (score of 0-4) for the TDPD along with the Posture component score for comparison of effect. TABLE 51.

shows the actual Postural and Rest component score values in the TDPD cohort.

The percent change from Baseline exhibited the same trend as the CRST Tremor-Motor scores above. The change from Baseline at the 3 Month visit for the Posture scores was approximately 52% and 7% for the Exablate and Sham arms respectively.

In the Exablate TDPD Study, the posture scores improved markedly from baseline and compared to the Sham group **TABLE 51**. The percent improvement in the Exablate group was 51.7% and was 7.1% in the Sham control group.

TABLE 51. CRST PART A – POSTURE & REST - TREATED ARM BY TREATMENT GROUP SCORES BY VISIT THROUGH MONTH 12									
Visit / CRST, Part A – Posture calculation		Posture Observed scores		Posture Percent Change from Baseline		Rest Observed scores		Rest Percent Change from Baseline	
		Treated Side		Treated Side		Treated Side		Treated Side	
		Exablate	Sham	Exablate	Sham	Exablate	Sham	Exablate	Sham
Baseline	Mean	3.2	3.4	NA	NA	3.4	3.4	NA	NA
	Std	1.1	1.5	NA	NA	1.3	1.5	NA	NA
	Median	3.5	4.0	NA	NA	4	4	NA	NA
	N	20	7	NA	NA	20	7	NA	NA
1 Month FU	Mean	1.0	3.0	70.8	10.7	1.7	2.6	59.3	25.0
	Std	1.5	1.7	41.6	28.3	1.7	1.9	42.0	41.8
	Median	0.0	4.0	100.0	0.0	1	4	70.8	0
	N	20	7	20	7	20	7	18	6
3 Month FU	Mean	1.6	3.1	51.7	7.1	2.1	3.4	44.9	16.7
	Std	1.7	1.5	44.3	12.2	1.6	1.0	38.9	25.8
	Median	1.0	4.0	66.7	0.0	2	4	50	0
	N	20	7	20	7	20	7	18	6
12 Month FU	Mean	1.8	NA	32.9	NA	1.9	NA	48.7	NA
	Std	1.7	NA	89.1	NA	1.6	NA	49.2	NA
	Median	1.0	NA	58.3	NA	2	NA	50	NA
	N	20	NA	20	NA	7	NA	13	NA

Notes

1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100).

2. For cases of baseline value of 0 (where percent change cannot be defined, if the visit of comparison also had a value of 0, percent change was imputed as 0; otherwise, the percent change was not calculated.

2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

6.3.5 CRST Part C: Functional Disabilities

Functional disabilities improvements are presented in **TABLE 52** below. The Exablate treated group showed marked improvement (52.9%) improvement as compared to the Sham-treated group (13.4%), the same trend as demonstrated in the CRST Tremor-Motor outcomes. The p-value comparing between the Exablate and Sham Control groups was p = 0.057 even with the small sample size. Additionally, considering a unilateral treatment affecting only one side of their body, there was a measurable effect in these measures which assess both arms/hands.

TABLE 52. DESCRIPTIVE STATISTICS OF PERCENT IMPROVEMENT FROM BASELINE AT THREE MONTHS POST-TREATMENT IN FUNCTIONAL DISABILITIES TOTAL SCORE, AS MEASURED BY CRST PART-C BY TREATMENT GROUP

	Treatment Group				
CRST Part C Total	Exablate		Sham		p-Value
ITT Mean	20	52.9%	7	13.4%	0.057

Notes:
1. Wilcoxon rank-sum test was applied since the data differed appreciably from normal theory.
2. SE1 was calculated as Percent Change ({(Baseline - Visit)/Baseline}*100).
3. Higher SE1 values represent improvement.
4. Sham subject 106135 baseline CRST measures taken from screening visit.

Second, the functional disability improvement at 12-Months is shown in **TABLE 53** and **Figure 35**. Results for the 12 Month visit indicate that the improvements achieved at 3 Months were maintained through longer term follow-up. As shown in **TABLE 53**, at 12 Months improvement compared to baseline was 46%. Finally, the trend over time in the Exablate-treated group was the same as that observed in the ET trial (**Figure 36**, P150038).

TABLE 53. CRST PART C TOTAL SCORE FOR TREATED ARM BY TREATMENT GROUP BY VISIT THROUGH MONTH 12

Visit / CRST, Part C Total Score		Observed scores		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham
Baseline	Mean	14.1	16.7	NA	NA
	Std	5.7	3.9	NA	NA
	Median	13.0	17.0	NA	NA
	N	20	7	NA	NA
1 Month FU	Mean	5.7	15.6	58.3	6.3
	Std	7.5	3.3	49.3	7.4

TABLE 53. CRST PART C TOTAL SCORE FOR TREATED ARM BY TREATMENT GROUP BY VISIT THROUGH MONTH 12					
Visit / CRST, Part C Total Score		Observed scores		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham
	Median	2.0	16.0	82.8	9.5
	N	20	7	20	7
3 Month FU	Mean	6.4	14.6	52.9	13.4
	Std	6.6	4.2	44.2	18.2
	Median	3.5	16.0	72.1	14.3
	N	20	7	20	7
6 Month FU	Mean	6.4	NA	52.9	NA
	Std	6.6	NA	44.2	NA
	Median	3.5	NA	72.1	NA
	N	20	NA	20	NA
12 Month FU	Mean	6.9	NA	46.3	NA
	Std	7.2	NA	64.0	NA
	Median	3.5	NA	72.6	NA
	N	20	NA	20	NA

Notes:
1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100).
2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

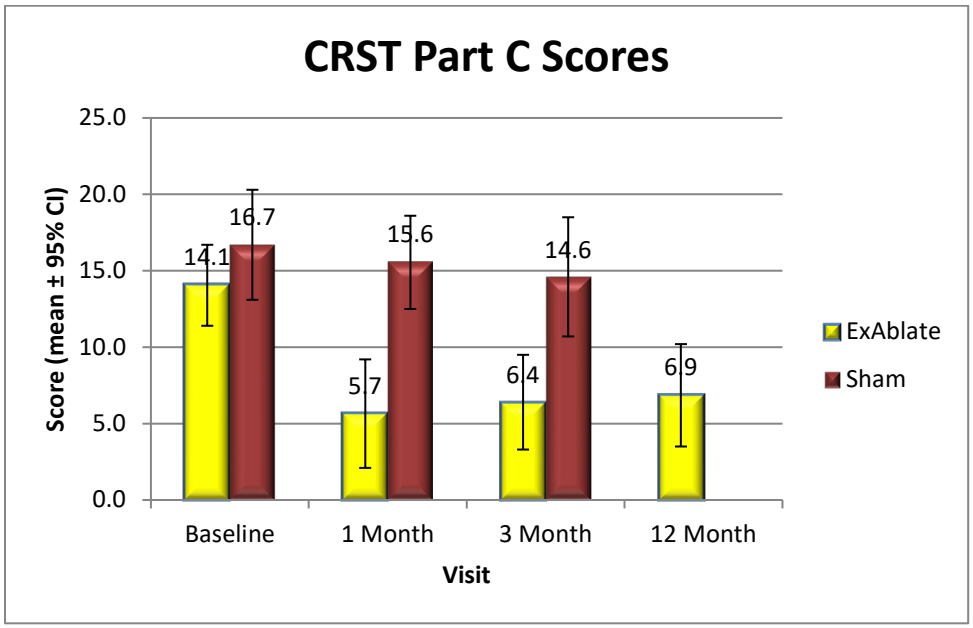


Figure 35. CRST Part C Scores show the treatment effect of Exablate thalamotomy was maintained over time

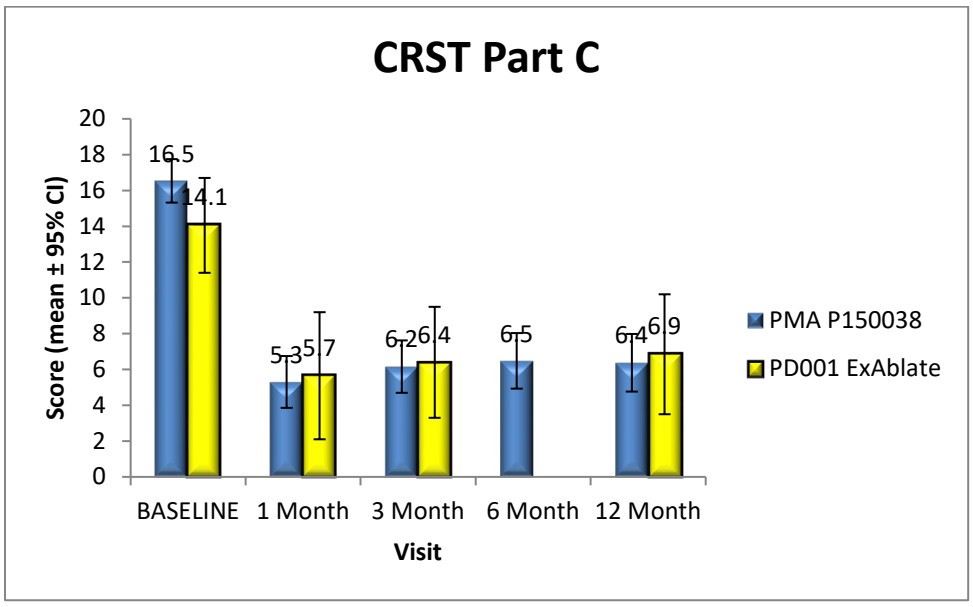


Figure 36. CRST Part C shows the TDPD trial produced similar treatment effects as observed in the ET pivotal trial

In summary, the CRST Tremor-Motor effect was clinically significant, and all secondary confirmatory endpoints exhibited the same clinically robust trend which was compared favorably to the ET PMA study.

6.3.6 Quality of Life in Essential Tremor Questionnaire - QUEST

QUEST is a Quality of Life measure specially designed for ET patients that indicates how much ET impacts their life across 5 dimensions: Communication, Work and Finances, Hobbies and Leisure, Physical, and Psychosocial. The Summary of Dimensions score (the average of all 5 dimensions) represents the impact of ET on the subject's overall quality of life, i.e., the subject disability. The results of this analysis mimic that of the primary endpoint at 3 months with a 40% improvement in the Exablate group as compared to Baseline, **TABLE 54**. This was comparable to the 43% improvement demonstrated in the pivotal trial.

TABLE 54. QUEST BY TREATMENT GROUP BY VISIT THROUGH MONTH 12					
Visit / QUEST		Total scores		Percent Change from Baseline	
		Treated Side		Treated Side	
		Exablate	Sham	Exablate	Sham
Baseline	Mean	36.2	46.2	NA	NA
	Std	22.6	26.0	NA	NA
	Median	36.0	52.8	NA	NA
	N	18	7	NA	NA
3 Month FU	Mean	25.5	41.4	39.6	18.6
	Std	23.4	28.5	34.5	22.4
	Median	16.7	45.8	35.8	16.3
	N	18	7	16	7
12 Month FU	Mean	26.1	NA	28.0	NA
	Std	23.0	NA	51.8	NA
	Median	11.1	NA	43.8	NA
	N	19	NA	17	NA

Notes:

1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100).

2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).

6.3.7 Summary of Efficacy Results

Exablate *Vim* thalamotomy for TDPD subjects resulted in significant improvement in treated side upper extremity tremor that was maintained through the 12-month study visit. Primary effectiveness was evaluated using validated scores: on medication, Upper Limb tremor-motor subscore from Parts A & B of the CRST. In the TDPD cohort study, the percent change from baseline for the Exablate-treated group was 51.6% compared to 12.7% for the Sham Control, a difference which resulted in a Wilcoxon rank-sum value of p = 0.030. We also evaluated the rest tremor components of the CRST and the UDysRS for Parkinson's patients. It is also especially noteworthy that the 51.6% improvement in the Exablate treated TDPD cohort was essentially the

same (46.9%) as that observed in the ET PMA trial (P150038). The upper extremity tremor score of 19.0 at baseline significantly improved to 9.6 at the 3 Month visit resulting in a Wilcoxon rank-sum value of $p < 0.001$. This response is quite robust, especially considering the small sample size used in this trial. The effect is also durable. The mean score at the 12 Month visit was 10.5 compared to the 9.6 at the 3 Month visit.

The improvement was quite robust given the sample size. Additionally, this improvement supported improvements in functional outcome and quality of life measures (non-statistically significant improvements in QUEST). **Figure 37** presents an overview of study outcomes compared to the ET PMA trial. Finally, improvements in upper extremity tremor of TDPD cohort patients (**Figure 33**, **Figure 34**) was similar to that reported in the PMA for essential tremor (P150038).

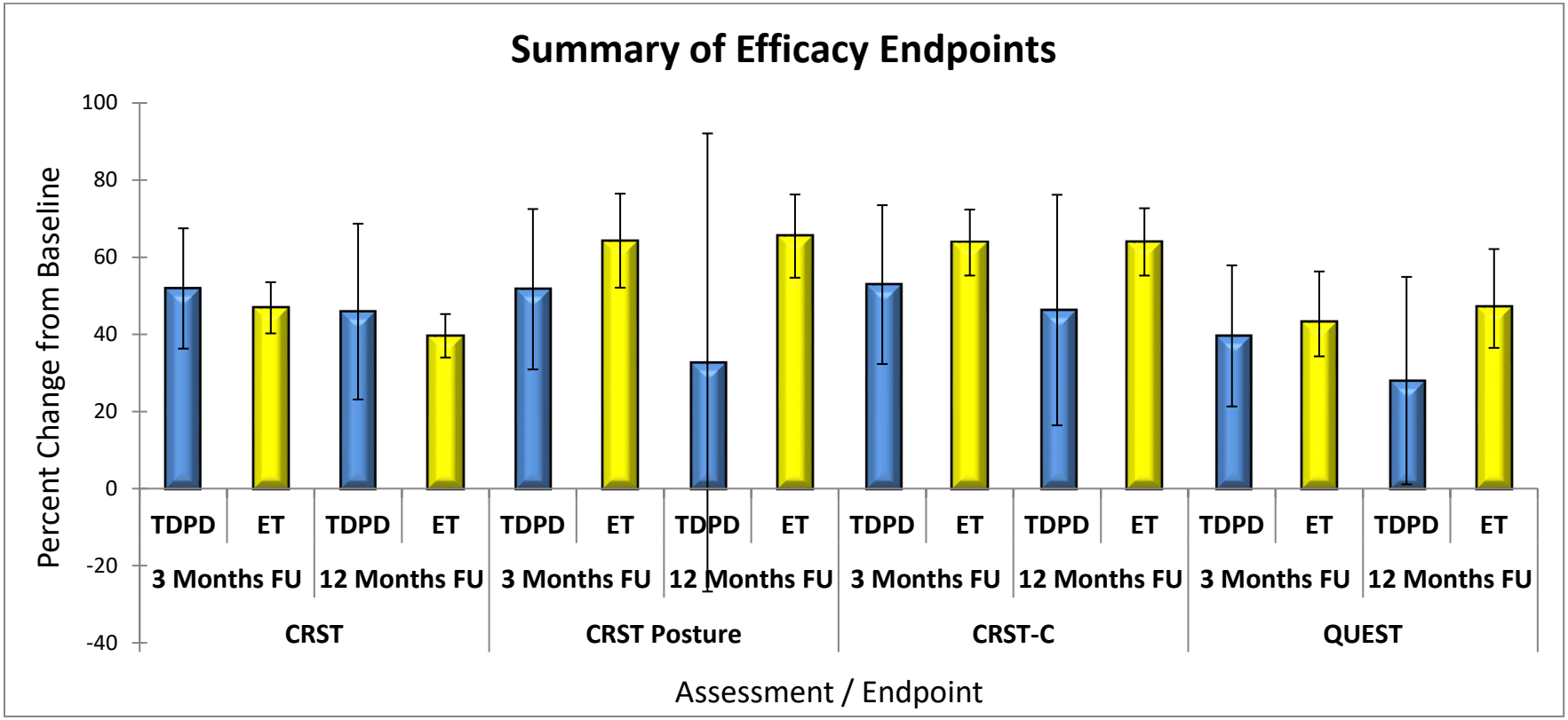


Figure 37. Efficacy TDPD outcomes compared to the ET PMA outcomes

6.3.8 Crossover group

Only 6 of the 7 Sham-treated TDPD subjects crossed over to an actual Exablate Treatment. While the results are similar, the sample size is small. The efficacy results were similar to the randomized portion. The safety profile did not change.

6.3 Overall Study Conclusions

The safety profile continues to be favorable and similar to previous experience with Exablate Thalamotomy for upper extremity tremor in the ET trial (P150038). In the Exablate-treated TDPD cohort 95% of all adverse events were Mild or Moderate in severity. This was similar to the TDPD Sham control group where 90% of adverse events were Mild or Moderate.

Out of the 100 adverse events reported in the Exablate-treated TDPD cohort50 (50%) were transient, resolving within 72 hours; 21 (21%) were unrelated to the device or procedure, 2 were related to progression of Parkinson's disease, 2 were procedure related and 22 (22%) were thalamotomy related. Thalamotomy related events were those associated with ablation of the Vim regardless of the method based on the literature. In this study Thalamotomy related events accounted for 22/100 (22%) of the adverse events. For comparison to the ET trial, Exablate Thalamotomy related adverse events occurred at frequencies as follows:

> Numbness/Tingling (7, 7%), Imbalance (4, 4%), Headache (0%), Gait disturbance (2, 2%) and Unsteady (1, 1%).

For these same events the ET trial reported the following frequencies:

> Numbness/Tingling (22, 12%), Imbalance (10, 5%), Ataxia (7, 4%), Headache (5, 3%), Gait disturbance (4, 2%), and Unsteady (4, 2%).

In the present PD study, there were two serious adverse events of Hemiparesis or Hemiparesis/Ataxia, both Serious Adverse Events. By comparison, there was one Serious Adverse Event of Hemiparesis that was moderate in severity reported in the PMA ET trial.

As with *Vim* thalamotomy for ET, we conclude that the safety profile in general is relatively benign, especially when compared to the safety profile reported in the literature for alternative surgical treatments for TDPD.

Exablate *Vim* thalamotomy has been demonstrated to be a safe and effective treatment for upper extremity tremor in ET. The present investigation in Parkinson's disease subjects indicates similar effectiveness and safety of Exablate treatment for upper extremity tremor in Tremor Dominant Parkinson's Disease.

CHAPTER 7: PALLIDOTOMY MOTOR COMPLICATIONS PARKINSON'S DISEASE

7.1 Pivotal Protocol Summary – PD006 IDE G170237

The study was designed as a prospective, two-arm, sham-controlled, crossover, randomized (3:1), multi-center pivotal study to evaluate the safety and efficacy of unilateral Exablate pallidotomy for medication-refractory, advanced idiopathic PD. Subjects considered to be medication-refractory are those who are significantly symptomatic in spite of best medication treatment, i.e., dyskinesias and/or debilitating OFF periods on meds (e.g., rigidity and bradykinesia/akinesia). Subjects underwent (actual or sham according to the randomization assignment) unilateral pallidotomy to the symptom-dominant side of the GPi. For subjects who had bilateral PD where both sides met study criteria, usually the dominant side was treated. It should be noted the final decision was based upon patient need and dominant symptom side. Subjects and neurologists assessing study efficacy endpoints were blinded through Month 3. Follow-up continued to Month 12 for long-term safety follow-up for the PMA submission. Subjects continue to be followed out to Year 5 for long-term FU.

The design of this study includes two stages: Main and Crossover. In the Main stage, a minimum of 92 and a maximum of 107 subjects were enrolled to the study and randomized in a 3:1 ratio to either Exablate or Sham Control (henceforth "Exablate" and "Sham," respectively). A Crossover stage of the study was designed for subjects randomized to the Sham group in the Main stage to receive an unblinded Exablate treatment, if eligible, at Month 3 follow-up post Sham treatment, and to be followed in a similar fashion as the Main stage of Exablate subjects in terms of planned follow-up visits and assessments. Additionally, any subjects randomized to the Exablate arm who were unable to receive a complete treatment were permitted to have a second treatment and considered as Crossover arm subjects; the second treatment for Exablate subjects who did not get a good treatment due to device issues was approved by FDA; all available Crossover data (unblinded Sham and Exablate subjects unblinded for second treatment) is included in the Crossover Arm in this submission.

7.1.1 Subject Selection Process

7.1.1.1 Inclusion Criteria

1. Men and women, age 30 years and older.
2. Subjects who are able and willing to give informed consent and able to attend all study visits through 12 Months.
3. Subjects with a diagnosis of idiopathic PD by UK Brain Bank Criteria as confirmed by a movement disorder neurologist at the site.
4. Levodopa responsive as defined by at least a 30% reduction in MDS-UPDRS motor subscale in the ON vs OFF medication state.

5. MDS-UPDRS score of ≥ 20 in the meds OFF condition.

   OR

   Motor complications of PD on optimum medical treatment characterized dyskinesia (MDS-UPDRS item 4.2 score of 2 or greater in the meds ON condition) OR motor fluctuations (MDS-UPDRS item 4.4 score of 2 or greater).

6. Subjects should be on a stable dose of all PD medications for 30 days prior to screening visit PD assessments as determined by medical records.
7. Subject is able to communicate sensations during the Exablate procedure.
8. Globus pallidus internus nucleus can be targeted by the Exablate device.
9. Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
10. Subjects on stable antidepressant medications for at least 3 months may be enrolled into this study (i.e., no change in medication drug or dosage for 3 months).

7.1.1.2 Exclusion Criteria

1. Hoehn and Yahr stage in the ON medication state of 3 or greater.
2. Presence of other central neurodegenerative disease suspected on neurological examination. These include multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and Alzheimer's disease.
3. Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications.
4. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia.
5. Presence of significant cognitive impairment using MMSE ≤ 24.
6. Unstable psychiatric disease, defined as active uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation. Unstable disease may include but is not limited to the following:

   a. Significant or active mood disorders requiring cognitive-behavioral therapy, transcranial magnetic stimulation, electroconvulsive therapy, or has been hospitalized within 12 months or screening.

   b. Depression with a score of 19 or greater on Beck Depression Inventory.

   c. Legal limitations as instituted by a neuropsychologist.

   Subjects with stable, chronic anxiety or depressive disorders may be included provided their medications have been stable for at least 3 months prior to study entry and if deemed appropriately managed by the site.

7. Subjects with an active alcohol or drug dependency or history of drug/alcohol abuse within the past year prior to screening as defined by DSM-5 criteria for Substance or Alcohol Use Disorders.
8. Subjects with unstable cardiac status including:
    a. Unstable angina pectoris on medication
    b. Subjects with documented myocardial infarction within six months of protocol entry
    c. Significant congestive heart failure defined with ejection fraction < 40
    d. Subjects with unstable ventricular arrhythmias
    e. Subjects with atrial arrhythmias that are not rate-controlled
9. Severe hypertension (diastolic BP > 100 on medication).
10. Current medical condition resulting in abnormal bleeding and/or coagulopathy.
11. Receiving anticoagulant (e.g., warfarin) or antiplatelet (e.g., aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g., Avastin) within one month of focused ultrasound procedure.
12. Subjects with risk factors for intraoperative or postoperative bleeding as indicated by: platelet count less than 100,000 per cubic millimeter; a documented clinical coagulopathy; or INR coagulation studies exceeding the institution's laboratory standard.
13. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m2 (or per local standards should that be more restrictive) and/or who is on dialysis.
14. Subjects with standard contraindications for MR imaging such as implanted metallic devices including cardiac pacemakers/defibrillators, neurostimulators, shunts/stents, or other metallic implants or brain implants, etc.
15. Significant claustrophobia that cannot be managed with mild medication.
16. Subjects who weigh more than the upper weight limit of the MR scanner table and who cannot fit into the MR scanner.
17. Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment.
18. History of intracranial hemorrhage, multiple strokes, or a stroke within past 6 months.
19. Subjects with a history of seizures within the past year.
20. Subjects with brain tumors.
21. Subjects with intracranial aneurysms requiring treatment or arterial venous malformations (AVMs) requiring treatment.
22. Are participating or have participated in another clinical trial in the last 30 days.

23. Any illness that in the investigator's opinion preclude participation in this study.
24. Subjects unable to communicate with the investigator and staff.
25. Pregnancy or lactation.
26. Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, liver failure, blood dyscrasias, etc.
27. All patients with severe premorbid risks [MDS-UPDRS Part II subsection: motor aspects of experiences of daily living scores of a three or four in question 2.1 (speech) or question 2.3 (chewing and swallowing), or a four on question 2.2 (saliva and drooling)] will be excluded.
28. Subjects who have an Overall Skull Density Ratio of less than 0.40 as calculated from the screening CT.

7.1.2 Patient Treatment

Patients who were randomized to sham treatment underwent a sham Exablate treatment with the sonication energy output disabled. Patients randomized to active treatment underwent pre-treatment planning. Any patient deemed not to have a device accessible target was considered a screen failure and was exited from the study. If the subject remained eligible, i.e., the target was device accessible, the patient had the planned treatment.

7.1.3 Study Follow up

All participating patients were consented for 5 years. Both active and sham treatment patients were seen for follow-up at 1 week and 1, and 3 months, at which time all patients were un-blinded for primary endpoint analyses. Subjects were evaluated for general health, efficacy measurements as well as for device/procedure related AEs that occurred during the follow-up period.

Following the Month-3 visit, study subjects in both arms were first evaluated per study requirements, and then unblinded. The Exablate Arm subjects continued with their planned long-term follow up that included 6-month and 12 months follow ups, followed with 2, 3, 4, and 5 years planned follow up visits.

The Sham Arm subjects were permitted to opt for a cross-over treatment with the Exablate. All the cross- over subjects will be followed up in the same manner as the active treatment group.

Analyses of the Primary endpoint were performed at 3 months and 12 months follow-up for the active Exablate Arm subjects.

Schedule of Events for this study is shown in **TABLE 55**.

TABLE 55. SCHEDULE OF EVENTS								
Procedures	**Screening**	**Day 0**	**Week 1 (± 3 days)**	**Month 1 (± 7 days)**	**Month 3 (±14 days)**	**Month 6- (± 21 days)**	**Month 12 (± 42 days)**	**Years 2-5 (± 4 mo.)**
Written Consent	X							
Eligibility Consensus	X							
Demographics, Medical History	X							
Labs	X							
CT	X							
MRI	X	X		X*				
General Physical Exam	X	X	X	X	X	X	X	X
Neurological Exam	X	X	X	X	X	X	X	
Visual Field Testing	X				X			
Gait (TGUG)	X			X	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
Unified Dyskinesia Rating Scale	X			X	X	X	X	X
Neuropsychological Assessment	X				X		X	
Patient Global Impression of Change				X	X	X	X	X
Clinician Global Impression of Change				X	X	X	X	X

TABLE 55. SCHEDULE OF EVENTS								
Procedures	**Screening**	**Day 0**	**Week 1 (± 3 days)**	**Month 1 (± 7 days)**	**Month 3 (±14 days)**	**Month 6- (± 21 days)**	**Month 12 (± 42 days)**	**Years 2-5 (± 4 mo.)**
Patient Satisfaction Questionnaire				X	X	X	X	X
Blinding form – Blinded Neurologist				X	X			
Blinding form – Subject		X	X	X	X			
Concomitant and PD Medications Levodopa equivalents (mg)	X	X	X	X	X	X	X	X
Exablate Pallidotomy		X						
Adverse Events		X	X	X	X	X	X	X
Exit Form								X

The schedule of MR Imaging is provided in .

TABLE 56. MR IMAGING REQUIREMENT SCHEDULE BY VISIT	
Screening	1. Structural/3-D T1 and T2 Weighted imaging exam 2. FGATIR or equivalent 3. DWI 4. GRE/SWI 5. DTI 6. resting state fMRI 7. Other MR imaging series may have been acquired as needed
Treatment	"Part of the Exablate procedure" 1. A localizer scan (quick T1) and a non-contrast T2-FSE MR scan 2. Planning imaging (e.g., T2 Weighted or FIESTA or other) exam along 3 axes: Axial, Coronal, and Sagittal 3. Other MR imaging series may have been acquired

TABLE 56. MR IMAGING REQUIREMENT SCHEDULE BY VISIT	
Immediately Post-procedure or within 24 hours of procedure	1. Structural/3-D T1 and T2 Weighted imaging exam 2. FGATIR or equivalent 3. DWI 4. GRE/SWI 5. DTI 6. resting state fMRI 7. Other MR imaging series may have been acquired as needed
Month 1 **Optional, as indicated**	1. Structural/3-D T1 and T2 Weighted imaging exam 2. FGATIR or equivalent 3. DWI 4. GRE/SWI 5. DTI 6. resting state fMRI 7. Other MR imaging series may have been acquired as needed

7.1.4 Covid-19 Impact

The impact of the COVID-19 virus pandemic on the follow-up of subjects in this study meant that follow-up visits may have been collected remotely and/or outside the scheduled window. All data that could be collected, was collected with the restraints of maintaining overall patient safety. While an in-person visit was preferred, there were concerns of COVID-19 transmission in certain geographic locations and thus remote visits were allowed. Some of the assessments or specific questions within an assessment could only be conducted in the clinic and thus were missed for the sake of subject safety. In cases where the outstanding Month 3 follow ups were conducted outside of the study visit window, the study assignment blinding was maintained until the follow up visit was completed, and these out of window data were used as the Month 3 observation (i.e., blinded); otherwise, the multiple imputation approach was adopted.

7.1.5 Study Endpoints

7.1.5.1 Safety Endpoint

The safety of the Exablate was determined by an evaluation of the incidence and severity of device-relatedadverse events and serious adverse events from treatment day through the Month 12 post-treatment time point.

7.1.5.2 Primary Effectiveness Endpoint

The primary efficacy endpoint of the study is a significant difference in the Responders Rate in Exablate group vs Responders Rate in the Control group. Response to the treatment, defined for each subject as "Responder" or "Non-Responder", was based on whether a patient improved on either MDS-UPDRS Part III (OFF meds motor exam for extremities on the treated side) OR UDysRS Objective Impairment (ON meds) without worsening on the other assessment.

Minimally clinically important difference for this study is defined as follows:

- MDS-UPDRS Part III (OFF meds motor exam) for extremities on the treated side:
  - Improvement is defined as reduction of more than 3 points at Month 3 from Baseline.
  - Worsening is defined as increase of 4 points or more at Month 3 from Baseline.
- UDysRS (ON meds)
  - Improvement is defined as reduction of more than 3 points at Month 3 from Baseline.
  - Worsening is defined as increase of more than 3 points at Month 3 from Baseline.

Subject response will be defined dichotomously as follows:

Responder ("1") If one of the following is fulfilled:

- Improvement on MDS-UPDRS Part III (OFF meds motor exam extremities treated side) AND no worsening on UDysRS Impairment (ON meds)

OR

- Improvement on UDysRS Impairment (ON meds) AND no worsening on MDS-UPDRS Part III (OFF meds motor exam)

Non-Responder ("0") Otherwise Non-Responder ("1")

7.1.5.2.1 Confirmatory Secondary Endpoints

The confirmatory secondary endpoints of the study are as follows:

- MDS-UPDRS Part IV – Motor Complication

  In the MDS UPDRS Part IV Motor complications included the sum of individual's score of items 4.1 to 4.6 in the MDS-UPDRS Part IV On medication.

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

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

  The individual patient mean score differences are then averaged and presented as the mean score and mean % change from Baseline

- MDS-UPDRS Part III Off-medication, Upper & Lower Extremity motor score

The OFF-meds upper and lower extremity motor endpoint will be calculated as the score difference for each patient on the treated side as well as the individual percent change from Baseline to Month 3 on MDS-UPDRS Part III, where percent change from baseline will be calculated as follows:

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

The individual patient outcomes are then averaged and presented as the mean score and mean % change from Baseline.

- MDS-UPDRS Part II – Motor Aspects of Experiences of Daily Living

  The activities of daily living endpoint will be calculated for each subject, comparing Baseline to Month 3 scores on MDS-UPDRS Part II, where an individual's score is the sum of items in the MDS-UPDRS Part II (sum of item 2.1 through 2.13). Individual percent change from Baseline will be calculated as follows:

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

  The data are presented as the group mean score difference and as the mean % change from Baseline.

7.1.5.2.2 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:

- MDS-UPDRS: Part III OFF Meds at all visits for each group (for treated side only, as defined for the primary efficacy analysis).
- MDS-UPDRS: Part II (sum of items 2.1-2.13) group mean, difference, and mean % change from Baseline at all visits for each group.
- MDS-UPDRS: Part IV ON Meds (sum of items 4.1-4.6) group means, mean change from Baseline, and mean % change from Baseline at all visits for each group.
- Unified Dyskinesia Rating Scale (UDysRS) Objective Impairment: Sum of items 16-22 at all visits, as well as the group mean % change from Baseline at each visit.

7.1.5.2.3 Additional Endpoints

The following additional efficacy endpoints will also be evaluated, including the calculated scores, change from Baseline and Percent Change from Baseline:

- Unified Dyskinesia Rating Scale (UDysRS): Historical (sum of items 1-15) and Objective (sum of items 16-26) sub-scores at all visits (total of all items for each sub-score) as well as Total UDysRS (sum of items 1-26).
- MDS-UPDRS: Total of Parts I, II, III OFF Meds (treated side), and IV ON Meds
- Clinician Global Impression of Change (CGIC)

- Patient Global Impression of Change (PGIC)
- Patient Satisfaction Questionnaire

7.1.6 Study Statistical Analysis Plan and Analysis Population

7.1.6.1 Study Analysis Population

The following analysis were used to evaluate study results:

- Intent to Treat (ITT) – which includes all randomized subjects who signed the informed consent.
- Safety Analysis Population – which includes all randomized subjects with at least one sonication (Exablate or Sham) in the main stage of the study.
- Modified Intent to Treat (mITT) – which includes all Safety subjects receiving at least one sonication for whom there exists primary efficacy data at Baseline and at least one post-Baseline assessment sufficiently to determine the primary efficacy endpoint (i.e., data for both MDS-UPDRS and UDysRS).
- Per Protocol Population (PP) – which includes all mITT subjects who have observed primary efficacy data at Baseline and Month 3, observed lesion on post-op image, and have no major protocol violations likely to affect outcome.

The mITT population will be the main analysis population used for the purpose of efficacy analyses, including primary and secondary confirmatory analyses.

7.1.7 Study Subject Accountability

A total of 166 subjects were recruited for the trial as presented in the consort chart in **Figure 38**. Of these potential study candidates, 72 subjects were considered screen fails and 94 subjects were randomized. Of the 94 subjects randomized, 92 subjects (68 Exablate, 24 Sham) were considered treated (received at least 1 sonication) at nine U.S sites and seven international sites.

Twenty (20) of the 24 Sham subjects crossed over to Exablate Crossover Arm after unblinding at Month 3. Additionally, two Exablate subjects unable to receive a complete treatment crossed over following their Month 3 blinded follow-up visits. Insightec consulted with FDA to allow these subjects to receive treatment as part of the Crossover Arm.

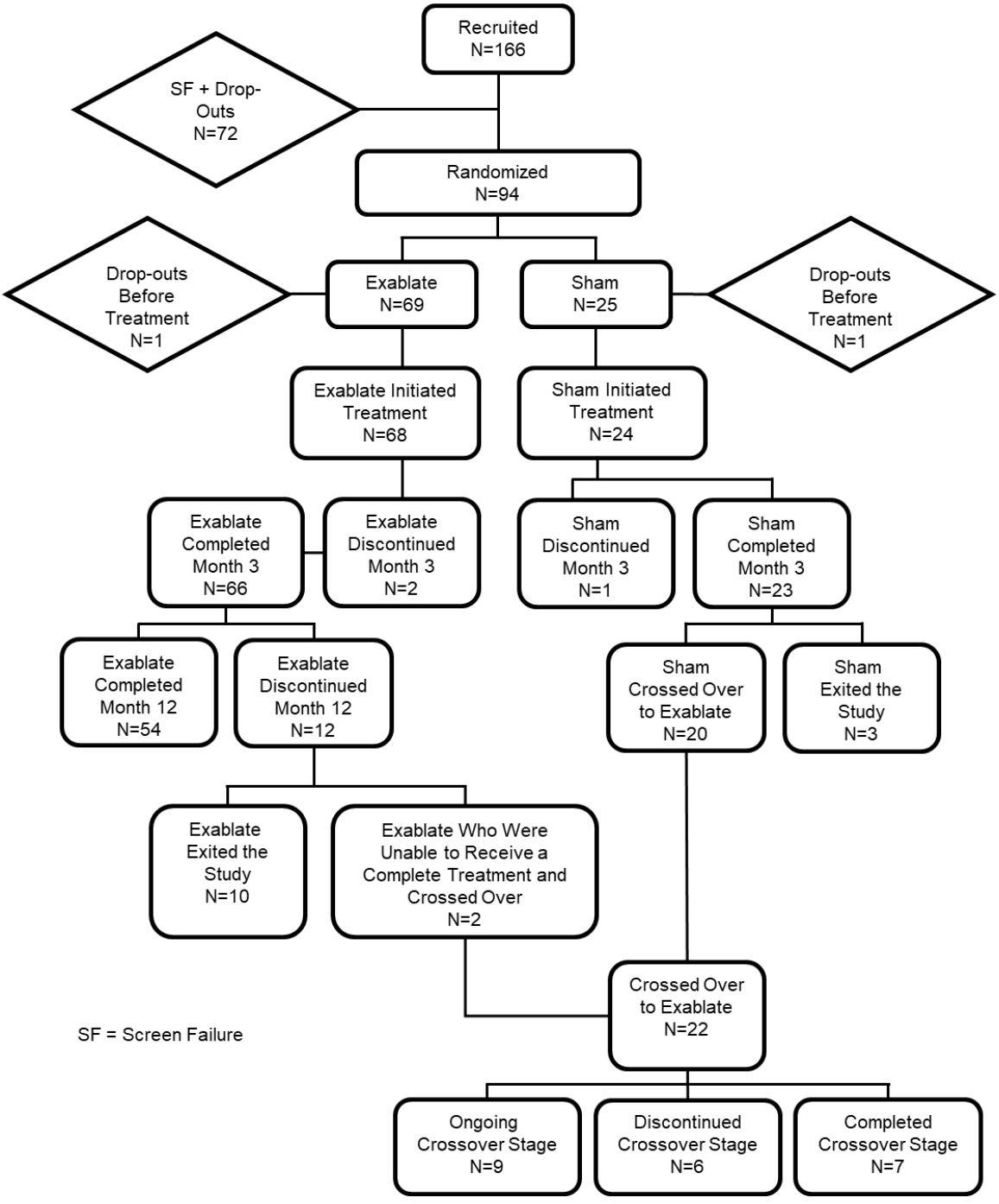


Figure 38. Consort Chart

In total, 97% (65/67 subjects) of Exablate study subjects and 96% (23/24 subjects) of Sham subjects completed the blinded portion of the study (Month 3) that serves as the basis for the study primary endpoint analysis. Due to COVID-19 pandemic and lockdowns, all efforts were made to collect as much data as possible from remote / telehealth visits, even outside of window.

As per approved SAP, missing data were imputed by means of multiple imputation for mITT analysis. The below disposition reflects the data that are available for mITT analysis by multiple imputation.

Table 57. Subject Disposition								
Category	Screening		1 Month FU		3 Month FU		6 Months FU	12 Months FU
	Exablate	Sham	Exablate	Sham	Exablate	Sham	Exablate	Exablate
Recruited	166	0						
SF / Dropout before randomization 1	72	0						
Randomized 2	69	25						
Dropouts before treatment 3	1	1						
Theoretical 4	68	24	68	24	68	24	68	68
Not Yet Due 5	0	0	0	0	0	0	0	0
Exited: Death	0	0	0	0	0	0	0	0
Exited: Failure 6	0	0	0	0	0	0	1	2
Exited: Other Reasons7	0	0	1	0	2	1	11	12
Expected 8	68	24	67	24	66	23	56	54
Actual 9	68	24	67	24	65	23	51	53
Actual % 10	100.0	100.0	100.0	100.0	98.5	100.0	91.1	98.1

1 - SF – Those subjects Recruited, but not meeting enrollment criteria.

2 - Randomized equals those Recruited minus SF.

3 – Drop-outs before treatment – Randomized subjects who have not received any sonication.

4 - Theoretical is equal to the number of subjects Recruited minus SF 1 minus Dropouts before treatment. Therefore, theoretical is equal to the number of subjects eligible to receive treatment in either group.

5 - Not Yet Due is equal to the number of subjects who have yet to reach the given visit window.

Table 57. Subject Disposition								
Category	Screening		1 Month FU		3 Month FU		6 Months FU	12 Months FU
	Exablate	Sham	Exablate	Sham	Exablate	Sham	Exablate	Exablate
6 - Failures include any subjects (Exablate or Sham) who discontinued the study due to beginning another treatment for their condition.								
7 - Exited the Main Stage for reasons other than Failure or Death.								
8 - Expected equals Theoretical minus Exited for any reason.								
9 - Actual is the number of subjects actually returning for the follow-up visit.								
10 - Actual % is the number of Actual subjects divided by Expected.								

7.1.8 Study Demographics and Baseline Characteristics

The demographics of the study population are typical for a Parkinson's Disease study performed in the United States. The demographics, baseline, and operative characteristics were similar between the two treatment groups, as shown in **TABLE 58** below.

TABLE 58. DEMOGRAPHIC CHARACTERISTICS (SAFETY POPULATION)

Demographic Characteristics		Treatment Group	
		Exablate	Sham
Age [Years]	Mean	64.2	63.3
	N	68	24
BMI [kg/m²]	Mean	27.1	24.5
	N	68	24
Height [cm]	Mean	169.3	168.6
	N	68	24
Weight [kg]	Mean	78.4	69.8
	N	68	24
Gender	Female	25 (36.8%)	10 (41.7%)
	Male	43 (63.2%)	14 (58.3%)
	N	68 (100.0%)	24 (100.0%)
Race	White	51 (75.0%)	17 (73.9%)
	Black or African American	1 (1.5%)	0 (0%)
	Asian	11 (16.2%)	4 (17.4%)
	Other	5 (7.4%)	2 (8.7%)
	N	68 (100.0%)	23[1] (100.0%)
Ethnicity	Hispanic	2 (3.0%)	2 (9.1%)
	Non-Hispanic	64 (97.0%)	20 (90.0%)
	Total	66[2] (100.0%)	22[2] (100.0%)
	Mean	10.5	11.1

TABLE 58. DEMOGRAPHIC CHARACTERISTICS (SAFETY POPULATION)			
Demographic Characteristics		Treatment Group	
		Exablate	Sham
Time from Initial PD Symptoms [Years]	N	68	24
Time from Initial PD Diagnosis [Years]	Mean	9.1	9.5
	N	68	24
Time from First PD Medical Therapy [Years]	Mean	8.8	8.8
	N	68	24
Levodopa Equivalent Dosage	Mean	1061.8	1052.2
	N	68	24
[1] One subject declined to report their Race at Baseline. [2] Four subjects (two in each Treatment Group) declined to report their Ethnicity at Baseline.			

7.1.9 Safety Endpoint

The analysis of safety was based on the ITT/Safety Population cohort of 92 subjects (68 Exablate subjects and 24 Sham subjects), available through the Month 12 evaluation. Note that the Sham subjects' AE data was only collected out to the Month 3 follow-up visit (i.e., primary endpoint), after which all Sham subject either crossed over to the Exablate treatment or withdrew. Thus, **TABLE 59** below reflects data through the Month 12 follow-up visit for the Exablate group and data through the Month 3 follow-up visit for Sham group.

A high-level summary of the safety profile is presented in **TABLE 59**. A total of 149 events were reported in a total of 92 subjects (Exablate:131 events, in 68 subjects; Sham:18 events, in 24 subjects). It should be noted 25 subjects in the Exablate arm had no adverse events and 12 subjects in the Sham arm had no events.

In the Exablate group, 91% of all events were Mild or Moderate in nature, whereas in the Sham group, 94% were Mild or Moderate in nature. Of all these events, only one (1) Serious event occurred that out of abundance of caution was labeled as Procedure related:

> One subject had a pulmonary embolism that was coincident with immediate travel pre- and post-procedure Exablate. The DSMB ruled it as procedure-related out of abundance of caution.

Additionally, 15 events in 11 subjects were all Unrelated to Exablate and related to comorbid diseases/medical history (14 Exablate; 1 Sham)

TABLE 59. SEVERITY OF ADVERSE EVENTS (SAFETY POPULATION)				
	Exablate		Sham	
	Frequency N=131	Incidence N=68	Frequency N=18	Incidence N=24
Mild	81 (61.8%)	28 (41.2%)	12 (66.7%)	9 (37.5%)
Moderate	38 (29.0%)	25 (36.8%)	5 (27.8%)	4 (16.7%)
Severe	10 (7.6%)	8 (11.8%)	1 (5.6%)	1 (4.2%)
Life-threatening (Unrelated)	2 (1.5%)	3 (4.4%)	0 (0%)	0 (0%)
Total	131 (100.0%)	43 (63.2%)	18 (100.0%)	12 (50.0%)
SAEs Procedure Related	1	1	0	0
SAEs Unrelated	14	10	1	1

7.1.9.1 Adverse Events

The primary analysis of safety population (N=68) was based upon the collection of adverse events during the study as collected by the investigators at each site. As shown in **TABLE 60**, an average of 1.9 events per subject (min 0, max 8 events) was recorded in the Exablate group and 0.8 events per subject (min 0, max 3 events) for the Sham-treated subjects.

TABLE 60. NUMBER OF AES PER SUBJECT (SAFETY POPULATION)		
Number of AEs per Subject	Treatment Group	
	Exablate	Sham
Mean	1.9	0.8
Std	2.2	0.9
Min	0.0	0.0
Median	1.0	0.5
Max	8.0	3.0
N (subjects)	68	24

TABLE 61 shows the number of subjects experiencing adverse events between the two study groups. Twenty-five subjects in the Exablate group and 12 subjects in the Sham group had no events.

TABLE 61. SUBJECTS WITH AND WITHOUT ADVERSE EVENT (SAFETY POPULATION)				
Experience of at Least One Adverse Event	Treatment Group			
	Exablate		Sham	
	N	%	N	%
Yes	43	63.2	12	50.0
No	25	36.8	12	50.0
Total	68	100.0	24	100.0

TABLE 62 below shows the Adverse Events by relation to the study events and grouping. Most of all events were Unrelated. Grouping term definitions are summarized below:

- The Unrelated events are events related to the stereotactic frame, IV, co-morbid conditions and events coded by PI as Unrelated
  - Exablate: 55 (42%) events in 30 (44%) subjects were Unrelated
  - Control: 12 (67%) events 9 (38%) subjects were Unrelated
- The **PD Disease Related/Disease Progression** events are events related to Parkinson's Disease progression or PD medication related.

- Exablate: 17 (13%) events in 14 (21%) subjects were PD disease related
- Control: 3 (17%) events 2 (8%) subjects were PD disease related

- Many of the Transient events are events that are used by the physician to steer targeting of the lesion prior to full ablation, but all of the events coded in this category occurred at the time of the procedure and resolved within 72 hours.
  - Exablate: 39 (30%) events in 26 (38%) subjects were Transient (resolved <72 hours)
  - Control: 3 events (17%) in 3 subjects (13%) resolved quickly
- The Pallidotomy related events are events normally reported when ablation/stimulation of the globus pallidum is undertaken.
  - Exablate: 11 (8%) events in 10 (15%) of subjects were Pallidotomy-related
- The Procedure related events are generally those events that are non-transient and related to undergoing the procedure, such as fatigue, headache, etc.
  - Exablate: 9 (7%) events in 6 (9%) of subjects were Procedure-related
    - All nine-procedure related event resolved.

TABLE 62. ADVERSE EVENTS BY GROUPING TERM (SAFETY POPULATION)				
	Exablate		Sham	
	Frequency N=131	Incidence N=68	Frequency N=18	Incidence N=24
Unrelated	55 (42.0%)	30 (44.1%)	12(66.7%)	9 (37.5%)
PD Disease Related/Disease Progression	17 (13.0%)	14 (20.6%)	3 (16.7%)	2 (8.3%)
Subtotal	72 (52.7%)	35 (51.5%)	15 (83.3%)	10 (41.7%)
Transient	39 (29.8%)	26 (38.2%)	3 (16.7%)	3 (12.5%)
Pallidotomy Related	11 (8.4%)	10 (14.71%)	0 (0%)	0 (0%)
Procedure Related	9 (6.9%)	6 (8.8%)	0(0%)	0 (0%)
Subtotal	20 (15.3%)	14 (20.6%)	0 (0%)	0 (0%)
Grand Total	131 (100.0%)	43 (63.2%)	18 (100.0%)	12 (50.0%)

7.1.9.2 Adverse Events Listing

The frequency and incidence of all adverse events is presented by treatment group and severity and by body system and coded term in **TABLE 63.** below. Important to emphasize that in this study there were no visual field deficits events.

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			Exablate		Sham	
			Number of events (% of events)	Number of subjects (% of subjects)	Number of events (% of events)	Number of subjects (% of subjects)
Disease Progression	Nervous	Decreased Biceps Reflex	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Decreased Foot Vibration	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Psychological	Reduced Verbal Fluency	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		**3 (2.3%)**	**2 (2.9%)**	**0 (0.0%)**	**0 (0.0%)**
Pallidotomy Related	Nervous	Dysarthria	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
		Facial Drooping	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Gait Imbalance	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Hiccups	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
		Imbalance	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Increased Salivation/Drooling	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Numbness/Tingling	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Paresthesia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			**Exablate**		**Sham**	
			Number of events (% of events)	**Number of subjects (% of subjects)**	**Number of events (% of events)**	**Number of subjects (% of subjects)**
	Vision	Blurred Vision	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		**11 (8.4%)**	**10 (14.7%)**	**0 (0.0%)**	**0 (0.0%)**
Parkinson's Disease Related	Cardiovascular	Palpitation	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Gastrointestinal	Constipation	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Nausea/Vomiting	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	General	Fall	4 (3.1%)	4 (5.9%)	0 (0.0%)	0 (0.0%)
	Musculoskeletal	Muscle Pain	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Nervous	Dizziness	0 (0.0%)	0 (0.0%)	2 (11.1%)	1 (4.2%)
		Dystonia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Loss of Concentration	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Pain/Discomfort	Leg Cramp	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Psychological	Anxiety	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Hallucination	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Perioperative Confusion	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (4.2%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			**Exablate**		**Sham**	
			Number of events (% of events)	**Number of subjects (% of subjects)**	**Number of events (% of events)**	**Number of subjects (% of subjects)**
	Vision	Eye Fatigue	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		**14 (10.7%)**	**12 (17.6%)**	**3 (16.7%)**	**2 (8.3%)**
Procedure Related	Cardiovascular	Pulmonary Embolism	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	General	Fatigue	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Nervous	Dizziness	3 (2.3%)	3 (4.4%)	0 (0.0%)	0 (0.0%)
	Pain/Discomfort	Headache	3 (2.3%)	3 (4.4%)	0 (0.0%)	0 (0.0%)
		Sonication Related Pain	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		**9 (6.9%)**	**6 (8.8%)**	**0 (0.0%)**	**0 (0.0%)**
Transient	Cardiovascular	Hypertension	4 (3.1%)	4 (5.9%)	1 (5.6%)	1 (4.2%)
	Gastrointestinal	Nausea/Vomiting	5 (3.8%)	5 (7.4%)	0 (0.0%)	0 (0.0%)
	Musculoskeletal	Muscle Stiffness	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Nervous	Dizziness	3 (2.3%)	3 (4.4%)	0 (0.0%)	0 (0.0%)
		Head Tilting	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
		Hoarseness	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Numbness/Tingling	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			**Exablate**		**Sham**	
			Number of events (% of events)	**Number of subjects (% of subjects)**	**Number of events (% of events)**	**Number of subjects (% of subjects)**
		Nystagmus	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Pain/Discomfort	Ear Pain	1 (0.8%)	1 (1.5%)	0 (0.0%)0	0 (0.0%)
		Headache	4 (3.1%)	4 (5.9%)	0 (0.0%)	0 (0.0%)
		Positional Pain	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
		Sonication Related Pain	11 (8.4%)	11 (16.2%)	1 (5.6%)	1 (4.2%)
		Sonication Related Warmth	1 (0.8%)	1 (1.5%)	1 (5.6%)	1 (4.2%)
	Vestibular	Vertigo	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		**39 (29.8%)**	**26 (38.2%)**	**3 (16.7%)**	**3 (12.5%)**
Unrelated	Cardiovascular	Deep Vein Thrombosis	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Hypertension	1 (0.8%)	1 (1.5%)	1 (5.6%)	1 (4.2%)
		Myocardial Infarction	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Syncope	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Dermatologic	Subcutaneous Cyst	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	EENT	Decreased Hearing	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Gastrointestinal	Bloating	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			Exablate		Sham	
			Number of events (% of events)	Number of subjects (% of subjects)	Number of events (% of events)	Number of subjects (% of subjects)
		Cholecystitis	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Diverticulitis	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Hernia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Stomach Infection	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	General	Cold Hands	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Metastatic Endometrial Cancer	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Skin Rash	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Tumor Resection	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Weight Loss	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Infection	Cytomegalovirus	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Uvulitis	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Musculoskeletal	Arthrosis	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Bone Fracture	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Hip Replacement	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Laminectomy	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (4.2%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			Exablate		Sham	
			Number of events (% of events)	Number of subjects (% of subjects)	Number of events (% of events)	Number of subjects (% of subjects)
		Leg Fracture	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Muscle Pain	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Nervous	Dysesthesia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Paresthesia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Stroke	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Stuttering	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Subdural Hematoma	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Subdural Hemorrhage	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Pain/Discomfort	Migraine	2 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Respiratory	Chest Congestion	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Interstitial Pneumonia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Respiratory Tract Infection	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (4.2%)
	Stereotactic Frame	Dizziness	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (4.2%)
		Facial Edema	3 (2.3%)	3 (4.4%)	1 (5.6%)	1 (4.2%)
		Headache	4 (3.1%)	4 (5.9%)	2 (11.1%)	2 (8.3%)

TABLE 63. FREQUENCY AND INCIDENCE OF ADVERSE EVENTS BY TREATMENT GROUP (SAFETY POPULATION)						
Grouping Term / Body System / Preferred Term			Exablate		Sham	
			Number of events (% of events)	Number of subjects (% of subjects)	Number of events (% of events)	Number of subjects (% of subjects)
		Pin Site Bruising	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Pin Site Infection	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Pin Site Numbness	1 (0.8%)	1 (1.5%)	3 (16.7%)	3 (12.5%)
		Pin Site Pain	3 (2.3%)	3 (4.4%)	2 (11.1%)	2 (8.3%)
		Pin Site Swelling	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Scalp Pain	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Urinary	Increased Urine Urgency	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Urinary Tract Infection	2 (1.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
	Vision	Blurred Vision	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Diplopia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Glaucoma	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
		Myopia	1 (0.8%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Total		55 (42.0%)	30 (44.1%)	12 (66.7%)	9 (37.5%)
Grand Total			131 (100%)	43 (63.2%)	18 (100%)	12 (50.0)

As shown in **TABLE 64** below, the Pallidotomy related out of the 11 Events, 8 (73%) are Mild and 3 (27%) are Moderate. Additionally, out of the 9 events that are Procedure related, 7 (64%) events are Mild, one (11%) Moderate and one (11%) Severe. The procedure related Severe event is a Pulmonary Embolism event that developed following the Subject air travel after the Exablate Procedure. Out of abundance of caution, this event is classified as procedure related.

TABLE 64. SEVERITY OF PALLIDOTOMY AND PROCEDURE RELATED ADVERSE EVENTS (SAFETY POPULATION)

Grouping Term / Body System / Preferred Term			Exablate		Severity			
			Number of events (% of events)	Number of subjects (% of subjects)	Mild	Moderate	Severe	Life-Threatening
Pallidotomy Related	Nervous	Dysarthria	2 (1.5%)	2 (2.9%)	1	1	0	0
		Facial Drooping	1 (0.8%)	1 (1.5%)	0	1	0	0
		Gait Imbalance	1 (0.8%)	1 (1.5%)	1	0	0	0
		Hiccups	2 (1.5%)	2 (2.9%)	2	0	0	0
		Imbalance	1 (0.8%)	1 (1.5%)	1	0	0	0
		Increased Salivation/Drooling	1 (0.8%)	1 (1.5%)	1	0	0	0
		Numbness/Tingling	1 (0.8%)	1 (1.5%)	1	0	0	0
		Paresthesia	1 (0.8%)	1 (1.5%)	1	0	0	0
	Vision	Blurred Vision	1 (0.8%)	1 (1.5%)	0	1	0	0
	Total		**11 (8.4%)**	**10 (14.7%)**	**8**	**3**	**0**	**0**
Procedure Related	Cardiovascular	Pulmonary Embolism	1 (0.8%)	1 (1.5%)	0	0	1	0
	General	Fatigue	1 (0.8%)	1 (1.5%)	1	0	0	0

	Nervous	Dizziness	3 (2.3%)	3 (4.4%)	3	0	0	0
	Pain/Discomfort	Headache	3 (2.3%)	3 (4.4%)	2	1	0	0
		Sonication Related Pain	1 (0.8%)	1 (1.5%)	1	0	0	0
	Total		**9 (6.9%)**	**6 (8.8%)**	**7**	**1**	**1**	**0**

As shown in **TABLE 65**, 101 (77%) of the 131 adverse events reported in the Exablate arm started within 30 days. Of those 131 events, 90 events (69%) resolved within 90 days. Similarly, for Sham Arm, most events 12 out of 18 (67%) occurred within 30 days of the treatment and resolved within 90 days. The safety profile here was favorable in this population of Parkinson's Disease patients. Events that began after 30 days were all related to comorbid conditions and disease progression.

TABLE 65. ADVERSE EVENTS ONSET VERSUS ADVERSE EVENT DURATION BY TREATMENT GROUP (SAFETY POPULATION)

Duration	Exablate						Sham					
	Onset ≤ 30 days		Onset 31-90 days		Onset > 90 days		Onset ≤ 30 days		Onset 31-90 days		Onset > 90 days	
	Freq N=131	Incidence N=68	Freq N=131	Incidence N=68	Freq N=131	Incidence N=68	Freq N=18	Incidence N=24	Freq N=18	Incidence N=24	Freq N=18	Incidence N=24
≤ 30 days	79 (60.3%)	33 (48.5%)	4 (3.1%)	4 (5.9%)	9 (6.9%)	7 (10.3%)	10 (55.6%)	8 (33.3%)	2 (11.1%)	2 (8.3%)	0	0
31-90 days	11 (8.4%)	9 (13.2%)	0	0	1 (0.8%)	1 (1.5%)	2 (11.1%)	1 (4.2%)	0	0	0	0
> 90 days	2 (1.5%)	2 (2.9%)	1 (0.8%)	1 (1.5%)	4 (3.1%)	4 (5.9%)	1 (5.6%)	1 (4.2%)	1 (5.6%)	1 (4.2%)	0	0
Ongoing	9 (6.9%)	8 (11.8%)	2 (1.5%)	2 (2.9%)	9 (6.9%)	6 (8.8%)	1 (5.6%)	1 (4.2%)	0	0	1 (5.6%)	1 (4.2%)
TOTAL	**101 (77.1%)**	**39 (57.4%)**	**7 (5.3%)**	**6 (8.8%)**	**23 (17.6%)**	**16 (23.5%)**	**14 (77.8%)**	**10 (41.7%)**	**3 (16.7%)**	**3 (12.5%)**	**1 (5.6%)**	**1 (4.2%)**

All Procedure related events resolved and all Pallidotomy related events resolved except for the following three Mild/Moderate events shown in **TABLE 66**:

TABLE 66. ONGOING PALLIDOTOMY RELATED ADVERSE EVENTS (SAFETY POPULATION)

AE Coded Term	Subject	AE Body System	AE Code	Mild	Moderate	Severe
Pallidotomy related	115011	Nervous	Dysarthria	0	1	0
	121002	Nervous	Increased salivation/drooling	1	0	0
	112009	Nervous	Numbness/tingling	1	0	0
Total				**3 (3 / 131 = 2.3%)**		

7.1.9.3 Serious Adverse Events

TABLE 67 presents serious adverse events (SAEs) reported in the study. There have been sixteen serious adverse events reported during this trial. Fifteen of the sixteen serious adverse events were categorized as Unrelated by PI and adjudicated by DSMB. There was one pulmonary embolism event that developed following a Subject air travel after the Exablate Procedure. Out of abundance of caution, this event is classified as procedure related.

TABLE 67. SERIOUS ADVERSE EVENTS (SAFETY POPULATION)

	Exablate		Sham	
	Frequency N=131	Incidence N=68	Frequency N=18	Incidence N=24
Unrelated SAE	14 (10.7%)	10 (14.7%)	1 (5.6%)	1 (4.2%)
Procedure Related* SAE	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
Total	15 (11.5%)	10 (14.7%)	1 (5.6%)	1 (4.2%)

***Procedure Related SAE:**

The PI classified pulmonary embolism event as Serious and Unrelated to Exablate device. At Week 1 follow-up visit, subject reported a pulmonary embolism that was coincident with immediate travel pre- and post-procedure Exablate and again for the Week 1 visit. Out of abundance of caution, this event was categorized as procedure related.

The full list of the Unrelated SAEs is shown in **TABLE 68** below.

TABLE 68. LISTING OF ALL UNRELATED SERIOUS ADVERSE EVENTS (SAFETY POPULATION)					
GROUPING TERM	SERIOUS ADVERSE EVENTS (SAEs)	EXABLATE		SHAM	
		FREQUENCY N= 131	INCIDENCE N=68	FREQUENCY N=18	INCIDENCE N=24
Unrelated	Cholecystitis	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Cytomegalovirus	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Deep vein thrombosis	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Diverticulitis	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Fall	2 (1.5%)	2 (2.9%)	0 (0%)	0 (0%)
	Hernia	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Interstitial pneumonia	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Laminectomy	0 (0%)	0 (0%)	1 (5.6%)	1 (4.2%)
	Leg fracture	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Metastatic endometrial cancer	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Myocardial infarction	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Stroke	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Subdural hematoma	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
	Subdural hemorrhage	1 (0.8%)	1 (1.5%)	0 (0%)	0 (0%)
Total SAE's		14 (11.5%)	10 (16.2%)	1 (5.6%)	1 (4.2%)

7.1.10 Primary Efficacy Endpoint

The primary efficacy analysis was performed on the mITT population, all of whom underwent a procedure and had post-procedure follow-up, to compare the responder rate between Exablate and Sham groups as shown in **TABLE 69**.

Each subject was defined as "Responder" or "Non-Responder" based on whether a patient improved on either MDS-UPDRS Part III questionnaire or UDysRS Objective Impairment (ON meds), without worsening on the other assessment at the Month 3 follow-up visit.

TABLE 69 shows that out of 67 mITT subjects randomized to the Exablate group, 46 subjects were Responders corresponding to 68.6% Responder rate, whereas the Responder rate of the Sham group was 33.3%. The imputation rates yielded the odds ratio between groups of 4.4. This result is strongly significant, with P=0.005.

TABLE 69. PRIMARY EFFICACY ENDPOINT - RESPONDER ANALYSIS (MITT)

	Treatment Group		
Statistics	**Exablate**	**Sham**	**Odds Ratio**
Total N	67	24	
Responder, n (min-max)	46 (45-47)	8 (7-9)	
Responder Rate	68.6	33.3	4.4
Lower 95% CL	56.3	17.1	1.6
Upper 95% CL	78.7	54.7	12.3
CL Interval	22.4	37.6	10.7
P-Value	**0.005**		

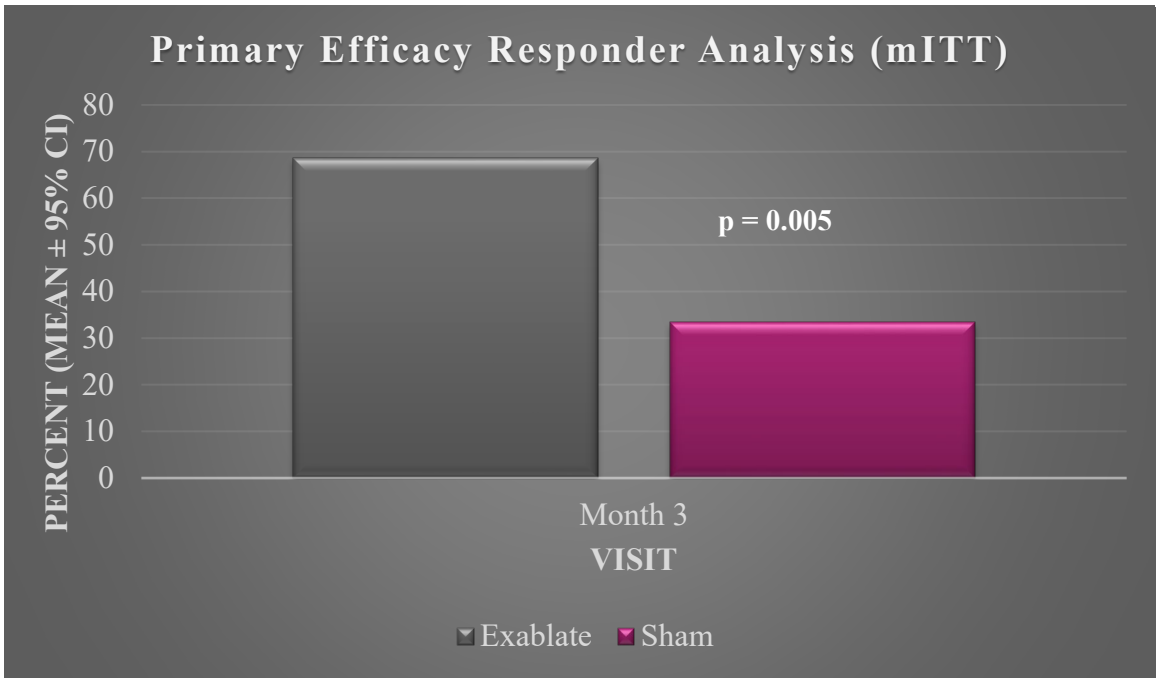


Figure 39. Primary Efficacy Endpoint - Responder Analysis

The Primary Endpoint Analysis was repeated using the PP population as shown in **TABLE 70**. The mean number of Responders in this population was 45 in Exablate (71%) and 7 in Sham (32%). This result is strongly significant, with P=0.002.

TABLE 70. PRIMARY EFFICACY ENDPOINT - RESPONDER ANALYSIS (PP)			
	Treatment Group		
Statistics	**Exablate**	**Sham**	**Odds Ratio**
Total N	63	22	
Responder, n (min-max)	45 (45-45)	7 (7-7)	
Responder Rate	71.4	31.8	5.4
Lower 95% CL	60.0	10.7	1.9
Upper 95% CL	82.9	53.0	15.3
CL Interval	22.9	42.3	13.4
P-Value	**0.002**		

7.1.11 Confirmatory Secondary Efficacy Endpoint

There are three confirmatory analyses performed using the mITT population comparing Exablate and Sham groups at Month 3.

7.1.11.1 MDS-UPDRS Part IV – Motor Complication Score

The MDS UPDRS Part IV On Medication assesses time spent with dyskinesia, functional impact of dyskinesia, time spent in the OFF state, functional impact of fluctuations, complexity of motor fluctuations and painful OFF state dystonia, i.e. the sum of the items 4.1 to 4.6 in the MDS-UPDRS Part IV On medication.

As shown in **TABLE 71** below, the study data demonstrated a 46% improvement compared to Baseline, while the Sham group demonstrated virtually no improvement to slight worsening in the Sham group. The difference between treatment groups was highly significant (p<0.001).

TABLE 71. CONFIRMATORY SECONDARY EFFICACY ENDPOINT - MDS-UPDRS PART IV (MITT)

		MDS-UPDRS Part IV- Motor Complication					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	10.6	10.3				
	Lower 95% CL	9.7	8.8				
	Upper 95% CL	11.4	11.8				
	N	67	24				
Month 3	Mean	5.6	10.1	5.0	0.2	46.1	1.8
	Lower 95% CL	4.8	8.7	4.1	-1.0	37.8	-10.3
	Upper 95% CL	6.5	11.6	5.9	1.3	54.4	14.0
	N	67	24	67	24	66*	23*
	Comparison to Baseline					<.001	0.615
	Between Group Difference	**<.001**					

* One patient in each Arm had a baseline score of “0”, %-Change from Baseline cannot be calculated for subject who have a baseline score of “0”

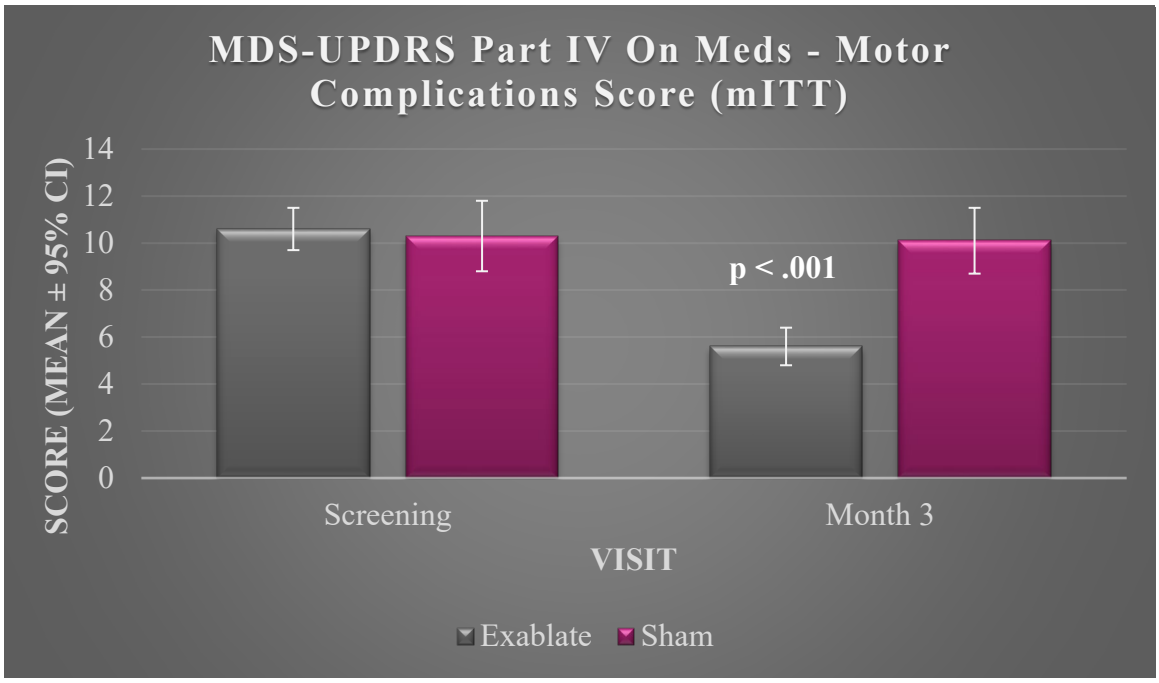


Figure 40. Confirmatory Secondary Endpoint - MDS-UPDRS Part IV On Medication

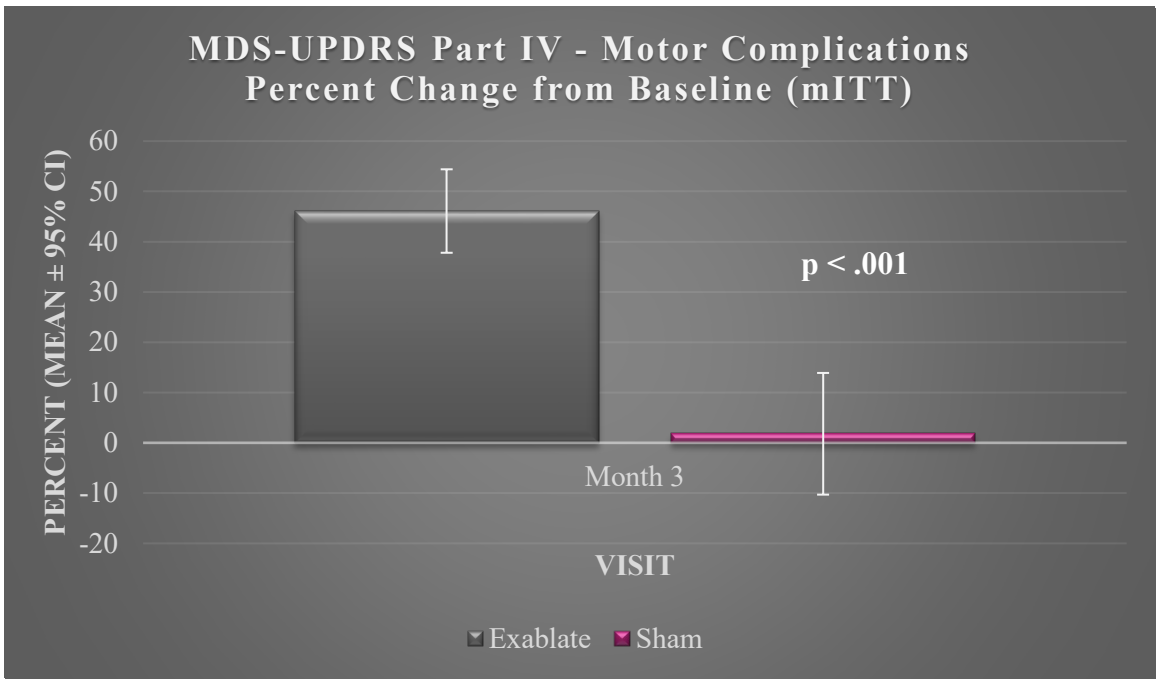


Figure 41. Confirmatory Secondary Endpoint - MDS-UPDRS Part IV On Medication (Percent Change from Baseline)

7.1.11.2 MDS-UPDRS Part III OFF Medication – Treated Side Motor Score

All measurements are taken in the OFF meds condition for the treated side only and have a maximum total score of 44 points. An individual's score is the sum of the treated side items from the MDS UPDRS Part III as follows: Items 3.3 Rigidity, 3.4 Finger Tapping, 3.5 Hand Movements, 3.6 Pronation-Supination Movement of Hands, 3.7 Toe Tapping, 3.8 Leg Agility, 3.15 Postural Tremor of the Hands, 3.16 Kinetic Tremor of the Hands, and 3.17 Rest Tremor Amplitude.

As shown in **TABLE 72** below, the study data demonstrated a 26% improvement compared to Baseline, while the Sham group demonstrated virtually minimal to no improvement in the Sham group. The difference between treatment groups was highly significant (p=0.015).

TABLE 72. CONFIRMATORY SECONDARY EFFICACY ENDPOINT - MDS-UPDRS PART III OFF MEDICATION TREATED SIDE MOTOR SCORE (MITT)

		Off- Medication MDS-UPDRS Part III Motor					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	18.1	17.3				
	Lower 95% CL	16.8	15.2				
	Upper 95% CL	19.5	19.5				
	N	67	24				
Month 3	Mean	13.1	16.0	5.0	1.3	26.4	5.6
	Lower 95% CL	11.6	13.7	3.6	-0.5	19.4	-8.6
	Upper 95% CL	14.7	18.3	6.4	3.2	33.4	19.9
	N	67	24	67	24	67	24
	Comparison to Baseline					<.001	0.182
	Between Group Difference	**0.015**					

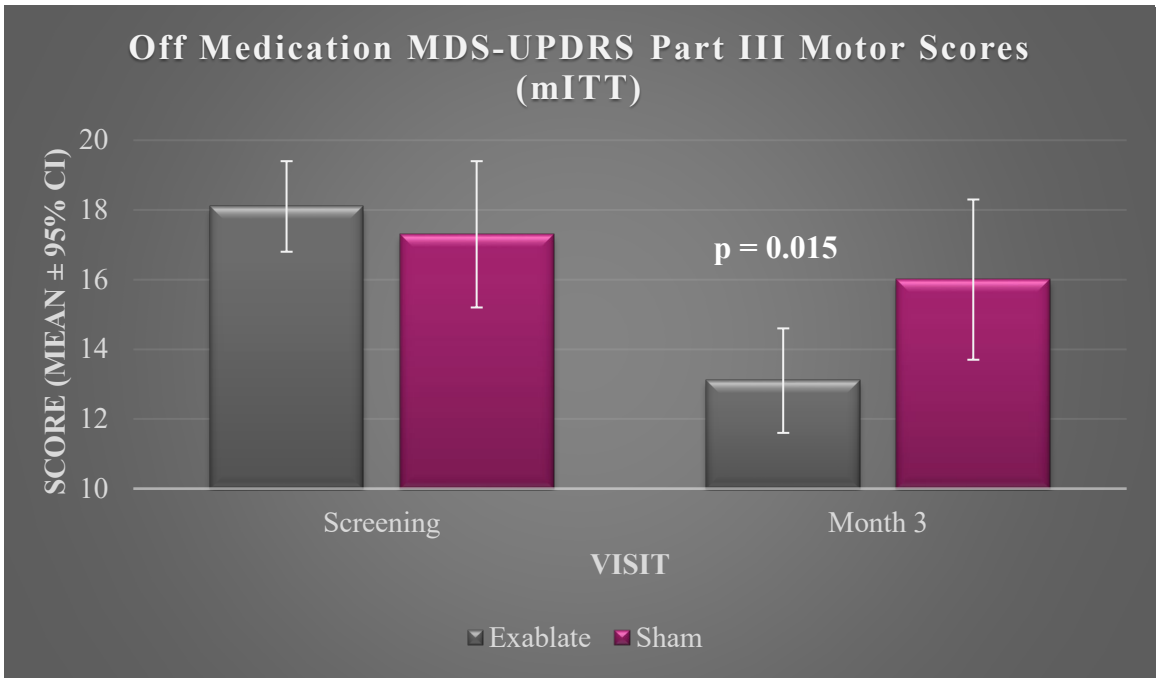


Figure 42. Confirmatory Secondary Endpoint - MDS-UPDRS Part III Off Med Treated Side

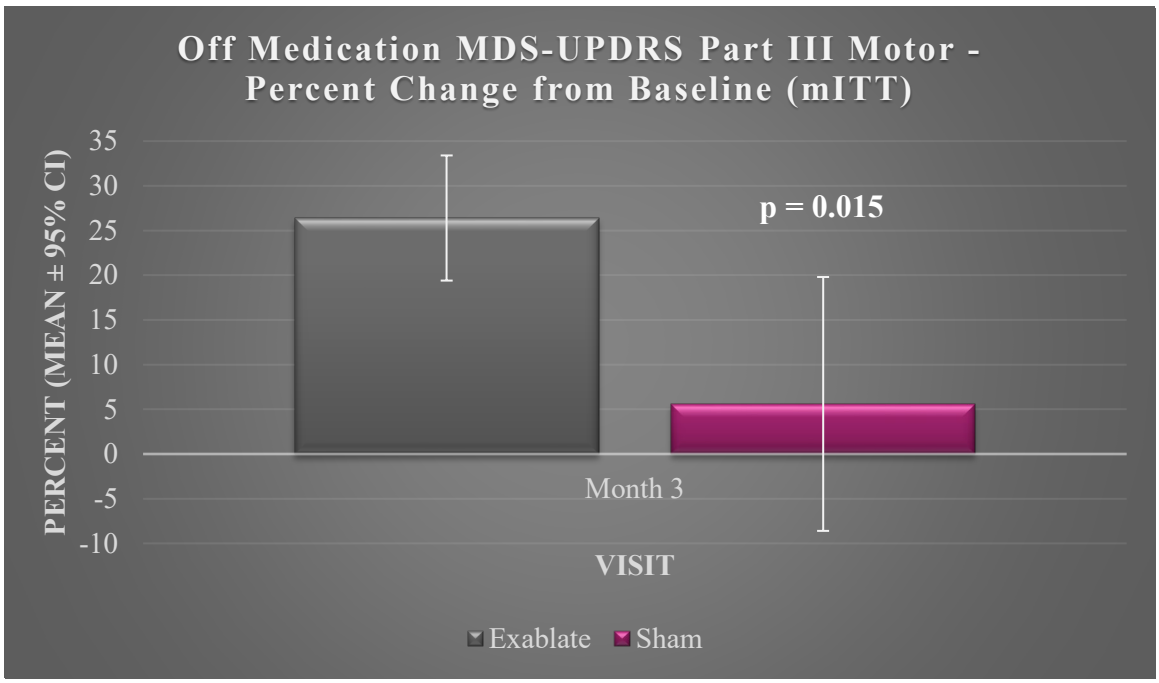


Figure 43. Confirmatory Secondary Endpoint - MDS-UPDRS Part III Off Med Treated Side (Percent Change from Baseline)

7.1.11.3 MDS-UPDRS Part II – Daily Living Score

The MDS UPDRS Part II focuses on the impact of PD symptoms on motor aspects of daily living: speech, saliva, and drooling, chewing, and swallowing, eating, dressing, hygiene, handwriting, hobbies, and other activities, turning in bed, tremor, getting out of bed or a car or a deep chair, walking and balance, and freezing. An individual's score is the sum of items in the MDS-UPDRS Part II (sum of item 2.1 through 2.13).

As shown in **TABLE 73** below, the study data demonstrated a 16% improvement compared to Baseline, while the Sham group demonstrated a 30% worsening in the Sham group. The difference between treatment groups was highly significant (p=0.013).

TABLE 73. CONFIRMATORY SECONDARY EFFICACY ENDPOINT - MDS-UPDRS PART II DAILY LIVING SCORE (MITT)

		Motor Aspects of Experiences of MDS-UPDRS Part II Daily Living					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	15.1	13.2				
	Lower 95% CL	13.6	10.3				
	Upper 95% CL	16.6	16.0				
	N	67	24				
Month 3	Mean	12.3	13.2	2.7	-0.0	16.4	-30.0
	Lower 95% CL	10.8	11.1	1.4	-1.8	7.9	-72.2
	Upper 95% CL	13.9	15.2	4.1	1.8	25.0	12.2
	N	67	24	67	24	67	24
	Comparison to Baseline					<.001	0.916
	Between Group Difference	**0.013**					

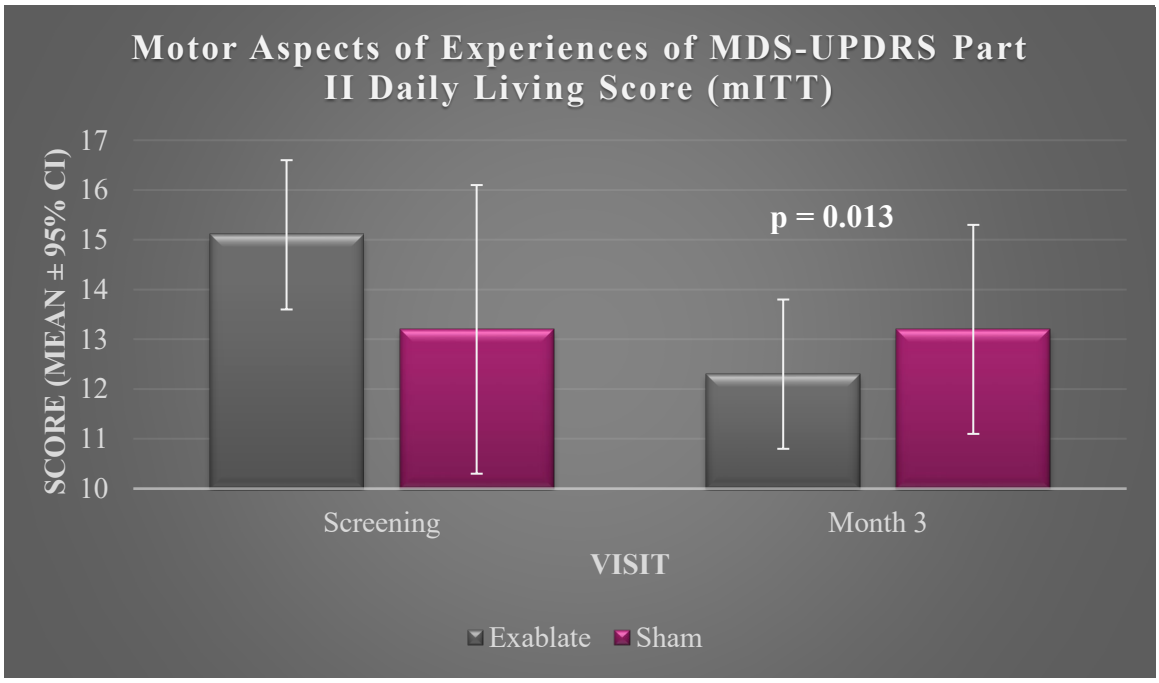


Figure 44. Confirmatory Secondary Endpoint - MDS-UPDRS Part II

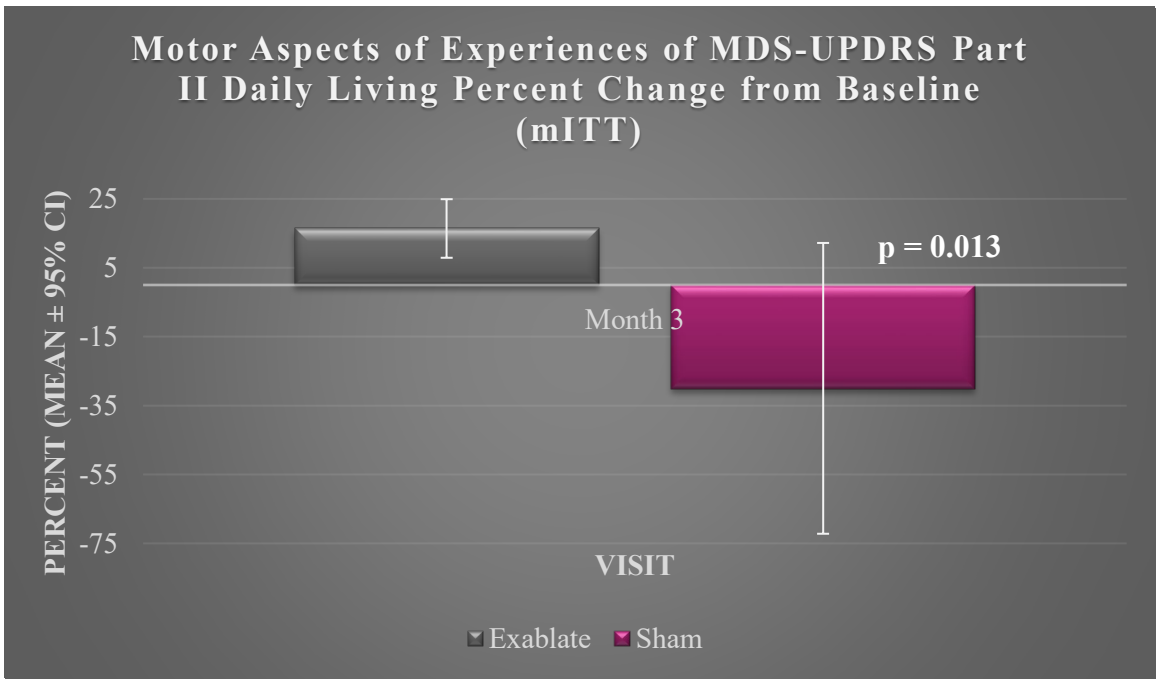


Figure 45. Confirmatory Secondary Endpoint - MDS-UPDRS Part II (Percent Change from Baseline)

7.1.12 Secondary Efficacy Endpoint

There are four secondary efficacy analysis performed on the mITT population based on Month 12 results to assess the durability of treatment response.

7.1.12.1 MDS-UPDRS Part III OFF Medications – Treated Side Motor Score through Month 12

As shown in **TABLE 74.** below, the Exablate treated group showed improvement (26%) as compared to the Sham-treated group (6%) at Month 3. Additionally, the Percent (%) of Change from Baseline (improvement) in the Exablate Arm through Month 12 was stable (20% at Month 1, 26% at Month 3, 26% at Month 6, and 22% at Month 12).

TABLE 74. SECONDARY ENDPOINT - MDS-UPDRS PART III OFF MEDICATION - TREATED SIDE MOTOR SCORE THROUGH MONTH 12 (MITT)

		Off- Medication MDS-UPDRS Part III Motor					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	18.1	17.3				
	Lower 95% CL	16.8	15.2				
	Upper 95% CL	19.5	19.5				
	N	67	24				
Month 1	Mean	14.2	16.6	3.9	0.7	19.7	1.5
	Lower 95% CL	12.6	14.3	2.5	-1.0	12.5	-10.4
	Upper 95% CL	15.8	18.9	5.4	2.5	26.9	13.4
	N	67	24	67	24	67	24
Month 3	Mean	13.1	16.0	5.0	1.3	26.4	5.6
	Lower 95% CL	11.6	13.7	3.6	-0.5	19.4	-8.6
	Upper 95% CL	14.7	18.3	6.4	3.2	33.4	19.9
	N	67	24	67	24	67	24
Month 6	Mean	13.1		5.0		26.0	
	Lower 95% CL	11.7		3.7		18.4	

TABLE 74. SECONDARY ENDPOINT - MDS-UPDRS PART III OFF MEDICATION - TREATED SIDE MOTOR SCORE THROUGH MONTH 12 (MITT)							
		Off- Medication MDS-UPDRS Part III Motor					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
	Upper 95% CL	14.6		6.3		33.5	
	N	67		67		67	
Month 12	Mean	13.6		4.5		22.1	
	Lower 95% CL	12.1		2.9		13.8	
	Upper 95% CL	15.2		6.1		30.4	
	N	67		67		67	

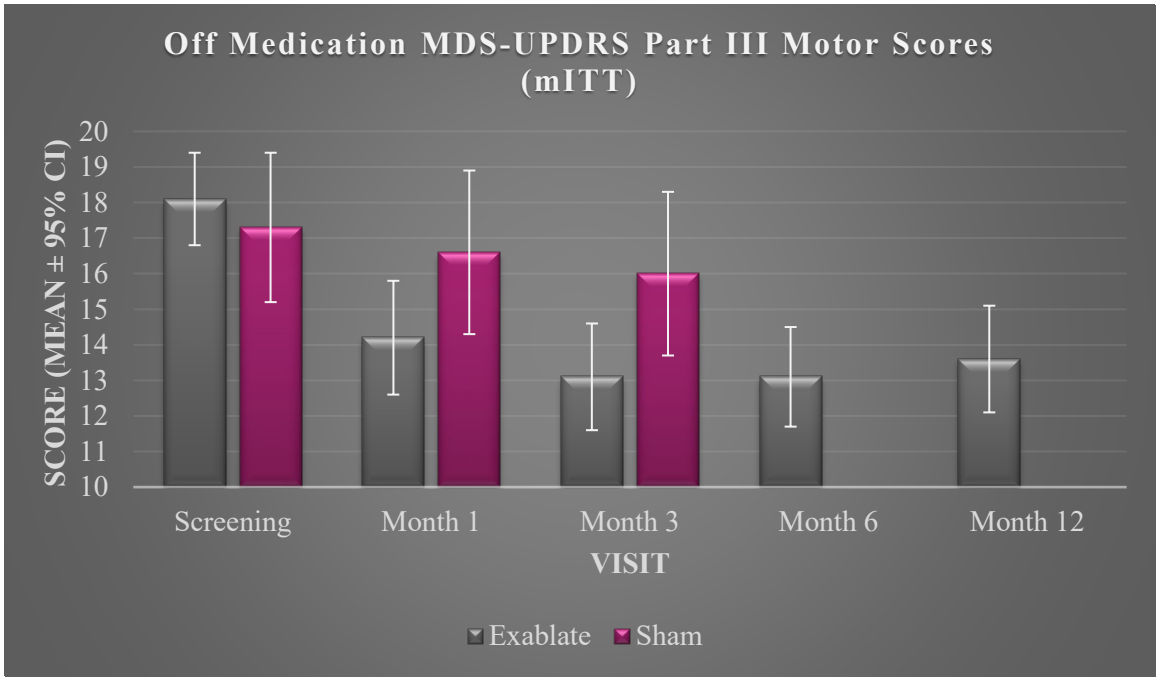


Figure 46. Secondary Endpoint - MDS-UPDRS Part III Off Meds Treated Side

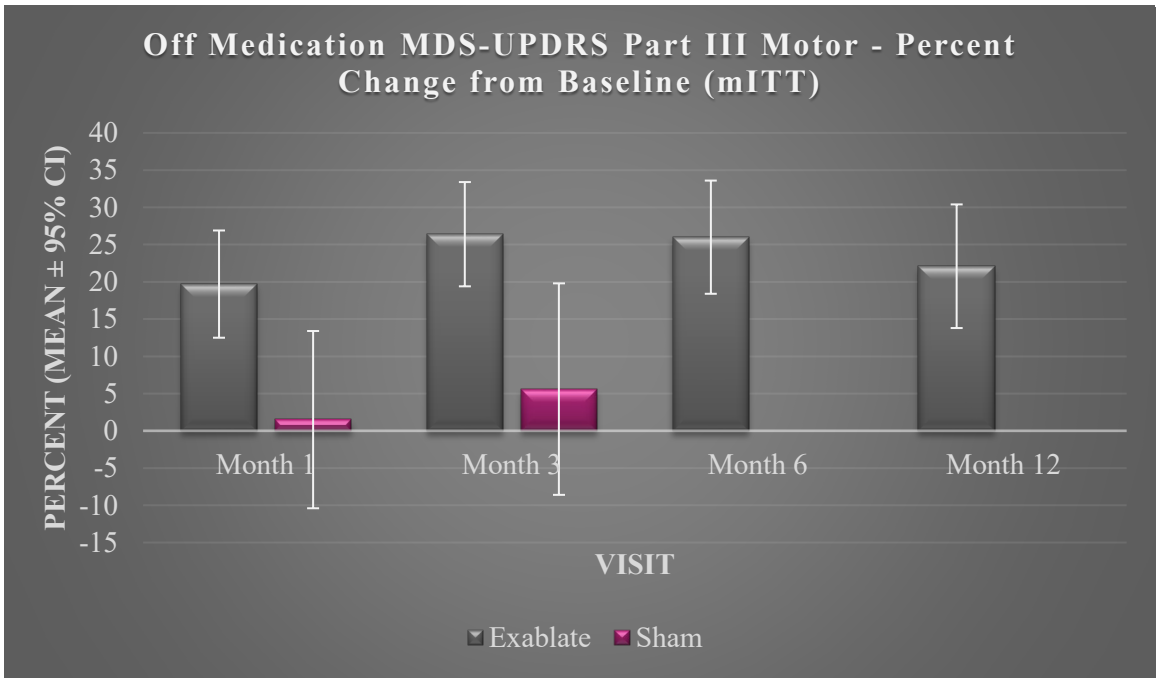


Figure 47. Secondary Endpoint - MDS-UPDRS Part III Off Meds Treated Side (Percent Change from Baseline)

7.1.12.2 MDS-UPDRS Part IV – Motor Complication Score through Month 12

As shown in **TABLE 75** below, the Exablate treated group showed improvement (46%) as compared to the Sham-treated group (2%) at Month 3. Additionally, the Percent (%) Change from Baseline (improvement) in the Exablate Arm through Month 12 was stable (45% at Month 1, 46% at Month 3, 45% at Month 6, and 38% at Month 12).

TABLE 75. SECONDARY ENDPOINT - MDS-UPDRS PART IV - MOTOR COMPLICATION SCORE THROUGH MONTH 12 (MITT)

		MDS-UPDRS Part IV- Motor Complication					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	10.6	10.3				
	Lower 95% CL	9.7	8.8				
	Upper 95% CL	11.4	11.8				
	N	67	24				

TABLE 75. SECONDARY ENDPOINT - MDS-UPDRS PART IV - MOTOR COMPLICATION SCORE THROUGH MONTH 12 (MITT)							
		MDS-UPDRS Part IV- Motor Complication					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Month 1	Mean	5.9	9.2	4.7	1.1	45.3	10.0
	Lower 95% CL	5.0	7.5	3.8	-0.1	37.4	-3.5
	Upper 95% CL	6.8	10.9	5.5	2.3	53.2	23.5
	N	67	24	67	24	66*	23*
Month 3	Mean	5.6	10.1	5.0	0.2	46.1	1.8
	Lower 95% CL	4.8	8.7	4.1	-1.0	37.8	-10.3
	Upper 95% CL	6.5	11.6	5.9	1.3	54.4	14.0
	N	67	24	67	24	66*	23*
Month 6	Mean	5.8		4.8		44.9	
	Lower 95% CL	5.0		4.0		37.6	
	Upper 95% CL	6.6		5.6		52.2	
	N	67		67		66*	
Month 12	Mean	6.5		4.1		38.1	
	Lower 95% CL	5.5		3.2		29.8	
	Upper 95% CL	7.4		5.1		46.5	
	N	67		67		66*	
* One patient in each Arm had a baseline score of “0”, %-Change from Baseline cannot be calculated for subjects who have a baseline score of “0”.							

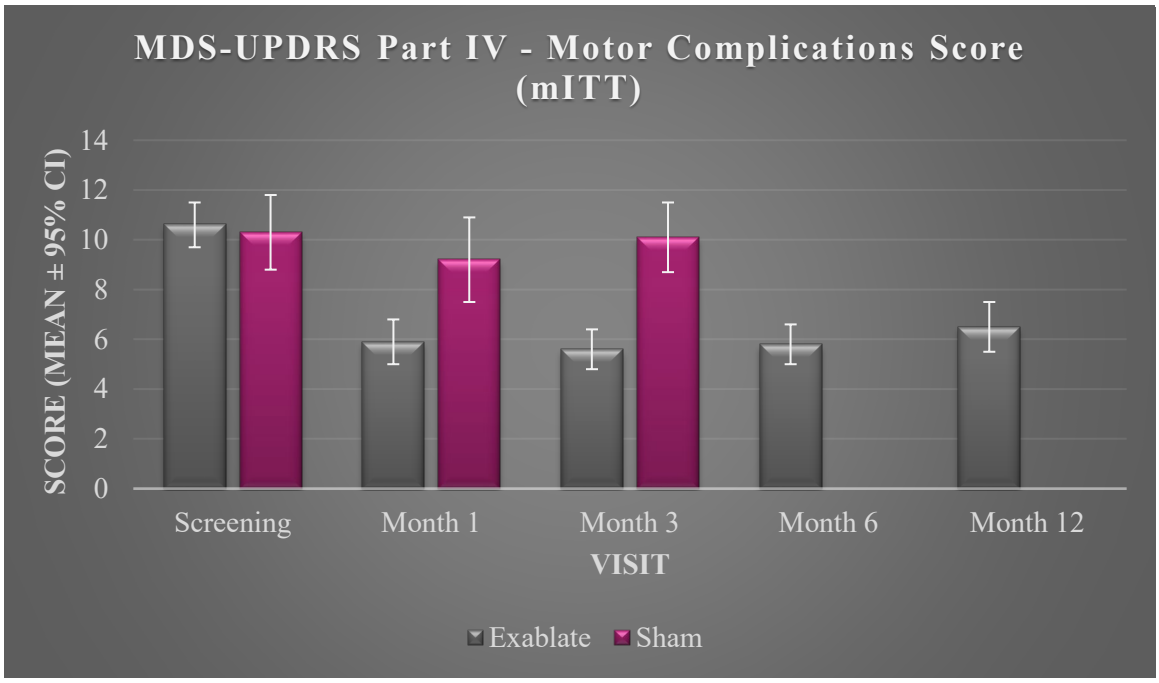


Figure 48. Secondary Endpoint - MDS-UPDRS Part IV

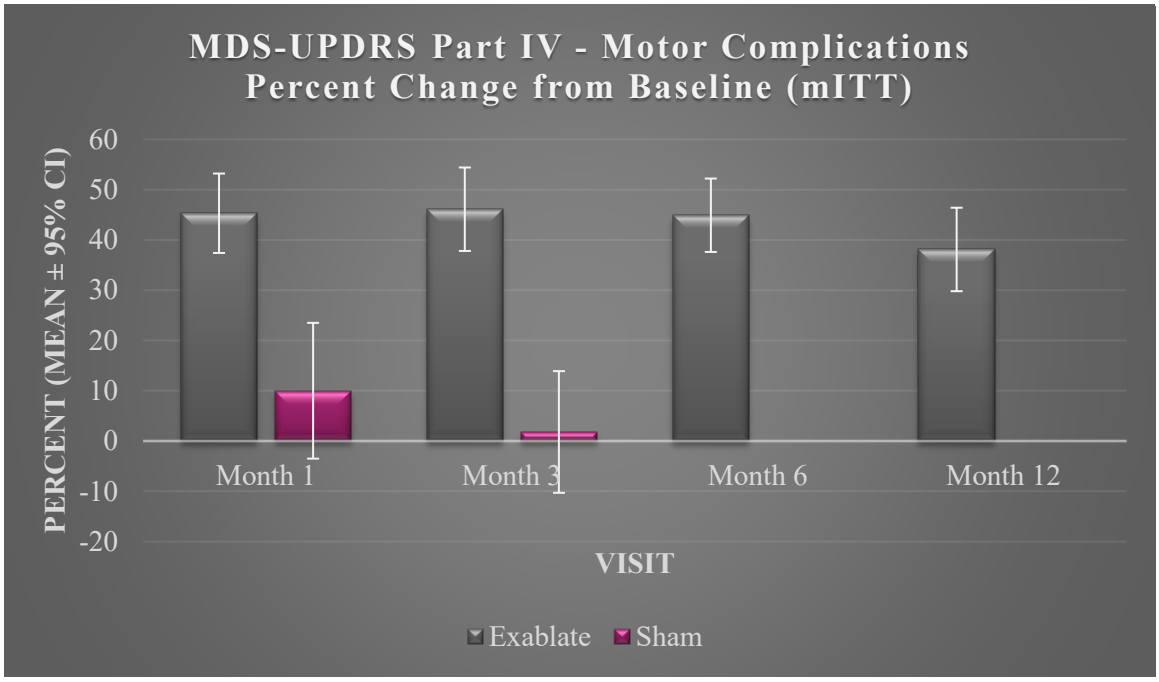


Figure 49. Secondary Endpoint - MDS-UPDRS Part IV (Percent Change from Baseline)

7.1.12.3 UDysRS – Part III Objective Impairment Score

The Part III UDysRS is an objective measure of subject four-daily activities: Communication, Drinking from a cup, Dressing, and Ambulation. This measure was assessed through Month-12.

As shown in **TABLE 76.** below, the Exablate treated group showed improvement (38%) as compared to the Sham-treated group worsening (-3.8%) at Month 3. Additionally, the Percent (%) Change from Baseline (improvement) in the Exablate through Month 12 was 42% at Month 1, 38% at Month 3, 32% at Month 6, and 9% at Month 12.

TABLE 76. SECONDARY ENDPOINT - UDYSRS PART III OBJECTIVE IMPAIRMENT SCORE THROUGH MONTH 12 (MITT)

		UDysRS Objective Impairment					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	6.8	6.3				
	Lower 95% CL	5.6	4.5				
	Upper 95% CL	8.0	8.0				
	N	67	24				
Month 1	Mean	3.5	6.5	3.2	-0.2	42.2	-22.0
	Lower 95% CL	2.5	4.4	2.3	-1.9	29.1	-81.0
	Upper 95% CL	4.5	8.5	4.2	1.5	55.3	37.0
	N	67	24	67	24	60*	22*
Month 3	Mean	3.9	6.1	2.8	0.2	37.5	-3.8
	Lower 95% CL	2.9	4.5	1.8	-0.7	23.1	-32.7
	Upper 95% CL	4.9	7.7	3.8	1.1	51.8	25.0
	N	67	24	67	24	60*	22*
Month 6	Mean	4.0		2.7		32.4	
	Lower 95% CL	3.1		1.7		15.7	
	Upper 95% CL	5.0		3.8		49.0	
	N	67		67		60*	
Month 12	Mean	4.9		1.9		8.7	

TABLE 76. SECONDARY ENDPOINT - UDYSRS PART III OBJECTIVE IMPAIRMENT SCORE THROUGH MONTH 12 (MITT)							
		UDysRS Objective Impairment					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
	Lower 95% CL	3.8		0.7		-13.3	
	Upper 95% CL	5.9		3.1		30.7	
	N	67		67		60*	
* Some subjects had a score of "0" at baseline. %-Change from Baseline cannot be calculated for subjects who have a baseline score of "0".							

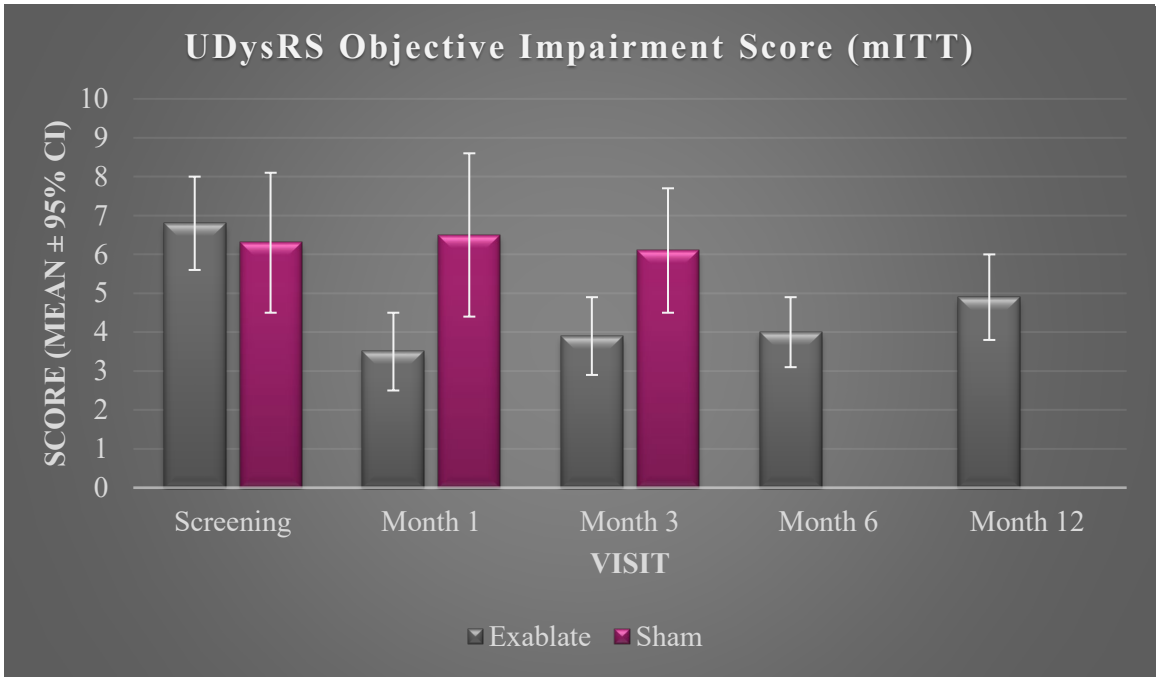


Figure 50. Secondary Endpoint - UDysRS Part III Objective Impairment

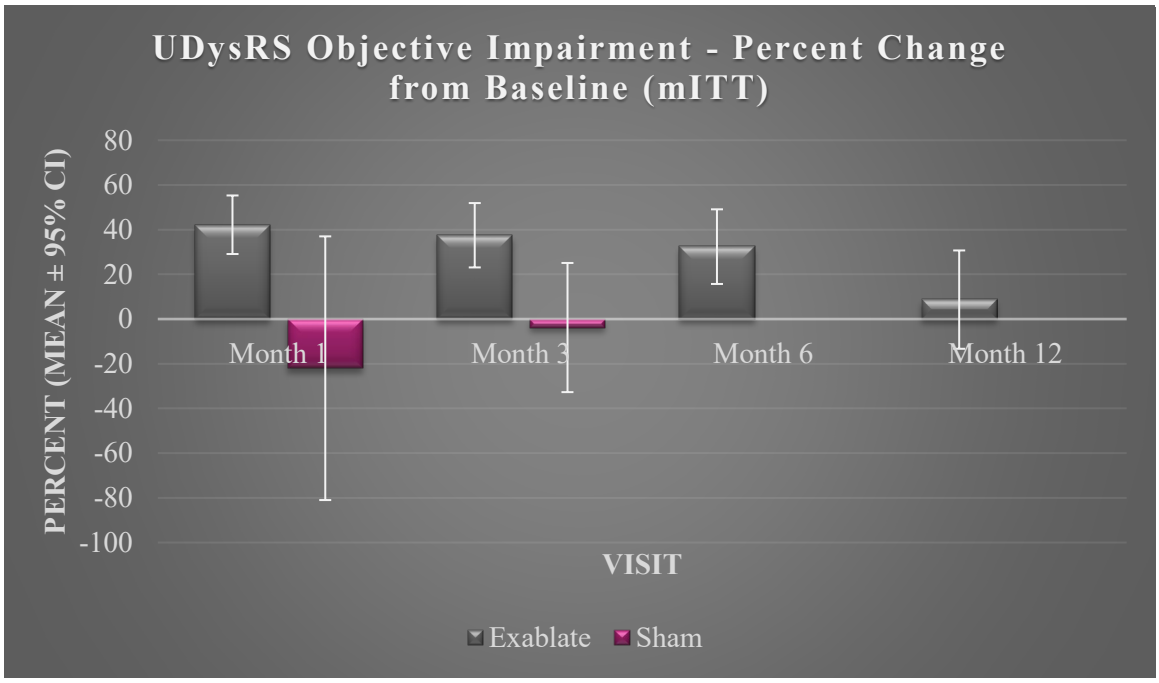


Figure 51. Secondary Endpoint - UDysRS Part III Objective Impairment (Percent Change from Baseline)

7.1.13 Additional Efficacy Endpoints

7.1.13.1 UDysRS – Total Score (Historical +Objective)

The Unified Dyskinesia Rating Scale (UDysRS) is a tool to evaluate dyskinesias (involuntary movements) associated Parkinson's disease subject On Medication. The UDysRS has two primary sections:

- Historical
  - Part 1: On-Dyskinesia
  - Part 2: Off-Dystonia
- Objective
  - Part 3: Impairment
  - Part 4: Disability

TABLE 77. presents descriptive statistics of the total score of UDysRS (Historical+ Objective). The Exablate treated group showed improvement (48%) as compared to the Sham-treated group (7%) at Month 3. Additionally, the Percent (%) Change from Baseline (improvement) in the Exablate through Month 12 was 52% at Month 1, 48% at Month 3, 43% at Month 6, and 32% at Month 12.

TABLE 77. ADDITIONAL ENDPOINT - UDYSRS TOTAL SCORE (MITT)							
		Unified Dyskinesia Rating Scale (UDysRS)					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	30.4	29.3				
	Lower 95% CL	26.3	22.9				
	Upper 95% CL	34.4	35.7				
	N	67	24				
Month 1	Mean	13.9	28.0	16.5	1.3	52.1	12.0
	Lower 95% CL	10.9	20.8	13.3	-1.4	44.1	-2.4
	Upper 95% CL	16.9	35.3	19.7	4.0	60.2	26.3
	N	67	24	67	24	62*	23*
Month 3	Mean	15.3	28.9	15.1	0.5	47.5	6.6
	Lower 95% CL	12.2	22.2	11.9	-2.8	35.6	-10.8
	Upper 95% CL	18.4	35.5	18.2	3.8	59.4	24.1
	N	67	24	67	24	62*	23*
Month 6	Mean	16.6		13.7		42.7	
	Lower 95% CL	13.5		10.4		32.0	
	Upper 95% CL	19.8		17.0		53.4	
	N	67		67		62*	
Month 12	Mean	19.4		10.9		32.4	
	Lower 95% CL	15.8		7.4		17.4	
	Upper 95% CL	23.1		14.5		47.4	
	N	67		67		62*	

* Some patients had a score of “0” at baseline, %-Change from Baseline cannot be calculated for subjects who have a baseline score of “0”.

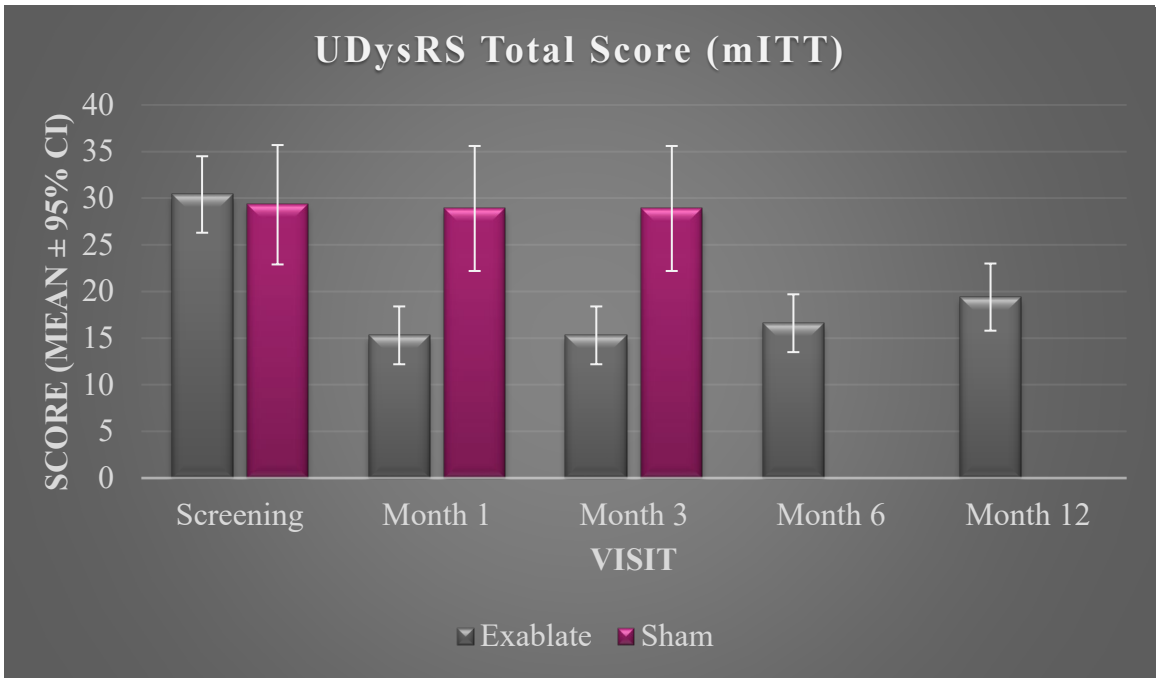


Figure 52. Additional Endpoint - UDysRS Total Score

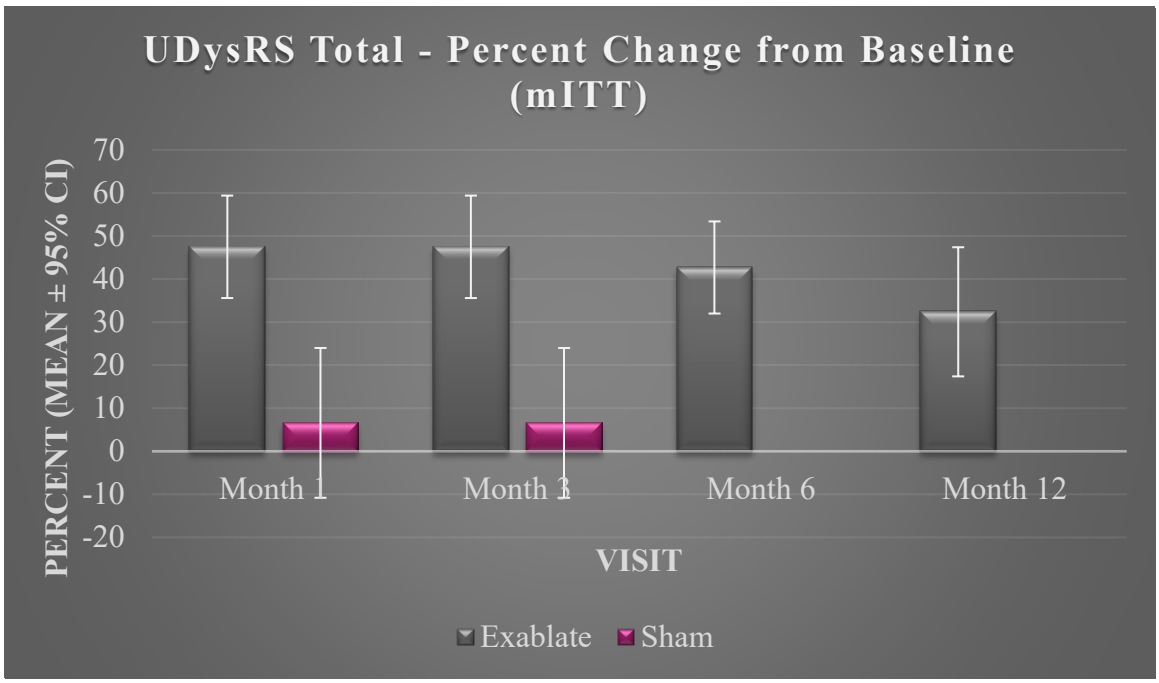


Figure 53. Additional Endpoint - UDysRS Total Score (Percent Change from Baseline)

7.1.13.2 MDS-UPDRS Total Score (Parts I, II, III OFF, IV)

The overall MDS-UPDRS tool covers the following four sections:

- Part I: Non-Motor Aspects of Experiences of Daily Living
- Part II: Motor Aspects of Experiences of Daily Living
- Part III OFF Meds: Motor Examination
- Part IV: Motor Complications

TABLE 78. Presents descriptive statistics of the total score of MDS-UPDRS (Part I+ Part II+ Part III OFF Med (extremities treated side) + Part IV). The Exablate treated group showed improvement (26%) as compared to the Sham-treated group (3%) at Month 3. Additionally, the Percent (%) Change from Baseline (improvement) in the Exablate Arm through Month 12 was 27% at Month 1, 26% at Month 3, 23% at Month 6, and 20% at Month 12.

TABLE 78. ADDITIONAL ENDPOINT - TOTAL MDS-UPDRS SCORE (MITT)							
		Total MDS-UPDRS Score					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
Screening	Mean	55.1	51.8				
	Lower 95% CL	51.8	44.7				
	Upper 95% CL	58.4	58.8				
	N	67	24				
Month 1	Mean	40.4	47.4	14.6	4.4	26.7	5.2
	Lower 95% CL	36.3	42.1	11.1	-0.0	20.6	-5.4
	Upper 95% CL	44.6	52.7	18.2	8.8	32.8	15.8
	N	67	24	67	24	67	24
Month 3	Mean	40.7	48.7	14.4	3.1	26.4	2.6
	Lower 95% CL	36.3	43.0	10.8	-1.4	20.1	-9.2
	Upper 95% CL	45.0	54.4	18.1	7.6	32.7	14.4
	N	67	24	67	24	67	24
Month 6	Mean	42.0		13.1		23.0	
	Lower 95% CL	37.8		9.4		16.2	

TABLE 78. ADDITIONAL ENDPOINT - TOTAL MDS-UPDRS SCORE (MITT)							
		Total MDS-UPDRS Score					
Visit / Statistics		Calculated Score		Change from Baseline		Percent Change from Baseline	
		Exablate	Sham	Exablate	Sham	Exablate	Sham
	Upper 95% CL	46.1		16.9		29.9	
	N	67		67		67	
Month 12	Mean	43.8		11.3		19.8	
	Lower 95% CL	39.5		7.5		13.1	
	Upper 95% CL	48.1		15.1		26.6	
	N	67		67		67	

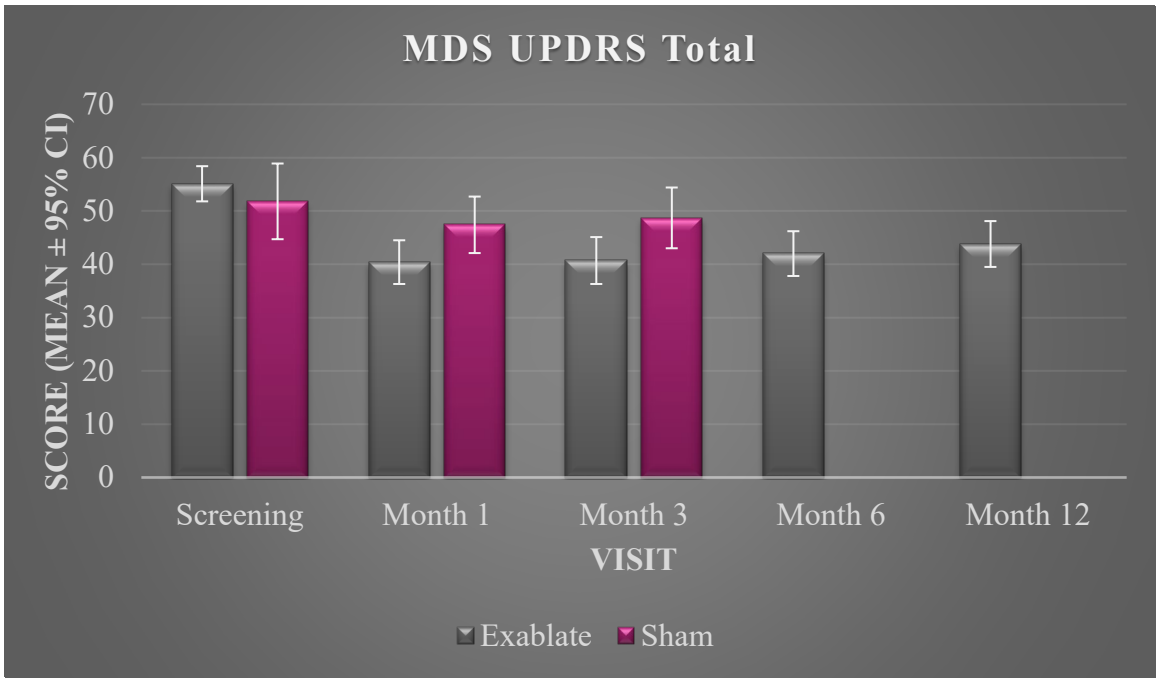


Figure 54. Additional Endpoint - MDS-UPDRS Total Score

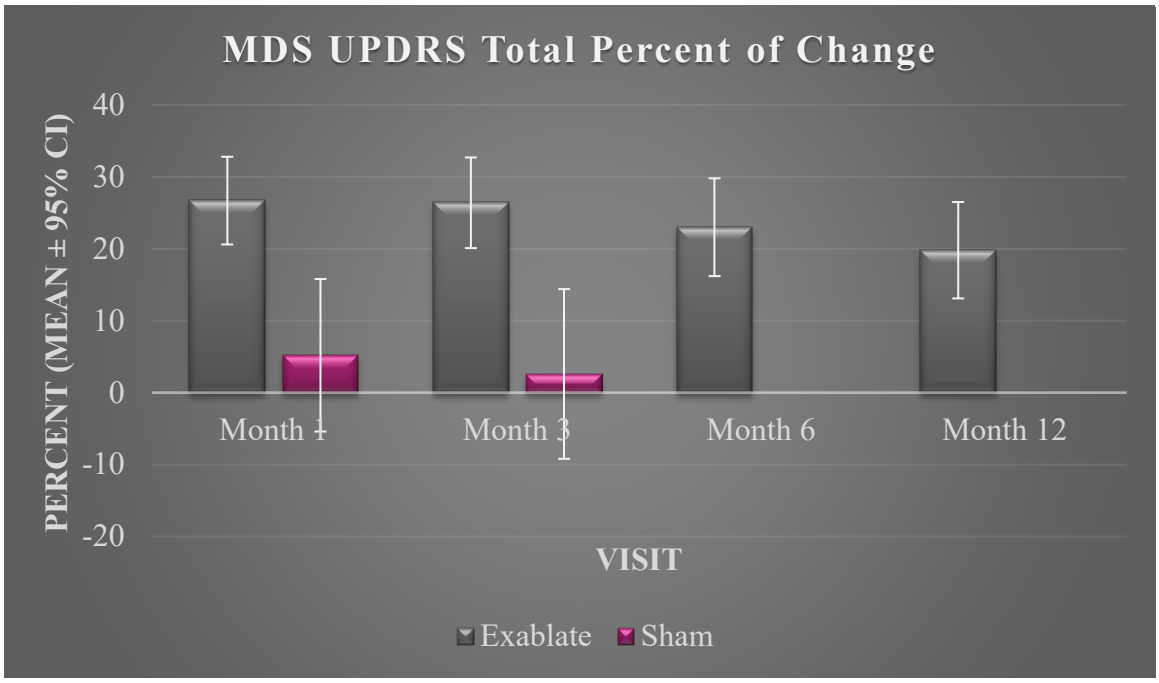


Figure 55. Additional Endpoint - MDS-UPDRS Total Score (Percent Change from Baseline)

7.1.14 Levodopa Equivalent Usage Dose

As shown in **TABLE 79.** , Subject's mean Levodopa Dose remained fairly stable through Month 12 visit in both treatment arms. It should be noted that Subjects of this study were counseled to keep their L-dopa dosing unchanged at least during the first 3-Months post procedure.

TABLE 79. LEVODOPA EQUIVALENT USAGE DOSE

Visit / Levodopa Equivalent Usage Dose		Treatment Group	
		Exablate	Sham
Day 0 Pre- Treatment	Mean	1051.6	1044.7
	Std	473.8	660.6
	N*	67	23
Week 1	Mean	1035.8	1015.1
	Std	463.8	673.2
	N*	67	24
Month 1	Mean	1051.3	1083.7
	Std	498.6	707.7
	N*	66	23
Month 3	Mean	1041.5	1091.8
	Std	503.9	677.8
	N*	65	23
Month 6	Mean	1034.1	0
	Std	517.0	0
	N*	51	0
Month 12	Mean	1073.7	0
	Std	587.6	0
	N*	52	0

*N is based on observed data.

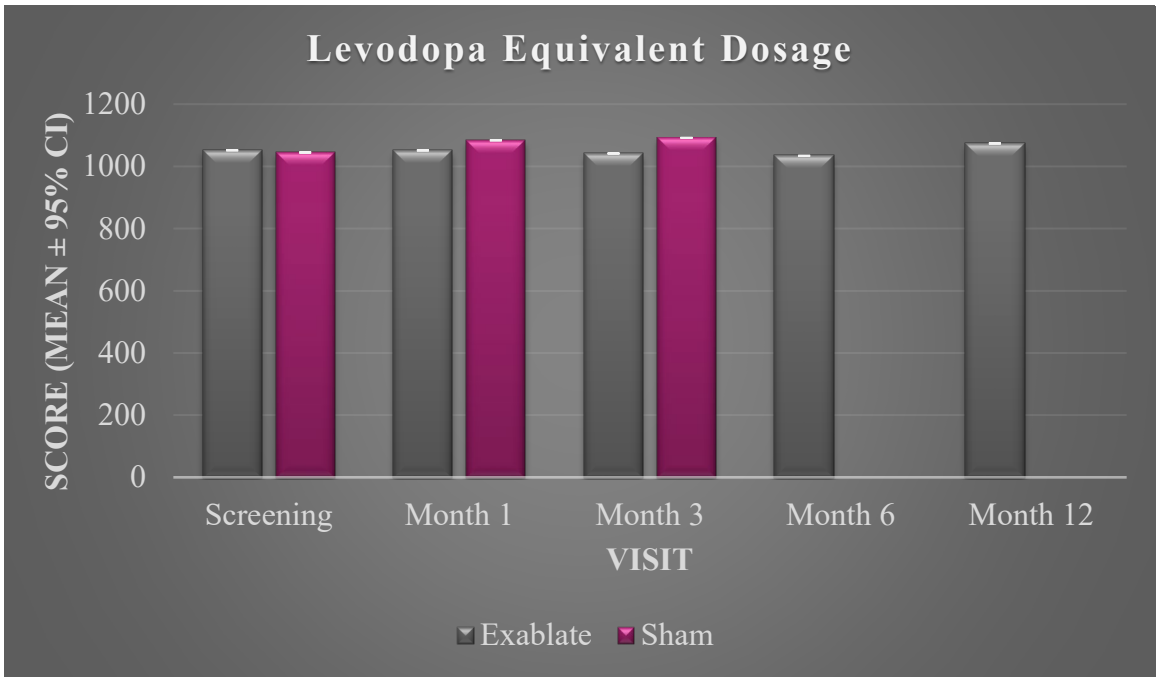


Figure 56. Levodopa Equivalent Usage Dose

7.1.15 Efficacy Summary

In summary, the primary endpoint and all confirmatory secondary endpoints were met and were highly statistically significant. At Month 3, the primary efficacy analysis showed that 69% of the subjects in the Exablate arm were Responders to treatment compared to 33% in the Sham arm. These rates yielded the odds ratio between Exablate and Sham groups of 4.4. Thus, the probability of an Exablate subject to be "Responder" as opposed to "Non-Responder" is 4.4 times greater than the same probability for a Sham patient. A summary of the p-values of the primary and confirmatory effectiveness endpoints are shown in **TABLE 80**.

TABLE 80. EFFICACY SUMMARY

P Value by Population	mITT	PP	ITT
Primary Endpoint			
Responder Analysis at Month 3	0.005	0.002	0.004
Confirmatory Secondary Endpoint			
MDS-UPDRS Part IV at Month 3	<0.001	<0.001	<0.001
MDS-UPDRS Part III OFF Med Treated Side at Month 3	0.015	0.004	0.013
MDS-UPDRS Part II at Month 3	0.013	0.007	0.015

7.1.15.1 Sensitivity Analysis

Two out of 67 Exablate subjects and 2 subjects out of the 24 Sham subjects that were included in the mITT population were missing the primary endpoint at Month 3. Thus, a total of 4 subjects were imputed with worst-case and best-case scenarios.

TABLE 81 presents the results of the primary analysis on non-imputed data, along with worst-case and best-case imputations. The result of the primary analysis performed on observed data remained statistically significant (P=0.003) with 69.2% of Exablate subjects classified as Responders compared to 31.8% in Sham. Under best-case imputation, 70.1% and 29.2% of Exablate and Sham subjects were Responders, respectively. Under worst-case imputation, the primary endpoint remained statistically significant (P=0.013) with 67.2% Responders in Exablate and 37.5% in Sham. In other words, when the 4 missing subjects were imputed as "Non-Responders", the result of the study remained significant, and therefore is robust.

TABLE 81. SENSITIVITY ANALYSIS						
	Observed Data		Worst Case		Best Case	
Statistics	Exablate	Sham	Exablate	Sham	Exablate	Sham
Total N	65	22	67	24	67	24
Responder	45	7	45	9	47	7
Responder Rate	69.2	31.8	67.2	37.5	70.1	29.2
Lower 95% CL	56.5	13.8	54.6	18.7	57.7	12.6
Upper 95% CL	80.1	54.9	78.2	59.5	80.8	51.1
CL Interval	23.6	41.1	23.6	40.8	23.1	38.5
P-Value	0.003		0.013		<.001	

7.1.15.2 COVID-19 Sensitivity Analysis

In order to evaluate the influence of the COVID-19 pandemic on the study's results, all three of the sensitivity analyses described above were repeated using the set of results collected according to schedule and imputing all cases impacted by the pandemic or missing the primary endpoint.

Out of 67 Exablate subjects that were included in the mITT population, 5 had a Month 3 visit out-of-window due to COVID-19, whereas out of 24 Sham subjects, 1 had an out-of-window visit due to COVID-19.

Therefore, a total of 6 subjects (5 Exablate and 1 Sham) were imputed under the COVID-19 sensitivity analysis, as presented in .

TABLE 82. COVID-19 SENSITIVITY ANALYSIS						
	Observed Data		Worst Case		Best Case	
Statistics	Exablate	Sham	Exablate	Sham	Exablate	Sham
Total N	60	21	65*	22*	65*	22*
Responder	40	7	40	8	45	7
Responder Rate	66.7	33.3	61.5	36.4	69.2	31.8
Lower 95% CL	53.3	14.5	48.6	17.1	56.5	13.8
Upper 95% CL	78.4	57.0	73.4	59.4	80.1	54.9
CL Interval	25.1	42.5	24.8	42.3	23.6	41.1
P-Value	0.010		0.044		0.003	

TABLE 82. COVID-19 SENSITIVITY ANALYSIS						
	Observed Data		Worst Case		Best Case	
Statistics	Exablate	Sham	Exablate	Sham	Exablate	Sham
* Patients who missed Month 3 visit due to other reasons were excluded from the COVID sensitivity analysis.						

As can be seen, the result of the primary analysis performed on observed data remained statistically significant (P=0.010) with 66.7% of Exablate subjects classified as Responders compared to 33.3% in Sham. Under best-case imputation, 69.2% and 31.8% of Exablate and Sham subjects were Responders, respectively. Under worst-case imputation, the primary endpoint remained statistically significant (P=0.044) with 61.5% responders in Exablate compared to 36.4% in Sham. Hence, the results of the primary endpoint remained robust under all scenarios and were not impacted by out-of-window visits due to COVID-19.

7.1.16 Covariate Analysis

The Covariate analyses were performed in this study:

The data were tested for potentially confounding variables through use of a Covariate analysis. Age, MDS-UPDRS part III OFF Score, Baseline UDysRS Objective Assessment on Meds Score, Brain treated side, Gender and Center were all assessed for the primary endpoint and all confirmatory secondary endpoints. No significant interaction was found on the study results with any of these variables.

7.2 Conclusion Drawn from the Studies

The present study shows a favorable safety profile in this patient population. Overall, the summary of safety demonstrated that no Severe or Life-threatening events related to device occurred. Moreover, there were no visual field events reported.

A total of 131 events were reported in this study for the Exablate Arm (1.9 events per Exablate subject). All events were either Transient, Unrelated, Procedure related, Parkinson's Disease Progression, and/or Pallidotomy related. Thirty-nine (39) Transient (resolved within 72 hours) events were reported. Another 72 events were categorized as Unrelated to Exablate or PD Disease Progression. Nine (9) events were categorized as Procedure related (e.g., fatigue, weakness, headache, and one sonication-related head pain) lasting longer than 3 days. Eleven (11) events were categorized as Pallidotomy related events.

Of the 149 events (131 Exablate Arm; 18 Sham Arm), 91% of all events were categorized as Mild or Moderate.

All Procedure related events resolved and all Pallidotomy related events resolved with the exception of the following three Mild events: 1) Dysarthria, 2) Increased salivation/drooling, and 3) Numbness/tingling.

There was a careful consideration for reporting any visual field deficits because of the targeting location being in close proximity with the optic tract. There were no visual field events reported.

Overall, the safety profile is favorable in this patient population, especially in comparison to alternative surgical treatments for Parkinson's Disease.

The primary endpoint and all confirmatory secondary endpoints were met and were highly statistically significant. At Month 3, the primary efficacy analysis showed that 69% of the subjects in the Exablate arm reached a minimal clinically important difference compared to 33% in the Sham arm. These rates yielded the odds ratio between Exablate and Sham groups of 4.4. Thus, the probability of an Exablate subject to be "Responder" as opposed to "Non-Responder" is 4.4 times greater than the same probability for a Sham patient. A summary of all the primary, confirmatory, secondary, and additional endpoints by Efficacy Population are shown in **TABLE 83**.

TABLE 83. EFFICACY SUMMARY

P Value by Population	mITT	PP	ITT
Primary Endpoint			
Responder Analysis at Month 3	0.005	0.002	0.004
Confirmatory Secondary Endpoint			
MDS-UPDRS Part IV at Month 3	<0.001	<0.001	<0.001
MDS-UPDRS Part III OFF Med Treated Side at Month 3	0.015	0.004	0.013
MDS-UPDRS Part II at Month 3	0.013	0.007	0.015

Covariate analysis was performed and indicated that no interactions with any Baseline characteristics were present. Similarly, a sensitivity analysis showed that the effect was robust.
In summary, the Exablate provides a safe and effective treatment option for medication-refractory, moderate to severe dyskinesias and/or motor complications as an adjunct to PD medication in subjects with advanced, idiopathic Parkinson's disease. The durability of the treatment and effectiveness after 1 year has not been evaluated and is unknown.

7.2.1 Study Overall Conclusions

The data from the pivotal clinical study support 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 advanced, idiopathic Parkinson's disease the Exablate Neuro treatment is a reasonable alternative to existing treatments. The result from the pivotal study demonstrates that it is efficacious, and the safety profile is reasonable within 1 year after the procedure and does not cause any increased 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.

CHAPTER 8: SUMMARY OF PIVOTAL STUDY FOR STAGED, CONTRALATERAL UNILATERAL TREATMENT OF ESSENTIAL TREMOR

8.1 Pivotal Protocol Summary – ET005 (IDE # G190162)

The study was designed as a prospective, open-label, multi-center, single-arm pivotal study to evaluate the safety and efficacy of staged bilateral Exablate thalamotomy for medication-refractory, advanced idiopathic ET. Subjects considered to be medication-refractory are those who are significantly symptomatic in spite of best medication treatment. Subjects with clinically significant bilateral disease in their untreated arm were recruited from the pivotal trial or from commercial treatments. They underwent a staged, unilateral thalamotomy to their second or contralateral brain side. Subjects for this study were selected based on their disease severity without any lingering moderate or severe adverse events related to their first Exablate thalamotomy procedure.

8.1.1 Eligibility Criteria

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

8.1.1.1 Inclusion Criteria

1. Men and women aged 22 years or older.
2. Subject was able and willing to give consent and able to attend all study visits.
3. Subject was diagnosed with Essential tremor as confirmed by a movement disorder specialist.
4. Subject's tremor was refractory to adequate trials of at least two medications, one of which being a first line therapy of either propranolol or primidone. An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
5. Subject was diagnosed with medication-refractory Essential tremor.
6. A subject who underwent an Exablate index procedure in a clinical trial or in a commercial setting at least 9 months prior to enrolling in this trial.
7. Subject had a baseline CRST Part A score of 2 or above for postural or intention tremor severity in the upper extremity for the contralateral tremor side while on stable medication.
8. Subject was able to communicate sensations during the Exablate thalamotomy procedure.
9. Subject had a baseline CRST Part C score of 2 or above in any one of the items (speaking, eating, drinking, hygiene, dressing, writing, working, and social activities).

8.1.1.2. Exclusion Criteria

1. Subject experienced any non-transient neurological event or worsening following the Exablate index procedure.

2. Subject had physical subscale score ≥ 16.5 on the Dysphagia Handicap Index or has been diagnosed with dysphagia.
3. Subject had score < 22 on the Montreal Cognitive Assessment (MoCA).
4. Subject had any non-transient hemiparesis as determined by physical examination.
5. Subject with clinically significant abnormal speech function as determined by a speech pathologist.
6. Subject of childbearing potential was pregnant or breastfeeding.
7. Subject with unstable cardiac status including:
    a. Unstable angina pectoris on medication;
    b. Documented myocardial infarction within six months of enrollment;
    c. Unstable or worsening congestive heart failure;
    d. History of a hemodynamically unstable cardiac arrhythmia;
    e. Cardiac pacemaker;
    f. Severe hypertension (diastolic BP > 100 on medication).
8. Subjects who exhibited any behavior(s) consistent with ethanol or substance abuse.
9. Subject had history of abnormal systemic or intracranial bleeding, hemorrhage, or coagulopathy.
10. Subject had abnormal coagulation profile: PLT < 100,000/µl, PT > 14 sec or PTT > 36 sec, and INR > 1.3.
11. Subject was receiving anticoagulant (e.g., warfarin) or antiplatelet (e.g., aspirin) therapy within one week of Exablate procedure or drugs known to increase risk of hemorrhage within one month of Exablate procedure.
12. Subject with cerebrovascular disease, including but not limited to, intracranial aneurysms, dural arteriovenous malformations (AVM), stroke, intracranial atherosclerotic disease, dural arteriovenous fistulas (AVF).
13. Subject with an intracranial tumor.
14. Subject with active or suspected acute or chronic uncontrolled infection.
15. Subject had deep brain stimulation or a prior stereotactic ablation of the basal ganglia or thalamus.
16. Patients with implanted objects in the skull or the brain.
17. More than 30% of the skull area traversed by the sonication pathway is covered by scars, scalp disorders (e.g., eczema), or atrophy of the scalp.
18. Subjects who had been administered botulinum toxins into the arm, neck, or face for 5 months prior to baseline.
19. Subject had an overall Skull Density Ratio of less than 0.40 (±0.05) as calculated at screening.

20. Subject was unable or willing to tolerate the required prolonged stationary supine position during Exablate procedure (approximately 2-3 hours).
21. Subject was currently participating in another clinical investigation with an active treatment arm.
22. Subject was unable to communicate with the investigator and staff.
23. Subject was considered to be a poor surgical or study candidate, which may include, but is not limited to the following: any medical, social, or psychological problem that could complicate the required procedures and evaluations of the study in the judgment of the investigator.

8.1.2. Patient Treatment

If at any point it was determined that the subject did not meet all inclusion and exclusion criteria or cannot be treated for any other reason, the subject was removed from the study. These subjects were considered screen failures and would not be included in any of the safety or efficacy outcome analyses. The Screening and Study Exit Case Report Form (CRF) would be completed with reason for screen failure.

Patients who met the inclusion and exclusion criteria received an Exablate thalamotomy of the bilateral side.

8.1.3. Study Follow Up

Subjects were followed-up at 48-hours and at Months 1, 3, 6, and 12. Subjects were evaluated for general health, neurological changes, and ET symptomology measurements, as well as for device/procedure/ET disease progression-related adverse events that may have occurred during the follow-up period.

Analyses of the primary outcome were performed at 3 months and 6 months follow-up for safety at the time of submission; 12 month follow-up for all subjects is continuing. Commercially treated subjects were consented for 5 years follow-up.

Special assessments were added to this study in order to capture any potential adverse events of the bilateral thalamotomy.

- Physical and neurological examinations, inclusive of walking and ataxia
- Clinical Rating Scale for Tremor (CRST)
- Dysphagia Handicap Index (DHI)
- Speech Function
- Montreal Cognitive Assessment (MoCA)
- Epworth Sleepiness Scale (ESS)

The schedule of events is shown below:

TABLE 84. SCHEDULE OF EVENTS

Activity \ Visit	Screening/Baseline[1]	Exablate procedure[3]	48 Hours ± 4 hours	1 Month ± 7 days	3 Month ± 14 days	6 Month ±21 days	12 Month ± 120 days	Years 2 – 5[5] ± 120 days
Informed Consent	X							
Medication Review	X	X	X	X	X	X	X	X
Demographics & Medical History	X							
Physical Exam	X	X	X	X	X	X	X	X
Neurological Exam[6]	X	X	X	X	X	X	X	
Laboratory Tests	X							
Pregnancy Test (if applicable)	X							
CRST	X			X	X	X	X	X
DHI	X			X	X	X	X	
Speech Function	X			X	X	X	X	
MoCA	X			X	X	X	X	
ESS	X			X	X	X	X	
CT	X[2]							
MR	X[2]	X[4]						
Exablate procedure		X						
Adverse Events		X	X	X	X	X	X	X

[1]After informed consent is obtained, the screening and baseline activities can take place during a combined visit or across separate visits.

[2]MR/CT only needs to be repeated if it cannot be found or if medical history may have changed.

[3]Assessments performed on the day of the Exablate procedure will be done after the procedure is complete.

[4]Post-procedure MR should be obtained within 24 hours of procedure.

[5]Follow-up years 2 – 5 is applicable only to subjects who did not participate in G120246.

[6]The neurological exam should be performed within 48 hours prior to the Exablate bilateral procedure and 48 hours after the procedure by the same examiner.

Safety Outcome

Incidence and severity of device and treatment related adverse events associated with Exablate bilateral thalamotomy through Month 6 post procedure. Month 6 follow up for safety is proposed in view that 1) under PMA P150038, all device and or procedure events occurred within 30-days post ablation, 2) as per the proposed study design, subjects will be followed up for up to 12 months for study patients, and up to 5 years for non-study subjects.

All serious adverse events (SAEs) will be adjudicated by the Data and Safety Monitoring Board (DSMB) and the DSMB will review the safety profile at periodic intervals to ensure patient safety on the trial. The following stopping rules were set up in the protocol. This study may be stopped if, in the opinion of the DSMB, serious risks to the health and welfare of subjects are observed that are directly related to the use of the device. The following scenarios would create cause for stopping the study to evaluate patient safety:

- Any death that is deemed to be caused by the Exablate treatment.
- 2 or more events of intracranial hemorrhage deemed to be caused by the Exablate device.
- 2 or more subjects with significant (moderate to severe) new dysarthria/ speech/ swallowing adverse events that lasts longer than 3 months.
- 2 or more subjects with significant (moderate to severe) new ataxia/imbalance that lasts longer than 3 months.
- 3 or more subjects with significant (moderate to severe) new sensory deficits that lasts longer than 3 months.
- Any other unanticipated serious, device related event that causes significant disability/ harm to the subject.

Primary Effectiveness Outcome

Effectiveness outcomes include:

- Percent change from baseline to 3 months post bilateral Exablate thalamotomy for Tremor/Motor Function (Parts A and B) of the Clinical Rating Scale for Tremor (CRST) for the bilaterally treated side.
- Percent change from baseline to 3 months post bilateral thalamotomy for Upper Extremity Posture (Part A) of the CRST for the bilaterally treated side.
- Percent change from baseline to 3 months post bilateral thalamotomy for Functional Disability (Part C) of CRST.

The primary effectiveness outcome of the study is percent change from baseline at 3 months post-treatment in the bilateral Exablate thalamotomy for Tremor/Motor Function (Parts A and B) of the CRST in the secondary tremor side treated during this protocol.

For each subject, the primary outcome will be calculated as follows:

1. Identify which side of the brain was treated (bilateral treatment), as indicated by CRF field “Side of the brain being treated” on the Exablate Treatment Form.

2. If the RIGHT side of brain was treated, then the CRST variables from the LEFT side of the CRST assessment (contralateral side) will be used:
    - Part A = item #6 (LUE tremor): Rest + Posture + Action/Intention

      Note:

      ➔ If only two individual rates are obtained, the sum will be calculated over the two available rates.
    - If a single individual rate is obtained, Part A will be considered as missing and should be imputed Part B = item #11 Left* + item #12 Left + item #13 Left + item #14 Left + item #15 Left

      *Item #11 will be taken into account only for left-handed subjects. For right-handed subjects Part B will be the sum of 4 items only, without item #11.

      Note:

      ➔ If a single item is missing, the sum will be calculated over the available items – four items for left-handed subjects and three items for right-handed subjects.

      ➔ If more than one item is missing, Part B will be considered as missing and should be imputed.
3. Denote the treated (contralateral) CRST sub score at visit [k] as $\text{CRST}_{[\text{contralateral, k}]}$, then:

$$\text{CRST}_{[\text{contralateral, k}]} = \frac{Part\ A + Part\ B}{Total}$$

Where, *Total* is the maximal sum that could be achieved in Part A and Part B, based on the available items (obtained and imputed). Note that Total should be re-adjusted for each patient based on his/her available information.

For example, if the following conditions for a subject hold

- The treated side of the body is ipsilateral to handedness,
- One item in Part A is missing
- All five items in Part B are obtained

then the Total = 8 (Maximum that could be achieved in Part A) + 20 (Maximum that could be achieved in Part B) = 28

Note: Lower $\text{CRST}_{[\text{contralateral, k}]}$ scores are better than higher scores.

4. The primary efficacy outcome (denoted as PE) – Percent Change from Baseline at three months post-treatment in the treated (contralateral) CRST sub score – will be calculated as follows:

$$PE = \frac{CRST_{[contralateral,\ Baseline]} - CRST_{[contralateral,\ 3\ months\ FU]}}{CRST_{[contralateral,\ Baseline]}} \times 100$$

Note: Higher PE values represent improvement.

Baseline is defined as the last score obtained prior to bilateral treatment initiation.

8.1.4 Confirmatory Secondary Outcomes

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

1) **Secondary Outcome 1 (SE1)**
    - The secondary effectiveness outcome 1 (SE1) is percent change from baseline to 3 months post bilateral Exablate thalamotomy in Upper Extremity Posture (Part A) of the CRST for the secondary tremor side.
2) **Secondary Outcome 2 (SE2)**
    - The secondary effectiveness outcome 2 (SE2) is percent change from baseline to 3 months post bilateral Exablate thalamotomy in Functional Disability (Part C) of the CRST.

8.1.4.1 Additional Exploratory Outcomes

- **Additional ET005 Outcomes**

The following outcomes will examine the effectiveness of bilateral treatment provided in this study assessed by different CRST subscales at all available follow-up visits. Specifically, calculated score and percent change in the following scores at Visits 1, 3, and 6 months post bilateral Exablate thalamotomy will be evaluated:

1) Tremor/Motor Function (Parts A and B) of the CRST in the secondary tremor side treated during this protocol.
2) Upper Extremity Posture (Part A) of the CRST for the secondary tremor side treated during this protocol.
3) Functional Disability (Part C) of the CRST.

8.1.5. Study Statistical Analysis Plan and Analysis Population

8.1.5.1. Study Sample Size

The study was approved for a minimum of 50 and a maximum of 60 open-label subjects at up to 8 sites. The additional 10 subjects above 50 was requested in order to accommodate treatment of subjects who had undergone the extensive screening and baseline evaluations from confirmation of eligibility to scheduling treatment within the center based upon availability of MR time.

This sample size will allow bilateral ablation to be performed to provide good evidence of the performance/usability across multiple centers.

8.1.6 Study Statistical Analysis Plan and Analysis Population

8.1.6.1 Study Analysis Population

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

- Intention to treat (ITT group) - which consists of 51 subjects who signed consent and underwent the bilateral Exablate treatment.
- Safety Analysis Population - which consists of 51 subjects who received treatment (received at least "1" sonication). This analysis group is identical to the ITT for purposes of this protocol.
- Modified ITT (mITT) - consists of all Safety subjects for whom there exists valid baseline measurement and at least one post-baseline measurement on the primary effectiveness data. In this group, 51 treated subjects were all included as there were no dropouts or exclusions of subjects.
- Per Protocol (PP) - consists of 49 subjects, who had observed primary effectiveness data at Baseline and Month 3, and had no major protocol violations to affect outcome.

The mITT is the preferred population used for the purpose of effectiveness analyses, including primary and secondary confirmatory analyses.

8.1.7. Study Subject Accountability

Sixty-two subjects were recruited for the study. Ten subjects did not meet inclusion/exclusion criteria and one subject withdrew consent prior to treatment. Therefore, 11 subjects were screen failures. Fifty-one subjects received a staged, bilateral Exablate thalamotomy. Follow-up is complete through Month 6, but one subject at each of the Month 3 and Month 6 assessments missed a study visit.

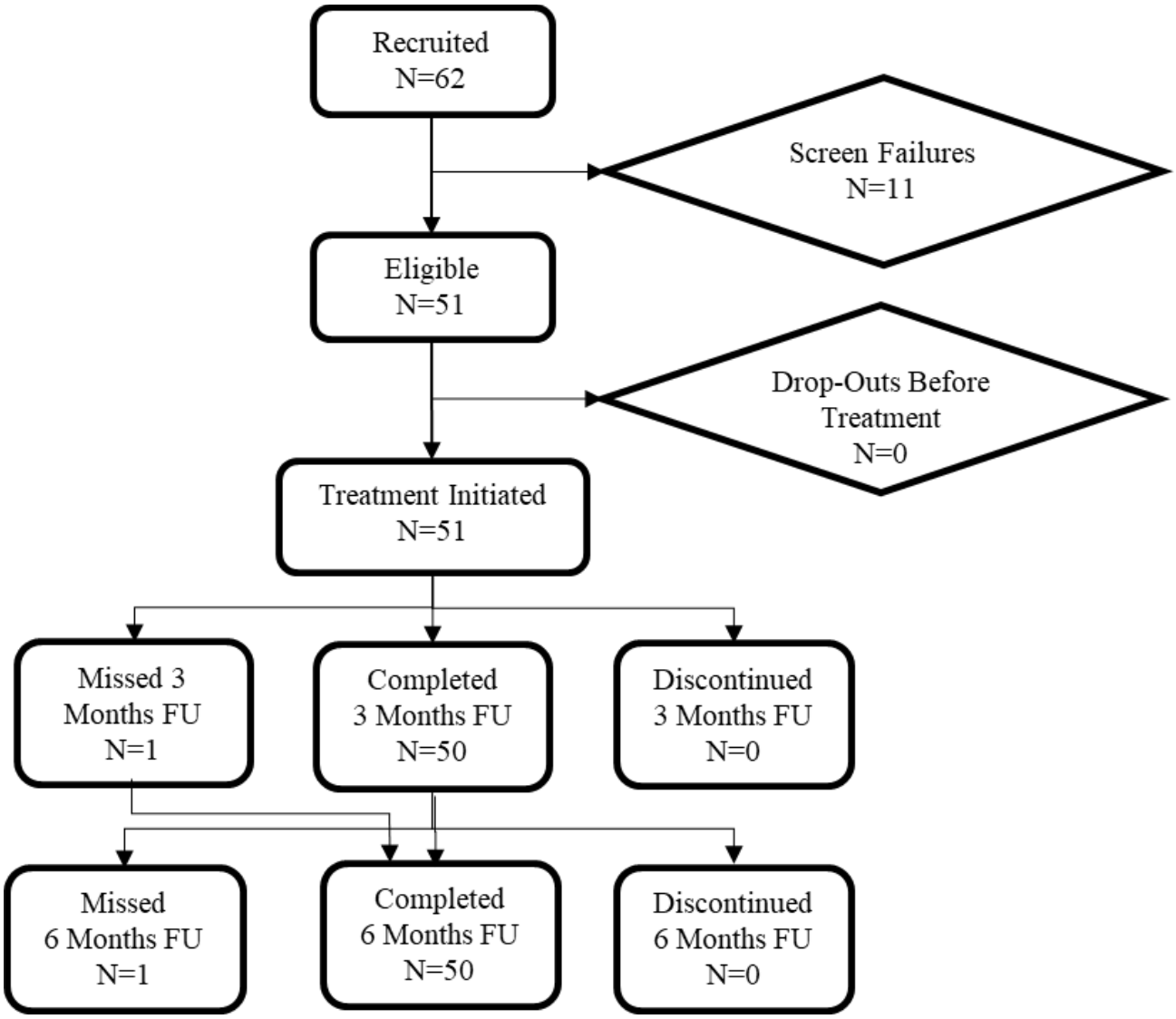


Figure 57. Study Flow Chart

Subject accountability by visit is shown in **TABLE 85** below.

TABLE 85. SUBJECT DISPOSITION

Category	Baseline	Treatment	48 Hours	Month 1	Month 3	Month 6
Consented	62					
Screen Failures[1]	11					
Eligible	51					
Treated		51				
Theoretical[2]	51	51	51	51	51	51
Death	0	0	0	0	0	0
Failure[3]	0	0	0	0	0	0
Expected[4]	51	51	51	51	51	51
Actual[5]	51	51	51	51	50	50
Actual %[6]	100%	100%	100%	100%	98%	98%

1 - SF – Those subjects Consented, but not meeting enrollment criteria.

2 - Theoretical is equal to the number of subjects Recruited minus SF 1. Therefore, theoretical is equal to the number of subjects eligible to receive treatment.

3 – Failures include any subjects who discontinued the study due to beginning another treatment for their condition.

4 - Expected equals Theoretical minus Exited for any reason.

5 - Actual is the number of subjects actually returning for the follow-up visit.

6 - Actual % is the number of Actual subjects divided by Expected.

The reasons for screen fail are shown in **TABLE 90**. Reasons for screen failure prior to treatment are shown in **TABLE 86**. Eleven subjects, after being consented, were either screen fails or decided not to pursue treatment under this protocol, and they were exited. Reasons for screen failure prior to randomization included the following reasons:

TABLE 86. SCREEN FAILS/DROPOUTS PRIOR TO RANDOMIZATION	
Number of Subjects	**Coded Reason for Screen Fail**
3	Tremor is significant, as measured by CRST, while on stable medication
3	Presence of dysphagia or elevated DHI
1	Skull Density Ratio
1	Clinically significant dysarthria
1	Contraindicated medication use
1	Persistent neurological event following Exablate index procedure
1	Withdrawal of consent during the screening period
Total: 11	

8.1.8 Study Demographics and Baseline Characteristics

8.1.8.1 Demographics

Baseline and demographic characteristics of the Safety population are presented in **TABLE 87**. This population had a mean age of approximately 73 years of age, was predominantly male, and were predominantly Caucasian and one Asian subject.

TABLE 87. DEMOGRAPHIC CHARACTERISTICS		
Demographic Characteristics		**Treatment Group**
Age [Years]	Mean	73.0
	N	51
BMI [kg/m²]	Mean	27.8
	N	50
Height [cm]	Mean	174.9
	N	51
Weight [kg]	Mean	84.9
	N	50
Gender	Female	7 (13.7)
	Male	44 (86.3)
	N	51
Race	White	50 (98.0)
	Black or African American	0
	Asian	1 (2.0)
	Other	0
	N	51
Ethnicity[1]	Hispanic	0
	Non-Hispanic	49 (100)
	Total	49[1]
Time from Initial ET Symptoms [Years]	Mean	36.5 (±18.1)
	N	50
Time from Initial ET Diagnosis [Years]	Mean	19.7 (±14.9)
	N	50
Time from First ET Medical Therapy [Years]	Mean	15.7 (±10.3)
	N	49
[1] – Note: two subjects declined to report their ethnicity.		

8.1.9 Safety Outcome

The primary analysis of safety was based upon the collection of adverse events during the study as collected by the investigators at each site from the time of the treatment to the Month 6 visit.

8.1.9.1 Adverse Events

The primary analysis of safety population (N=51) was based upon the collection of adverse events during the study as collected by the investigators at each site. As shown in **TABLE 88**, an average of 3.7 events per subject (min 0, max 9 events) was recorded. The literature surrounding bilateral thalamotomy is especially concerned with the rate of adverse events reported in left-sided treatments, therefore, the adverse events are summarized by side treated during bilateral procedure, as well as overall events. Three subjects had no adverse events at all.

TABLE 88. NUMBER OF AES PER SUBJECT

Number of AEs per Subject	Brain Side Treated During Bilateral Procedure		Total
	Left	Right	
Mean	4.4	3.6	3.7
Std	2.9	2.1	2.2
Min	1	0	0
Median	5	4	4
Max	8	9	9
N	5	46	51

A summary of the safety profile is presented in **TABLE 89**. Overall, the safety profile is acceptable. A total of 188 events were reported in a total of 48 subjects. A total of 97.9% of all events were mild or moderate in nature. Of all these events, only four (4) severe events occurred, and only one of these was procedure related. The procedure-related event was an urinary tract infection, following use of a catheter during the procedure. The other three severe events were unrelated to the device and procedure.

TABLE 89. SEVERITY OF ADVERSE EVENTS		
	Frequency N=188	Incidence N=51
Mild	159 (84.6%)	46 (90.2%)
Moderate	25 (13.3%)	16 (31.4%)
Severe	4 (2.1%)	4 (7.8%)
Life-threatening	0 (0.0%)	0 (0.0%)
Total	188 (100%)	48 (94.1%)
SAEs – Procedure Related[1]	1 (0.5%)	1 (2.0%)
SAEs – Unrelated	2 (1.1%)	2 (3.9%)

[1] The one procedure-related event was for an urinary tract infection following use of a foley catheter during the procedure.

All adverse events were coded by Grouping Term, Body System and Coded Term for analysis. **TABLE 90** presents the adverse event safety profile for the study by Grouping Term. The majority of all events were unrelated. Grouping term definitions are summarized below:

- The **Unrelated** events are events related to the stereotactic frame, IV, co-morbid conditions and events coded by PI as unrelated.
  - 60 (31.9%) events in 31 (60.8%) subjects were unrelated.
- The **ET Related/Disease Progression** events are events related to Essential Tremor progression or ET medication related.
  - 2 (1.1%) events in 2 (3.9%) subjects were ET disease related.
- Many of the **Transient** events are events that are used by the physician to steer targeting of the lesion prior to full ablation, but all of the events coded in this category occurred at the time of the procedure and resolved within 72 hours.
  - 30 (16.0%) events in 20 (39.2%) subjects were transient (resolved < 72 hours).
- The **Thalamotomy related** events are events normally reported when ablation/stimulation of the *Vim* nucleus is undertaken.
  - 90 (47.9%) events in 39 (76.5%) of subjects were thalamotomy-related.

- The **Procedure-related** events are generally those events that are non-transient and related to undergoing the procedure, such as fatigue, headache, etc.
  - 6 (3.2%) events in 4 (7.8%) of subjects were procedure-related.
    - Five of the procedure-related events resolved in less than 30 days from onset. The last event resolved in less than 4 months.
- **Device-related** events are defined as device-malfunction or mistargeting resulting in subject injury. No device-related events were reported in this trial.

TABLE 90. ADVERSE EVENTS BY GROUPING TERM		
	Frequency N=188	**Incidence N=51**
Subtotal Transient	30 (15.96%)	20 (39.22%)
Subtotal Unrelated	60 (31.91%)	31 (60.78%)
Subtotal Essential Tremor Related	2 (1.06%)	2 (3.92%)
Subtotal of Events	**92 (48.94%)**	**39 (76.47%)**
Subtotal Thalamotomy Related	90 (47.87%)	39 (76.47%)
Subtotal Procedure Related	6 (3.19%)	4 (7.84%)
Subtotal of Related Events	**96 (51.06%)**	**40 (78.43%)**
Grand Total	**188 (100.0%)**	**48 (94.1%)**

TABLE 91 below presents all the adverse events reported by grouping term, body system and coded term. There were eighteen (18) events for dysarthria reported within the study; most of these events (17 of 18) were mild in nature. Half of these events (9, 50%) had resolved at the time of the Month 6 visit. There were fifteen (15) events of ataxia reported and all of these were mild in nature. Most of these events (8, 53.3%) had resolved at the time of the Month 6 visit.

TABLE 91. THALAMOTOMY/PROCEDURE-RELATED ADVERSE EVENTS BY SEVERITY								
Grouping Term / Body System / Preferred Term			Number of events (%)	Number of subjects (%)	Severity			
					Mild	Moderate	Severe	Life-Threatening
Thalamotomy Related	Musculoskeletal	Weakness	1 (0.53%)	1 (1.96%)	1	0	0	0
	Nervous	Ataxia	12 (6.38%)	12 (23.53%)	12	0	0	0
		Decrease In Synchronicity Between Left And Right Hand	1 (0.53%)	1 (1.96%)	1	0	0	0
		Diplopia, Intermittent	1 (0.53%)	1 (1.96%)	1	0	0	
		Dizziness	1 (0.53%)	1 (1.96%)	1	0	0	0
		Dry Mouth	1 (0.53%)	1 (1.96%)	1	0	0	0
		Dysarthria	15 (7.98%)	15 (29.41%)	14	1	0	0
		Dysgeusia	7 (3.72%)	7 (13.73%)	6	1	0	0
		Dysmetria	2 (1.06%)	2 (3.92%)	2	0	0	0
		Dysphagia	4 (2.13%)	4 (7.84%)	3	1	0	0
		Gait Disturbance	5 (2.66%)	5 (9.8%)	5	0	0	0
		Hypoesthesia	2 (1.06%)	1 (1.96%)	2	0	0	0
		Hypogeusia	4 (2.13%)	4 (7.84%)	4	0	0	0
		Imbalance	5 (2.66%)	5 (9.8%)	4	1	0	0
		Sialorrhea	1 (0.53%)	1 (1.96%)	1	0	0	0
		Unsteadiness	5 (2.66%)	5 (9.8%)	5	0	0	0
		Voice Change	1 (0.53%)	1 (1.96%)	1	0	0	0

TABLE 91. THALAMOTOMY/PROCEDURE-RELATED ADVERSE EVENTS BY SEVERITY								
Grouping Term / Body System / Preferred Term			Number of events (%)	Number of subjects (%)	Severity			
					Mild	Moderate	Severe	Life-Threatening
	Pain/Discomfort	Numbness/Tingling	22 (11.7%)	16 (31.37%)	22	0	0	0
	Total		**90 (47.9%)**	**39 (76.5%)**	**86 (45.7%)**	**4 (2.1%)**	**0 (0.0%)**	**0 (0.0%)**
Procedure Related	General	Fatigue	2 (1.06%)	2 (3.92%)	2	0	0	0
	Nervous	Facial Droop	1 (0.53%)	1 (1.96%)	1	0	0	0
	Pain/Discomfort	Headache	1 (0.53%)	1 (1.96%)	0	1	0	0
		Numbness/Tingling	1 (0.53%)	1 (1.96%)	1	0	0	0
	Urinogenital	UTI	1 (0.53%)	1 (1.96%)	0	0	1	0
	Total		**6 (3.2%)**	**4 (7.8%)**	**4 (2.1%)**	**1 (0.5%)**	**1 (0.5%)**	**0 (0.0%)**

As shown in **TABLE 92**, 148 (78.7%) of the 188 adverse events reported started within 30 days. Of those 148 events, 77 events (41%) resolved within 90 days and 97 events (51.6%), by the end of the Month 6 visit. It should be noted, 85% of all the events were mild.

TABLE 92. ONGOING THALAMOTOMY RELATED ADVERSE EVENTS

System Term	Coded Term	Mild	Moderate	Severe
Musculoskeletal	Weakness	1	0	0
Subtotal Gastrointestinal		1 (0.5%)	0 (0.0%)	0 (0.0%)
Nervous	Ataxia	7	0	0
	Decrease in Synchronicity Between Left and Right Hand	1	0	0
	Dry Mouth	1	0	0
	Dysarthria	8	0	0
	Dysgeusia	2	1	0
	Dysmetria	1	0	0
	Dysphagia	2	1	0
	Gait disturbance	1	0	0
	Hypoesthesia	2	0	0
	Hypogeusia	4	0	0
	Sialorrhea	1	0	0
	Unsteadiness	1	0	0
Subtotal Nervous		31 (16.5%)	2 (1.1%)	0 (0.0%)
Pain/discomfort	Numbness/Tingling	13	0	0
Subtotal Pain/Discomfort		13 (6.9%)	0 (0.0%)	0 (0.0%)
	Total	**47 (25.0%)**		

8.1.9.2 Serious Adverse Events

TABLE 93 presents SAEs reported in the study. There have been three SAEs reported during this trial. Two of the three SAEs were unrelated. As mentioned above, there was one urinary tract infection which was reported as procedure-related following catheterization during the procedure.

TABLE 93. SERIOUS ADVERSE EVENTS		
	Frequency N=188	Incidence N=51
Unrelated SAE	2 (1.1%)	2 (3.9%)
Procedure Related* SAE	1 (0.5%)	1 (2.0%)
Total	3 (1.6%)	3 (5.9%)

***Procedure Related SAE: The PI classified urinary tract infection as serious and unrelated to the Exablate device.** Subject received a urinary catheter during the Exablate procedure. Following discharge, the subject complained of fever and was admitted to the hospital for a course of IV antibiotics. Subject was discharged and continued steroids and antibiotics at home for a total of two weeks. The event was considered resolved after 13 days total, without sequelae.

Per the study protocol, the safety data collected in this study has been reviewed periodically by the DSMB and all SAEs have been adjudicated. Final DSMB review was performed prior to submission and included review of the full safety and efficacy data prior of the completed study. Only one SAE was considered procedure related due to placement of catheter during the procedure. The other SAEs were related to the subjects' underlying medical conditions. Essential

8.1.10 Primary Effectiveness Outcome

The primary effectiveness analysis was performed on the mITT population, all of whom underwent a procedure, to compare the change from Baseline to the Month 3 visit as shown in **TABLE 94**.

Out of 51 mITT subjects treated with Exablate bilateral thalamotomy, 50 completed the Month 3 visit and had observed primary outcome.

The primary endpoint (PE) reflects the average change in combined "Tremor/Motor Function" of ET subjects. In our study, the primary effectiveness outcome was calculated based on each investigator's assessment of scoring of tremor function. The PE analysis evaluated the Month 3 post-treatment change compared to Baseline in the bilaterally treated upper extremity CRST sub-score (Part A and B) (hereinafter referred to as the Composite Tremor/Motor Function score). Analysis was conducted on the mITT analysis population and is shown in **TABLE 94** below. As shown, the data demonstrate a 66% improvement in the Composite Tremor/Motor Function score compared to Baseline. This percent change was significant ($p \leq 0.001$). This data demonstrates that the primary effectiveness outcome was successfully met.

TABLE 94. PRIMARY EFFICACY OUTCOME – DESCRIPTIVE STATISTICS OF RAW SCORE, CHANGE AND PERCENT CHANGE FROM BASELINE AT 3 MONTHS POST-TREATMENT IN THE TREATED (CONTRALATERAL) TREMOR/MOTOR FUNCTION (PARTS A AND B) CRST SUB SCORE (MITT)				
Visit / Statistics	Baseline Score	Score at Month 3 Visit	Change from Baseline	Percent Change from Baseline (%)
Mean	0.6	0.2	0.4	66.0
Std	0.2	0.2	0.1	22.1
Min	0.3	0.0	0.0	3.7
Median	0.6	0.2	0.4	68.7
Max	1.0	0.9	0.7	100
CL Interval	0.1	0.1	0.1	12.4
N	51	51	51	51
p-Value	**<.001**			
Note: In the mITT analysis group, subjects with missing data had data imputed via last observation carried forward (LOCF).				

The primary outcome analysis was repeated using the PP population as shown in **TABLE 95**. Subjects who had observed lesions in post-op imaging and observed effectiveness data were included in this analysis. The mean improvement from baseline was 66.2%. This result is also significant, with p = < 0.001.

TABLE 95. PRIMARY EFFECTIVENESS OUTCOME – DESCRIPTIVE STATISTICS OF RAW SCORE, CHANGE AND PERCENT CHANGE FROM BASELINE AT 3 MONTHS POST-TREATMENT IN THE TREATED (CONTRALATERAL) TREMOR/MOTOR FUNCTION (PARTS A AND B) CRST SUB SCORE (PP)				
Visit / Statistics	**Baseline Score**	**Score at Month 3 Visit**	**Change from Baseline**	**Percent Change from Baseline (%)**
Mean	0.6	0.2	0.4	66.2
Std	0.2	0.2	0.2	22.4
Min	0.3	0.0	0.0	3.7
Median	0.6	0.2	0.4	68.7
Max	1.0	0.9	0.7	100
CL Interval	0.1	0.1	0.1	12.9
N	49	49	49	49
p-Value	**<.001**			

This level of improvement was similar to the results demonstrated in the original PMA submission for P150038.

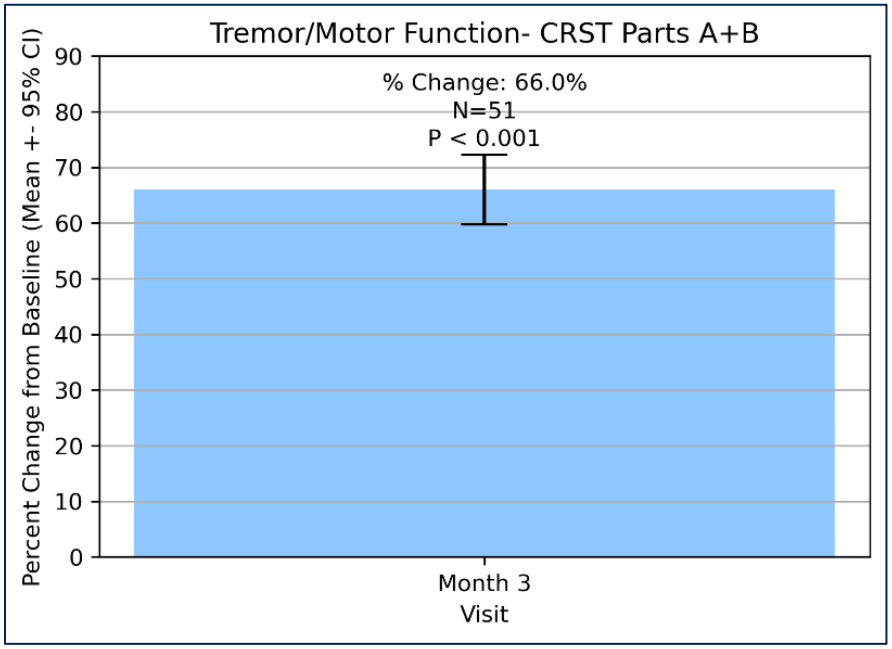


Figure 58. Primary Outcome – CRST A+B (mITT) (Percent Change from Baseline at Month 3)

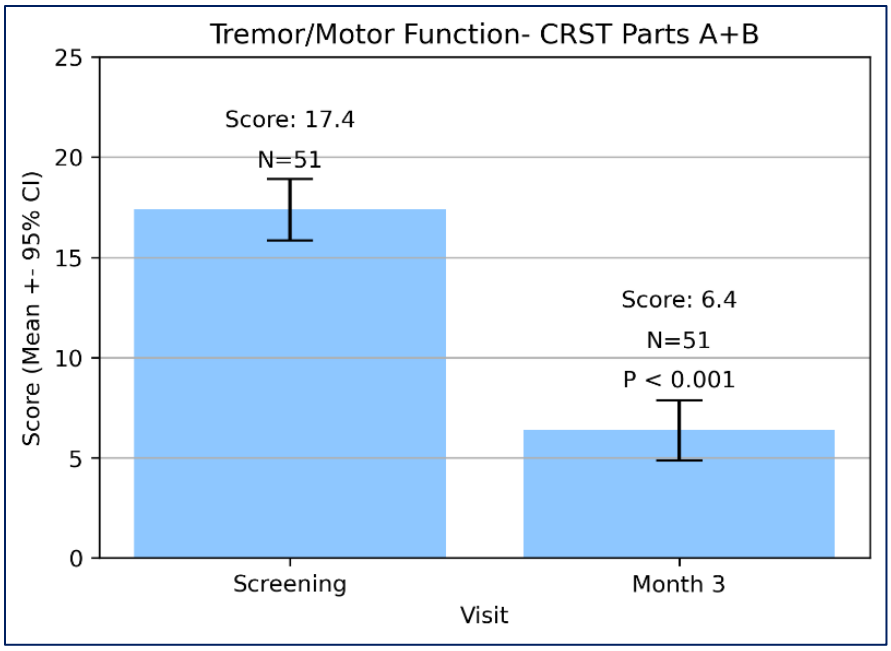


Figure 59. Primary Outcome – CRST A+B (mITT) (Average Score)

These results build on the history of established unilateral thalamotomy. There have also been recent, small studies published using MRgFUS in staged, bilateral thalamotomy. Although small populations, these studies saw trends towards improvement in tremor symptoms with limited adverse events.

8.1.11 Additional Effectiveness Outcomes

There are two additional analyses performed using the mITT population at Month 3 as part of the effectiveness outcome.

8.1.11.1 CRST Part A Upper Extremity Posture (Raw Score, Change, and Percent Change) from Baseline at Month 3 Post-Treatment (mITT)

One of the confirmatory outcomes is a CRST Part A sub-score of Upper Extremity Posture and percent change from Baseline at Month 3 post-treatment. This is assessed for each part of the body as a sub-set of the Part A of the CRST and quantifies tremor at posture across upper extremities. With a maximum score of 4 points, the scores were taken contralateral to the side of the body treated during the bilateral treatment. Higher scores represent a more severe tremor.

As shown in **TABLE 96** below, the study data demonstrated an 81.2% improvement compared to Baseline.

TABLE 96. SECONDARY EFFECTIVENESS OUTCOME – DESCRIPTIVE STATISTICS OF RAW SCORE, CHANGE AND PERCENT CHANGE FROM BASELINE AT 3 MONTHS POST-TREATMENT IN THE TREATED (CONTRALATERAL) UPPER EXTREMITY POSTURE (PART A) CRST SUB SCORE (MITT)				
Visit / Statistics	**Baseline Score**	**Score at Mont 3 Visit**	**Change from Baseline**	**Percent Change from Baseline (%)**
Mean	2.5	0.6	1.9	81.2
Std	0.8	0.9	0.8	26.6
Min	1.0	0.0	0.0	0.0
Median	3.0	0.0	2.0	100
Max	4.0	4.0	3.0	100
CL Interval	0.5	0.5	0.4	14.9
N	51	51	51	51

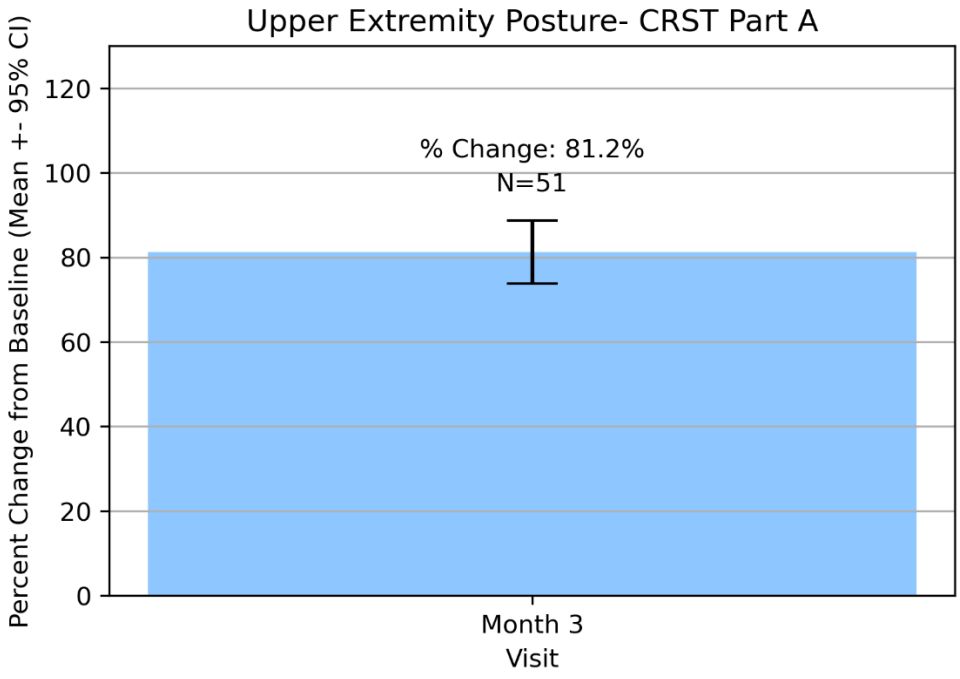


Figure 60. Secondary Outcome – CRST Part A (mITT) (Percent Change from Baseline at Month 3)

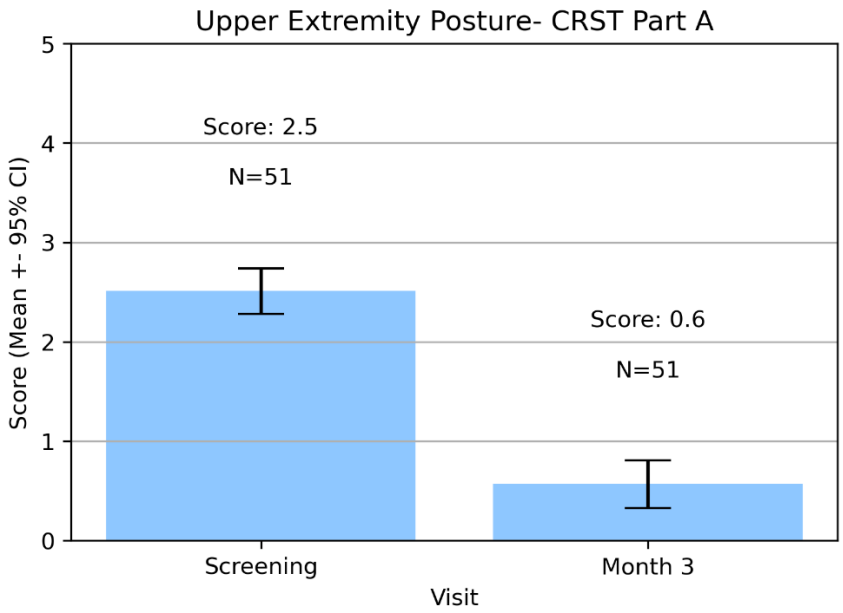


Figure 61. Secondary Outcome – CRST Part A (mITT) (Average Score)

8.1.11.2 CRST Part C Sub-Score (Raw Score, Change, and Percent Change) from Baseline at Month 3 Post-Treatment (mITT)

The other confirmatory outcome is a CRST Part C sub-score and percent change from Baseline at Month 3 post-treatment. Part C of the CRST assesses the impact of the subject's tremor on their ability to care for themselves (functional disability). With a maximum score of 32 points, the scores of each daily activity (such as speaking, eating, hygiene, and dressing) are summed together to represent impact of a subject's tremor. Higher scores represent a more severe tremor.

As shown in **TABLE 97** below, the study data demonstrated a 73.1% improvement compared to Baseline.

TABLE 97. SECONDARY EFFECTIVENESS OUTCOME - DESCRIPTIVE STATISTICS OF RAW SCORE, CHANGE AND PERCENT CHANGE FROM BASELINE AT 3 MONTHS POST-TREATMENT IN THE FUNCTIONAL DISABILITY (PART C) CRST SUB SCORE (MITT)				
SE2	Baseline Score	Score at Month 3	Change from Baseline	Percent Change from Baseline
Mean	10.3	2.2	8.2	73.1
Std	4.7	2.8	5.6	39.3
Min	2.0	0.0	-2.0	-100
Median	10.3	1.0	7.0	87.5
Max	24.0	11.0	24.0	100
CL Interval	2.6	1.6	3.2	22.1
N	51	51	51	51

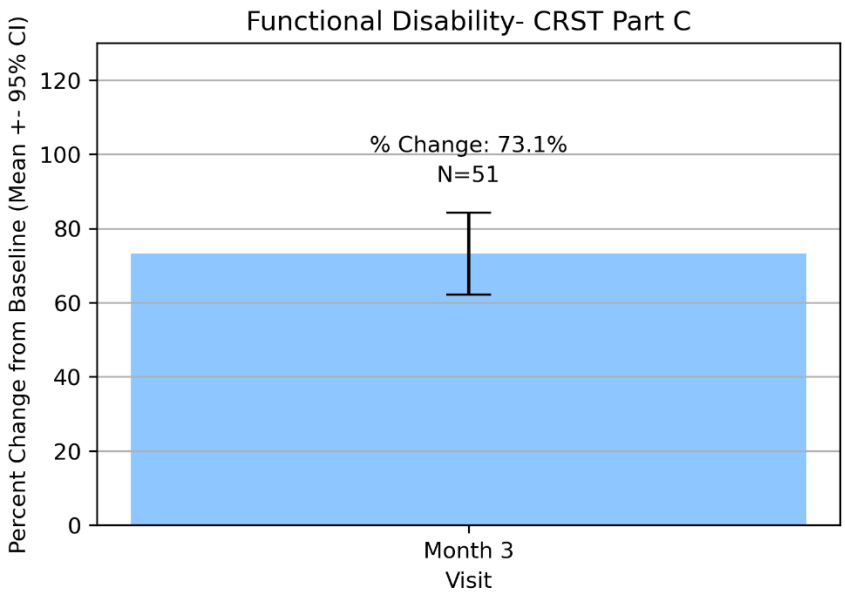


Figure 62. Secondary Outcome - CRST Part C (mITT) (Percent Change from Baseline at Month 3)

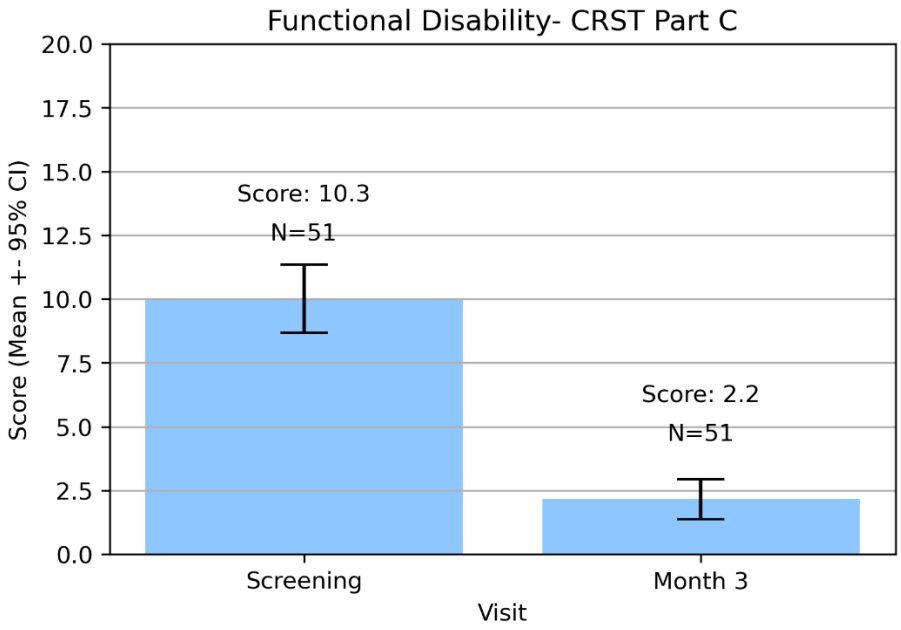


Figure 63. Secondary Outcome – CRST Part C (mITT) (Average Score)

8.1.12 Additional Outcomes

The following outcomes were also assessed based on across all assessments showing the differences between baseline and each successive visit.

8.1.12.1 Change from Baseline to Months 1, 3, and 6 post bilateral Exablate thalamotomy Tremor/Motor Function (Parts A and B) of the CRST

The first additional outcome was to look at the change from Baseline of the CRST Tremor/Motor Function combined across all follow-up time points at Months 1, 3, and 6. The figures below show the percent changes, as well as the average scores across these three visits. As the two figures show, the percent change and average score appears consistent across all three visits. The average percent change across Months 1, 3, and 6 are 68.1%, 66.0%, and 64.3% respectively. The average score drops from 17.4 at Baseline to 6.0, 6.4, and 6.7 at Months 1, 3, and 6. Note that in this assessment, a higher score indicates a more severe tremor intensity.

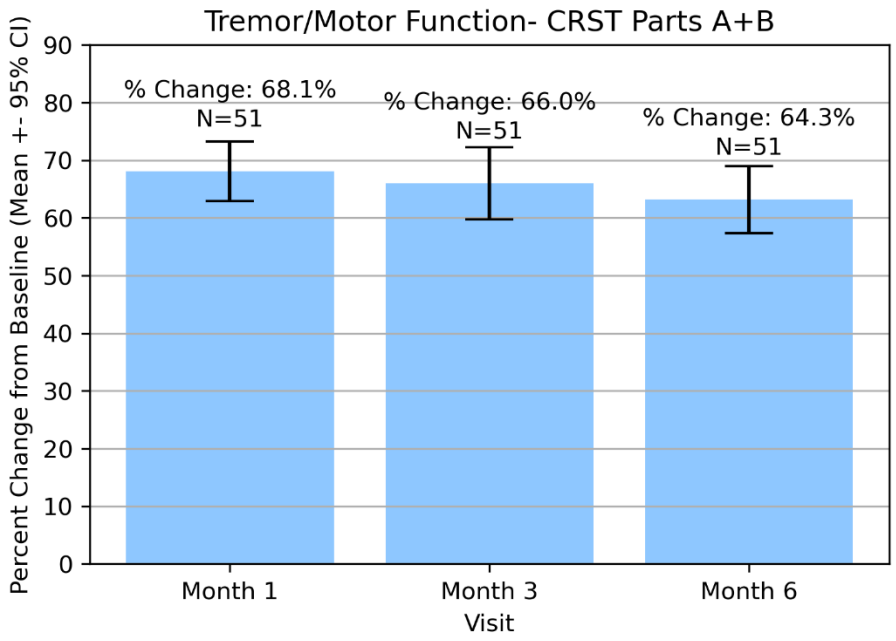


Figure 64. Additional Outcome – CRST A+B Tremor/Motor Score Percent Change

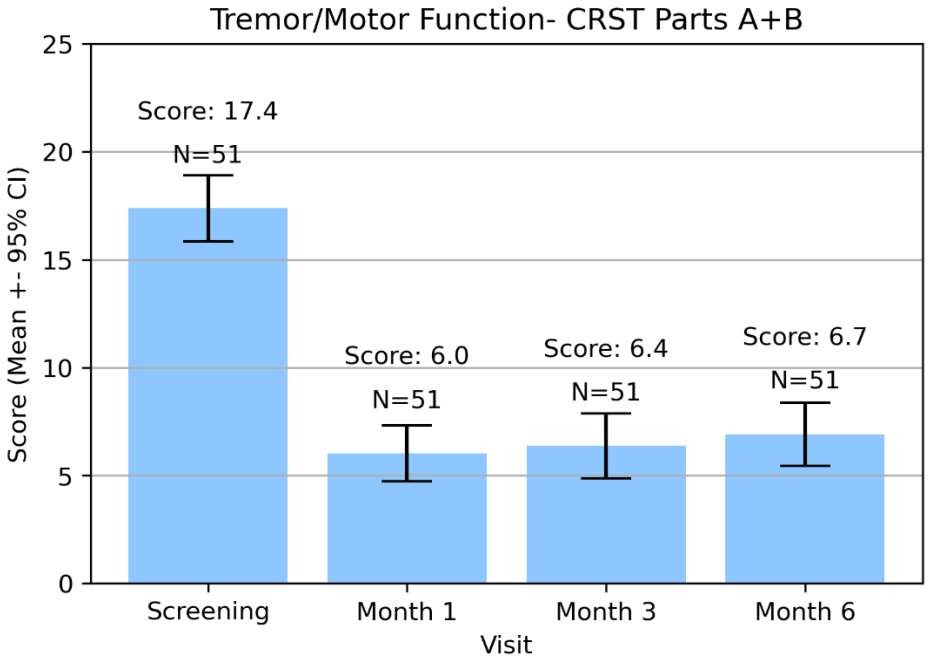


Figure 65. Additional Outcome – CRST A+B Tremor/Motor Function Average Score

This demonstrates that an effective improvement can be achieved immediately following treatment, and the results are sustained through at least six months of follow-up. These data are also consistent with the prior pivotal trial associated with PMA P150038.

8.1.12.2 Change from Baseline to Months 1, 3, and 6 post bilateral Exablate thalamotomy Upper Extremity Posture (Part A) of the CRST

The second additional outcome was to look at the change from Baseline of the CRST Upper Extremity Posture across all follow-up time points at Months 1, 3, and 6. The figures below show the percent changes, as well as the average scores across these three visits. As the two figures show, the percent change and average score appears consistent across all three visits. The average percent change across Months 1, 3, and 6 are 80.9%, 81.2%, and 80.2% respectively. The calculated score drops from 2.8 at Baseline to 0.5, 0.6, and 0.5 at Months 1, 3, and 6. Note that in this assessment, a higher score indicates a more severe tremor intensity.

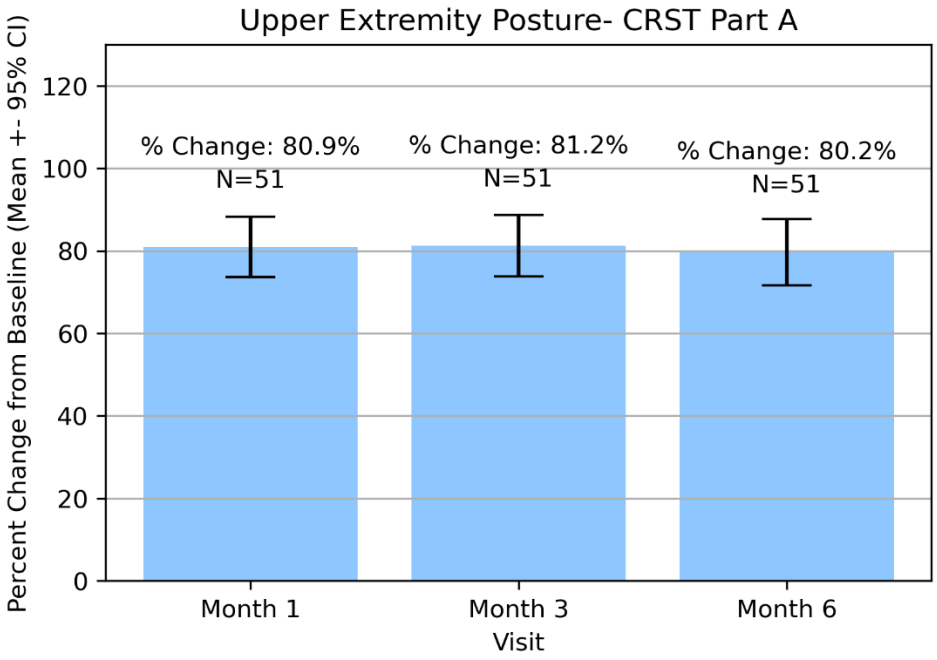


Figure 66. Additional Outcome – CRST Upper Extremity Posture Percent Change

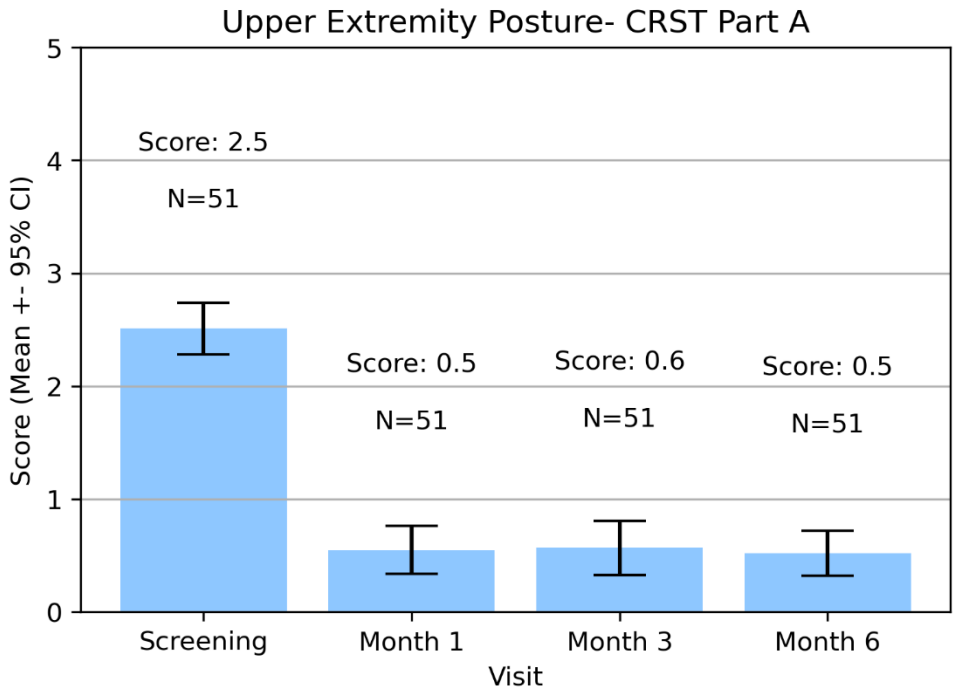


Figure 67. Additional Outcome – CRST Upper Extremity Posture Calculated Score

These results demonstrate that an effective improvement can be achieved immediately following treatment, and the results are sustained through at least six months of follow-up. These data are also consistent with the prior pivotal trial associated with PMA P150038 (see Chapter-3 of this document).

8.1.12.3 Change from Baseline to Months 1, 3, and 6 post bilateral Exablate thalamotomy Functional Disability (Part C) of the CRST

The next additional outcome was to look at the change from Baseline of the CRST Part C (Functional Disability) across all follow-up time points at Months 1, 3, and 6. The figures below show the percent changes, as well as the average scores across these three visits. As the two figures show, the percent change and average score appears consistent across all three visits. The average percent change across Months 1, 3, and 6 are 77.1%, 73.1%, and 74.3% respectively. The average score drops from 10.3 at Baseline to 1.9, 2.2, and 2.2 at Months 1, 3, and 6. Note that in this assessment, a higher score indicates a more severe tremor intensity.

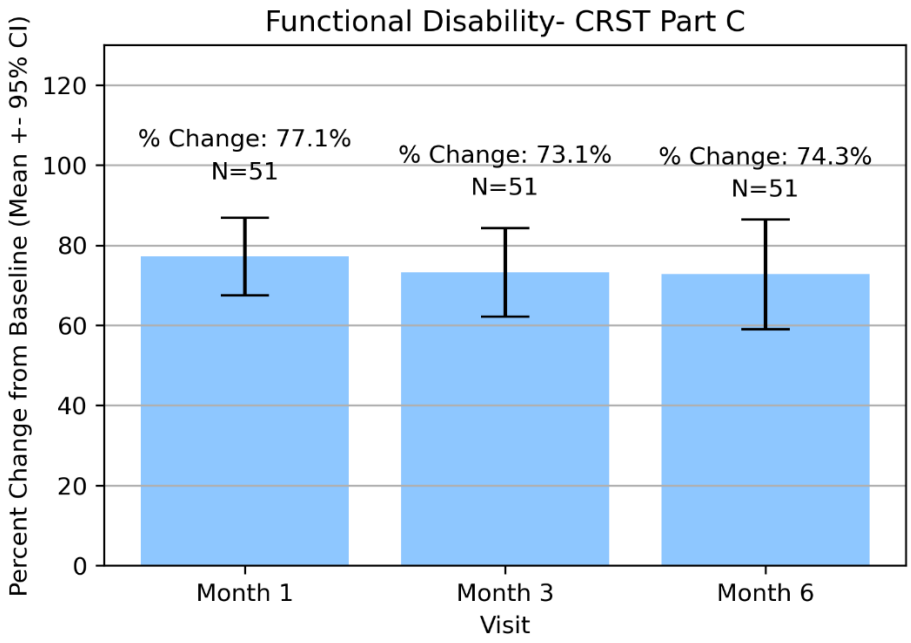


Figure 68. Additional Outcome – CRST C Functional Disability Percent Change

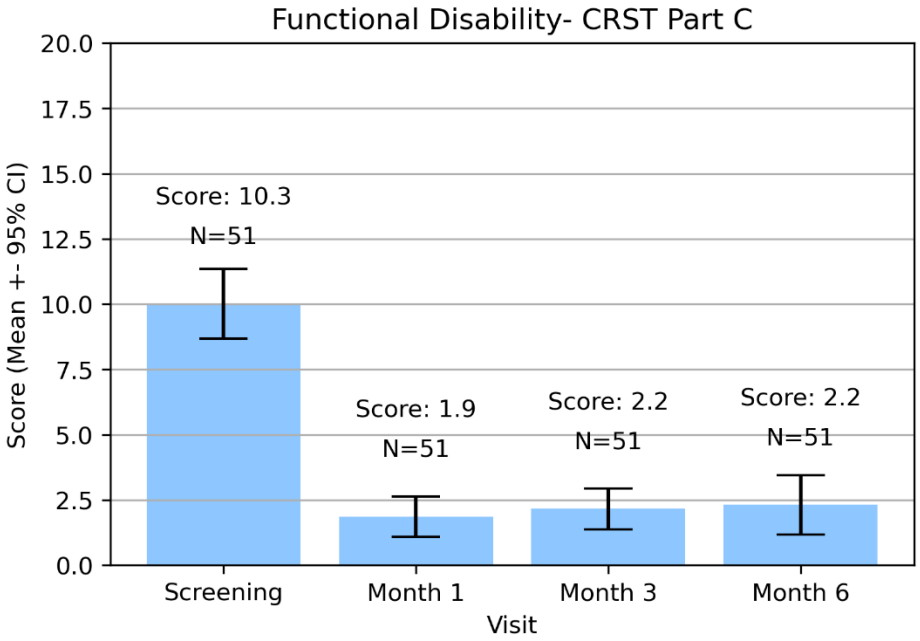


Figure 69. Additional Outcome – CRST C Functional Disability Calculated Score

These results demonstrate that an effective improvement can be achieved immediately following treatment, and the results are sustained through at least six months of follow-up. These data are also consistent with the prior pivotal trial associated with PMA P150038.

8.1.12.5 Covariate Analysis

The effects of covariates (age, baseline CRST, brain treated side, gender and center) were assessed for the primary effectiveness outcomes. The primary effectiveness outcome did not differ between the covariate levels in any of the tested covariates. Since the interaction effect was found to not influence the outcome, the effect of group and covariate level without interaction were further examined. The covariate effect was found to be non-significant for all covariates, while the group effect was significant for all covariates, indicating that the primary effectiveness outcome is from the treatment effect and not from the covariate effects.

8.2 Conclusion Drawn from the Study

In summary, the primary effectiveness outcome and all confirmatory secondary outcomes were met. At Month 3, the primary effectiveness analysis showed that subjects experienced a 66% improvement in the Composite Tremor/Motor Function score (CRST A+B) compared to Baseline.

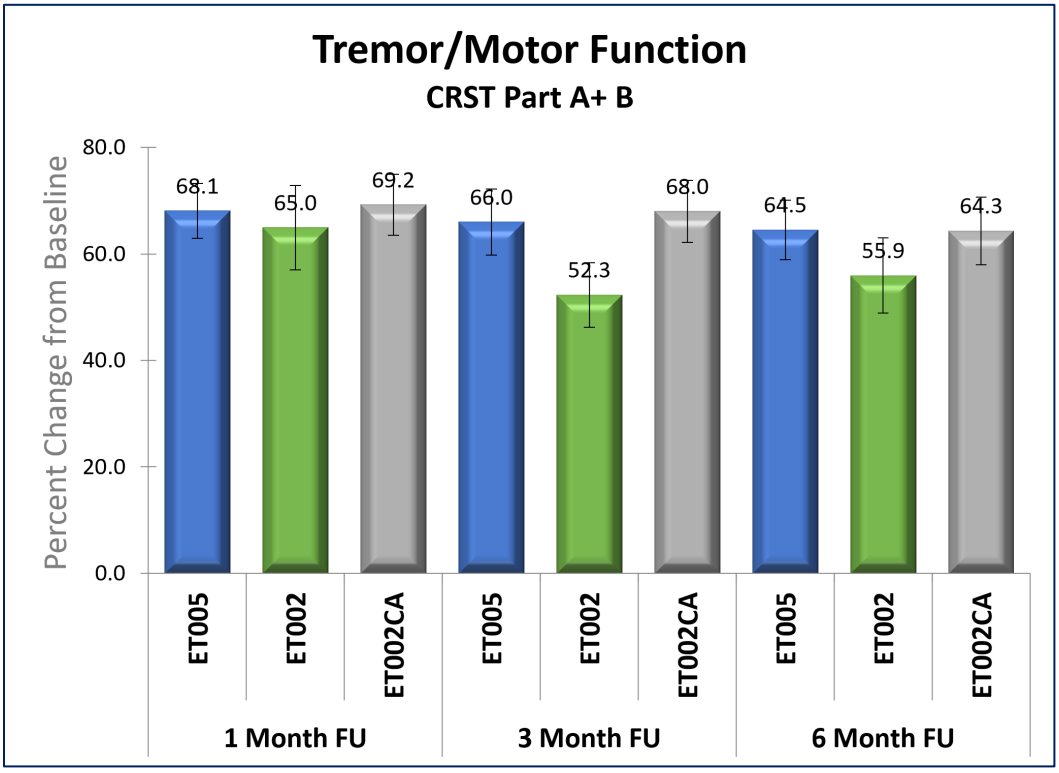
Overall, the summary of safety demonstrated that no severe or life-threatening events related to the device occurred. A total of 188 events were reported in this study (3.7 events per Exablate subject). This is similar to the G120246 study (see Chapter 3 of this document for more details) that served to support the initial P150038 submission. In the G120246 study, subjects in the treatment arm experienced an average of 3.1 events per subject, and events were overwhelmingly mild in nature. Moreover, no different than the original unilateral study (see Chapter 3), of the 188 events, about 98% of all events were categorized as mild or moderate.

All events were categorized as either transient, unrelated, procedure-related, Essential tremor progression, and/or thalamotomy-related. No device-related events were reported. Thirty (30) transient (resolved within 72 hours) events were reported. Another 62 events were categorized as unrelated to Exablate or Essential tremor or disease progression related. Six (6) events were categorized as procedure-related (e.g., fatigue, weakness, headache, and one sonication-related head pain) lasting longer than 3 days. Ninety (90) events were categorized as thalamotomy-related events.

By the Month 6 visit, all procedure-related events and approximately half of the thalamotomy-related events resolved. Numbness or tingling, dysarthria, and ataxia occurred with the highest frequency, and made up over half of the events, as is expected of thalamotomy procedures.

There was additional focus on events that affected balance or sensory deficits. Subjects were assessed during follow-up visits from baseline by neurological exams and questionnaires. Most of these types of events were mild in severity and none of them worsened over time. It should be noted that most of these events resolved within 3-months post procedure.

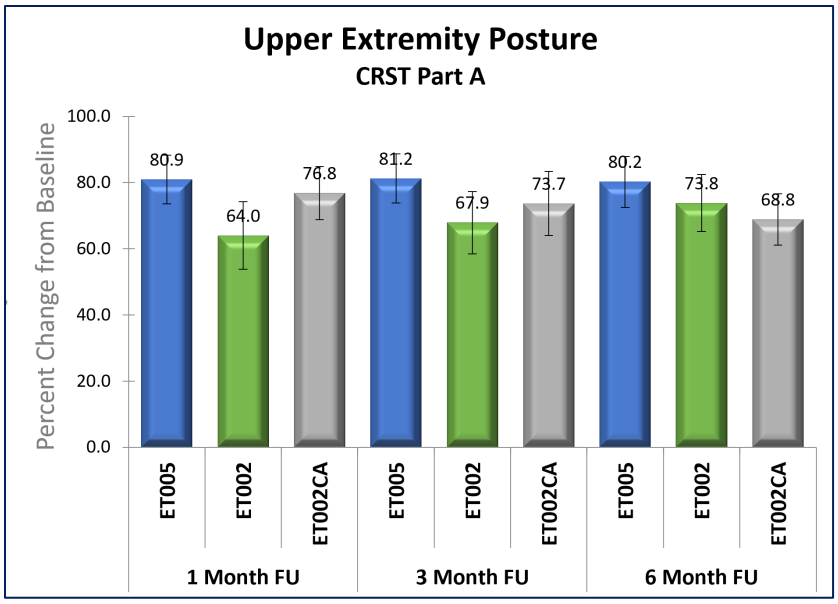
This trial builds on the history of Exablate unilateral thalamotomy in Essential tremor. Figure 70 below compares the percent change in CRST Tremor/Motor Function across the trials under IDE G120246 and IDE G190162. The following graphs compare the outcome of the staged unilateral thalamotomy study (ET005 – IDE G190162) to the original index unilateral thalamotomy outcome (ET002 – IDE G120246) and outcome of the subsequent continued access index unilateral thalamotomy trial for Essential tremor (ET002CA).



Note: ET005 refers to the outcome of the staged thalamotomy study, whereas ET002 refers to the outcome of the initial index unilateral thalamotomy study. ET002CA represents the outcome of the continued access cohort for index unilateral thalamotomy.

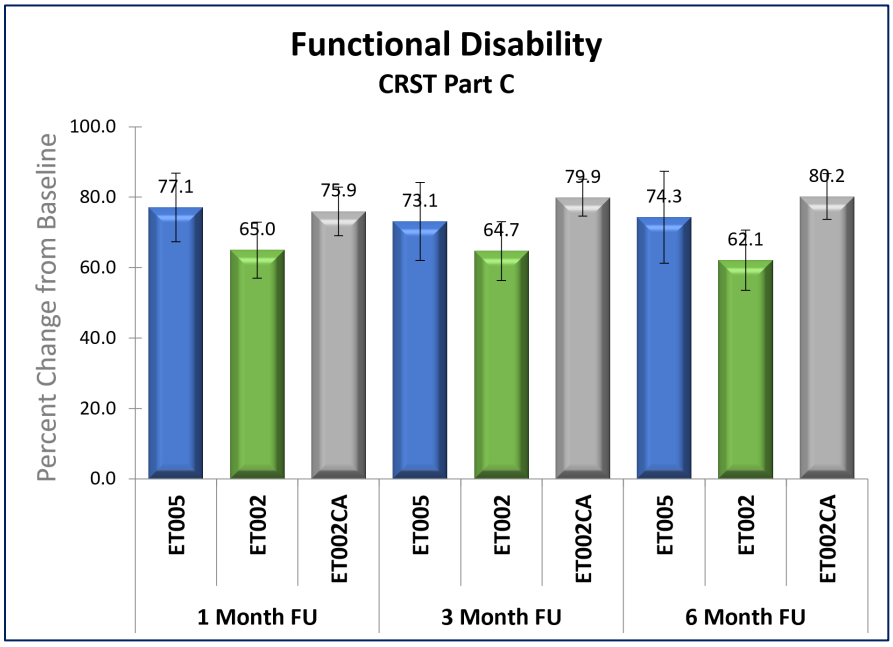
Figure 70. CRST Parts A+B in Exablate Thalamotomy Trials (Unilateral and Bilateral)

Figure 71 below compares the percent change in CRST Part A Posture and **Figure 72** below compares the percent change in CRST Part C Functional Disability across the trials under IDE G120246 and IDE G190162.



Note: ET005 refers to the outcome of the staged thalamotomy study, whereas ET002 refers to the outcome of the initial index unilateral thalamotomy study. ET002CA represents the outcome of the continued access cohort for index unilateral thalamotomy.

Figure 71. CRST Part A Posture in Exablate Thalamotomy Trials (Unilateral and Bilateral)



Note: ET005 refers to the outcome of the staged thalamotomy study, whereas ET002 refers to the outcome of the initial index unilateral thalamotomy study. ET002CA represents the outcome of the continued access cohort for index unilateral thalamotomy.

Figure 72. CRST Part C Functional Disability in Exablate Thalamotomy Trials (Unilateral and Bilateral)

All three of these trials demonstrate an immediate response from the subjects in reduction in tremor/motor function, posture score and functional disability, as well as sustained results out to at least Month 6 follow-up.

The types of events and severity of events in this trial are consistent with those noted in the pivotal unilateral thalamotomy associated with PMA P150038. **Figure 73** shows the proportion of severity of all reported adverse events in the ET002 trial (index unilateral thalamotomy used to support the original PMA P150038), and **Figure 74** shows the same for the ET005 trial (staged unilateral thalamotomy in medication-refractory Essential tremor patients). Within both trials, the events are predominantly mild and moderate in nature, regardless of relationship to the device and procedure. The proportion of mild and moderate events is higher in this trial utilizing staged bilateral thalamotomy to the unilateral treatments of the ET002 trial.

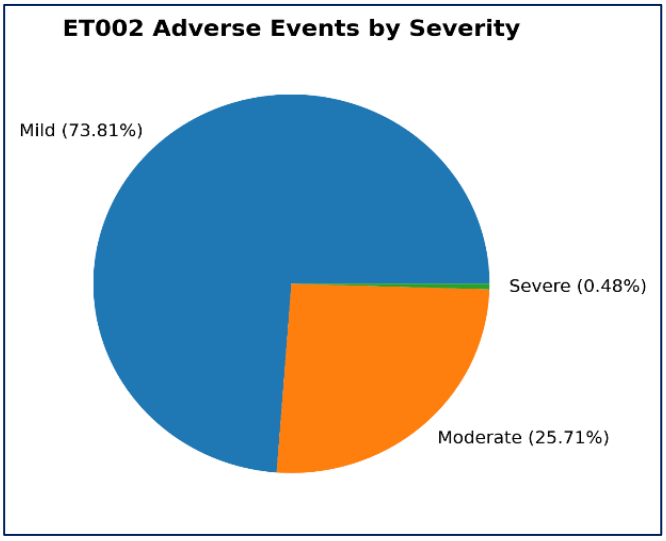


Figure 73. ET002 Adverse Events by Severity (Index Unilateral Thalamotomy in ET Patients)

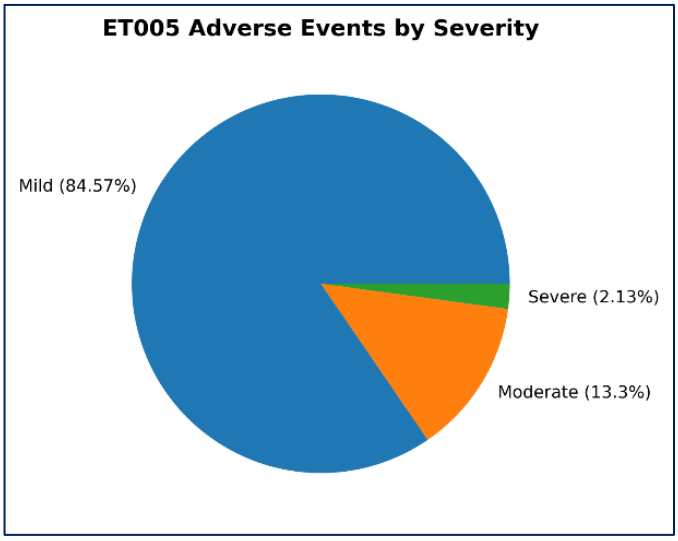


Figure 74. ET005 Adverse Events by Severity (Staged "Unilateral" Thalamotomy in ET Patients)

In summary, the pivotal ET005 study results support the safety and effectiveness of the Exablate device used for the staged, bilateral treatment of idiopathic Essential tremor patients with medication-refractory tremor.

CHAPTER 9: CONTINUED ACCESS STUDY FOR ESSENTIAL TREMOR WITH 5-YEAR FOLLOW-UP DATA

9.1 Study Purpose and Design

This section presents the results of the Post-Approval Study (PAS), ET002-CA (Continued Access), from enrollment and Exablate treatment for Essential Tremor through long term 5 Year follow up.

ET002-CA study was requested by Insightec and approved by FDA under IDE # G120246/S007 to continue Exablate thalamotomy procedures. Subjects were recruited as per the IDE trial inclusion/exclusion criteria. Treatment was performed in an open-label fashion for all subjects in this ET002-CA study. Follow-up schedules were also no different from the original IDE (G120246) schedule. ET002-CA was a prospective, open-label, multi-center study to treat up to 100 subjects at up to 10 sites.

The planned follow-up in the ET002 CA was continuous from the time of enrollment and treatment to the 5 Year visit (**Table 104**).

Table 104 ET002CA Summary of Study Schedules and Measurements

	Screening	Baseline Assessment*	Treatment	1 Day	1 Week	1 Month	3 Month	6 Month	12 Month	2 Year – 5 Year
Consent	X									
Eligibility Evaluation with labs	X	X								
Medications	X	X	X	X	X	X	X	X	X	
30 day meds stabilization		X								
Medical History	X									
Physical Exam	X	X		X	X	X	X	X	X	X
Neurological status	X		X	X	X	X	X	X	X	
CRST	X					X	X	X	X	X
QOL (QUEST)	X	X				X	X	X	X	X
PHQ-9	X					X	X	X	X	
CT	X									
MR		X	X						X	
Treatment			X							
Adverse Events			X	X	X	X	X	X	X	X

Forms "UB-04 (In Patient subjects) or CMS-1500 (Out Patient subjects)		X	X	X	X	X	X	X	X	
Month 12 completion form									X	
Exit Form										X

Objectives and Study Design

The objective of this prospective, multi-site, single-arm, open-label study was to capture the efficacy of treatment using the Exablate 4000 System, Type 1.0/1.1 and to further demonstrate safety in subjects with medication-refractory tremor essential tremor (ET).

Safety: Evaluate the incidence and severity of adverse events (AEs) associated with Exablate thalamotomy treatment of medication-refractory ET

Effectiveness: Collect further evidence of the effectiveness of the Exablate thalamotomy of medication-refractory Essential Tremor (i.e., ET). Efficacy will be determined utilizing the Clinical Rating Scale for Tremor (CRST) in ET from examinations at Baseline and 3 Months post-Exablate treatment.

Assessments of primary efficacy endpoints compare the 3-month visit after Exablate procedure to Baseline measurements for clinical symptom relief in the same manner as performed for the pivotal trial. All Safety events of Exablate in the treatment of ET were collected for one year after Exablate treatment. Any ongoing adverse events after Month 12 were followed for resolution to end of study. This study was performed on either 1.5T or 3T MR scanners.

No hypothesis testing was proposed. Results are presented as summary statistics, e.g., percent, mean, standard deviation and 95% confidence intervals of percent change from Baseline (prior to treatment as in the Pivotal study/Chapter 3) to further support the safety and efficacy of the Exablate thalamotomy procedure.

9.2 Study Population, Eligibility Criteria

Patients with confirmed medication-refractory ET as confirmed by screening were eligible for this study.

9.2.1 Inclusion Criteria

1. Men and women age 22 years or older
2. Subjects who are able and willing to give consent and able to attend all study visits,
3. A diagnosis of ET as confirmed from clinical history and examination by a neurologist or neurosurgeon specialized in movement disorder
4. Tremor refractory to adequate trials of at least two medications, one of which should be a first line therapy of either propranolol or primidone. An adequate medication trial is defined as a

therapeutic dose of each medication or the development of side effects as the medication dose is titrated.

5. Following the 1-month medication stability period, subject must be on stable medication for tremor
6. The 1-Month stability period visit will be 1-month post consent date
7. *Vim* nucleus of thalamus can be targeted by the Exablate device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
8. Able to communicate sensations during the Exablate procedure
9. Postural or intention tremor severity score of greater than or equal to 2 in the dominant hand/arm as measured by the CRST rating scale while stable on medication.
10. May have bilateral appendicular tremor
11. Significant disability due to essential tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])
12. Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
13. Subjects on stable antidepressant medications for at least 3 months may be enrolled into this study (i.e., no change in medication drug or dosage for 3 months).

9.2.2 Exclusion Criteria

1. Subjects with unstable cardiac status including:
    - Unstable angina pectoris on medication
    - Subjects with documented myocardial infarction within six months of protocol entry
    - Significant congestive heart failure defined with ejection fraction < 40
    - Subjects with unstable ventricular arrhythmias
    - Subjects with atrial arrhythmias that are not rate-controlled
2. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within a 12 month period:
    - Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).

- Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
- Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

3. Severe hypertension (diastolic BP > 100 on medication)
4. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
5. Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease
6. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m^2 (or per local standards should that be more restrictive) and/or who is on dialysis;
7. History of abnormal bleeding and/or coagulopathy
8. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
9. Active or suspected acute or chronic uncontrolled infection
10. History of immunocompromise including those who are HIV positive.
11. History of intracranial hemorrhage
12. Cerebrovascular disease (multiple CVA or CVA within 6 months)
13. Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).
14. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment
15. Are participating or have participated in another clinical trial in the last 30 days
16. Significant claustrophobia that cannot be managed with mild medication.
17. Subjects unable to communicate with the investigator and staff.
18. Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
19. Anyone suspected to have the diagnosis of idiopathic Parkinson's disease. Anyone with the presence of parkinsonian features including bradykinesia, rigidity, or postural instability will be

excluded. Subjects who exhibit only mild resting tremor but no other symptoms or signs of PD may be included.

20. Presence of significant cognitive impairment as determined with a score ≤ 24 on the Mini Mental Status Examination (MMSE)
21. Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
22. Subjects with a history of seizures within the past year
23. Subjects with presence or history of psychosis will be excluded. Subjects with significant or active mood disorders including depression will be excluded. For the purpose of this study, we consider a significant mood disorder to include any subject who:
    - Scores ≥ 20 on the PHQ-9 questionnaire
    - Is currently under the care of a psychiatrist
    - Is currently participating in cognitive-behavioral therapy
    - Has been hospitalized for the treatment of a psychiatric illness within 12 months
    - Has ever received transcranial magnetic stimulation
    - Has ever received electroconvulsive therapy
24. Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimeter, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
25. Subjects with brain tumors
26. Any illness that in the investigator's opinion preclude participation in this study.
27. Pregnancy or lactation.
28. Legal incapacity or limited legal capacity.
29. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
30. Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
31. Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening CT.

9.3 Long-term Study Follow Up

Participating subjects were consented for follow-up through 5 years. Subjects were initially seen for follow-up at 1 Day, 1 Week 1 Month, 3 Month, 6 Month and 12 Month visits. The post 12 Month long term schedule and evaluations were not specified in the protocol and consent. At the 12 Month visit

the subjects underwent an MRI assessment and filled out a Study Completion Form. Subjects were reconsented for a long-term visit schedule with 2 Year, 3 Year, 4 Year and 5 Year long-term follow up visits. Subjects were evaluated for general health, efficacy measurements, Clinical Rating Scale for Tremor (CRST) and Quality of life in Essential Tremor (QUEST), as well as for device/procedure related AEs that occurred during the follow-up period by the study Neurologist/Neurosurgeon. **Table 103** includes the summary of the long-term study visit schedule and assessments.

TABLE 103. SUMMARY OF LONG-TERM STUDY SCHEDULE EVALUATIONS

	2 YEAR	3 YEAR	4 YEAR	5 YEAR
PHYSICAL EXAM	X	X	X	X
CRST	X	X	X	X
QUEST	X	X	X	X
ADVERSE EVENTS	X	X	X	X
EXIT FORM				X

9.4 Study Endpoints

9.4.1 Safety Endpoint

Adverse events were recorded and categorized according to severity, relationship to procedure and relationship to device.

For ET002CA – All adverse events were followed from treatment through resolution/end of study.

Standard Code of Federal Regulation definitions for Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) were used to assess AEs.

A Data Safety Monitoring Board was used to review all AEs on the study and on an emergent basis as needed. Their role was to evaluate the overall safety profile and all SAEs that occurred throughout the study and determine if they were related to the Exablate, or some other cause.

9.4.2 Effectiveness Endpoint

The algorithms used to compute the ET002CA study outcomes presented in this report are the same as those used in the PMA (PM150038) as defined in the Statistical Plan.

The CRST and QUEST score for each subject at each visit are compared to their own baseline assessment prior to treatment. Change from the original baseline before treatment is calculated at each visit for each patient and for each endpoint used in the study. The % change from baseline for each patient is

then averaged across all subjects for assessing the mean value and mean % change from baseline for each of the following outcomes which is assessed at 1 Day, 1 Week, 3 Month, 6 and 12 Month, and annually at 2 Year, 3 Year, 4 Year, and 5 Year visits as follows:

1. Tremor Motor Function (TM) using the Clinical Rating Scale for Tremors (CRST) Parts A + B
2. Upper Extremity Posture using the CRST Part A
3. Functional Disability using the CRST Part C
4. Quality of life using the Questionnaire for Essential Tremor (QUEST)

The Tremor Motor Function (TM) scores were calculated the same as in the pivotal trial using a validated, tremor rating scale: the Clinical Rating Scale for Tremors (CRST) for ET subjects, based upon subjects in whom unilateral Exablate lesioning is attempted (i.e., Intent-to-Treat analysis).

Thus, the CRST score implemented for this study is the average of 8 components, combining the three components of the tremor CRST Part-A with the five components of the Motor Functions of the CRST Part-B from the treated side of the body:

TM = Contralateral (CRST PART A + CRST PART B)

Part A = Rest + **Posture** + Action/Intention

Part B = **all** 5 motor functions

9.4.3 Study Sample Size

There was no statistical hypothesis or sample size determination for this study. All Exablate treated subjects were included in this continued access PAS follow-up study.

9.4.4 Study Analysis Population

All enrolled and treated subjects were included in the analysis.

9.4.5 Study Subject Accountability

Ninety-five subjects were screened, and 61 subjects were treated on the Continued Access protocol. Thirty-four subjects screen failed for the following reasons:

- SDR disqualification - 13 subjects (2251, 2254, 2257, 2263, 23251, 115253, 115256, 115259, 115263, 43259, 106255, 120253, 112266)
- Cognitive impairment – 4 subjects (2255, 2259, 115251, 106260)
- FU Visit schedule: 2 subjects (112260, 106259)
- Misdiagnosed-had PD – 2 subjects (115267, 111254)
- Personal Health issues/claustrophobia/anxiety/kyphosis – 7 subjects (115264, 43252, 43254,

43260, 112257, 120252, 111255)

- Opted for DBS – 4 subjects (43256, 32357, 43258, 111251)
- Study closed prior to treatment – 1 subject (43264)
- Subject withdrew for own personal reasons (120255)

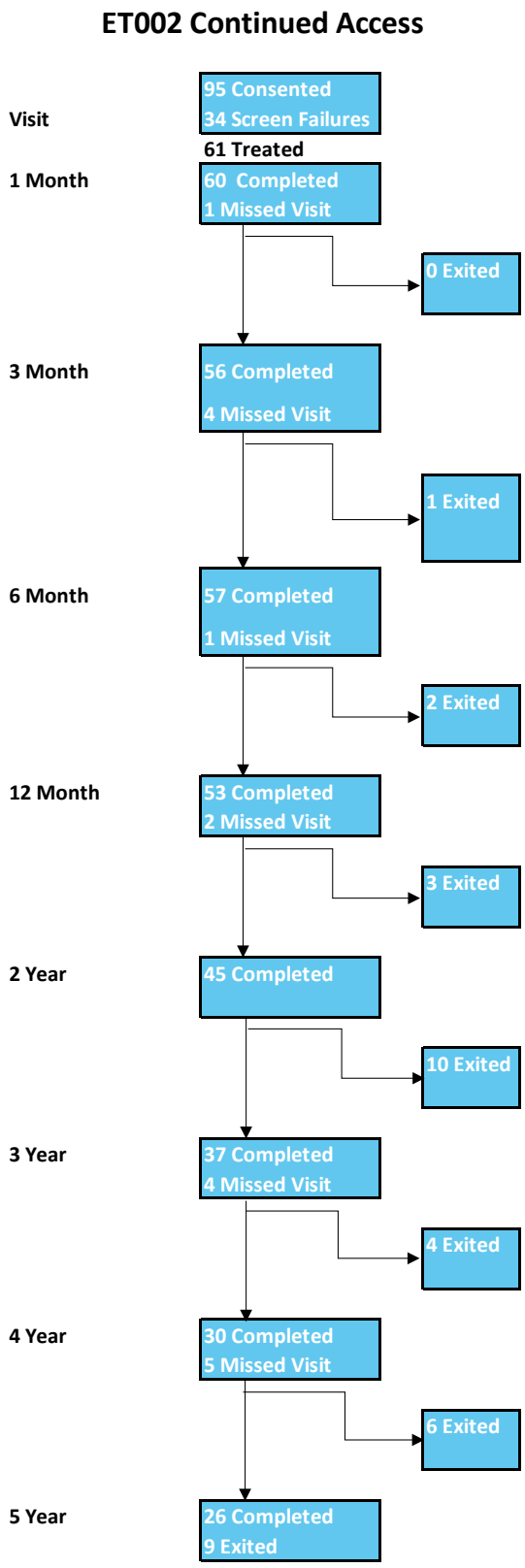


Figure 81. Subject participation in study visits through five years follow up ET002CA.

Sixty-one subjects were treated and continued through 3 Month follow up. One subject exited at the 3 Month visit and 60 continued into the 6 Month visit. Two subjects exited at the 6 Month, thus 58 continued into the 12 Month visit. Thus, 55 subjects continued into the annual 2 Year through 5 Year5 follow up.

Table 104 shows the subject disposition across the visit schedule.

Table 104 ET002CA Subject Accountability by Study Visit										
	Baseline	Treatment	1 Month FU	3 Month FU	6 Month FU	12 Month FU	2 Year FU	3 Year FU	4 Year FU	**5 Year FU**
Consented	95									
Screening Failure	34									
Theoretical	61	61	61	61	60	58	55	45	41	**35**
Exited	0	0	0	1	2	3	10	4	6	**9**
Expected	**61**	**61**	**61**	**60**	**58**	**55**	**45**	**41**	**35**	**26**
Missed Visit	0	0	1	4	1	2	0	4	5	**0**
Actual	61	61	60	56	57	53	45	37	30	**26**
Actual/Expected %	**100%**	**100%**	**98%**	**93%**	**98%**	**96%**	**100%**	**90%**	**86%**	**100%**

Table 105 shows the reasons subjects that exited the ET002CA study by study visit.

TABLE 105 SUBJECT EXIT BY REASON

Category	3 MONTH FU	6 MONTH FU	12 MONTH FU	2 YEAR FU	3 YEAR FU	4 YEAR FU	5 YEAR FU
Lost to follow-up	1	1	1	0	0	1	2
Alternative treatment received	0	0	1	2	0	1	0
Treatment failure	0	0	1	1	0	0	0
Other –not related to study	0	1	0	7	4	4	7
Total	1	2	3	10	4	6	9

Lost to follow up: site was unable to contact subject (6 subjects).

- 43251, 115265, 106261, 120251, 115257, 106253

Alternative treatment: subject had a follow-up treatment such as DBS or 2nd Exablate (4 subjects).

- 106256, 43255, 111253, 112263

Treatment failure: subject did not receive an effective treatment (2 subjects).

- 43266, 43253

Other- personal or health reasons specified by subject as unrelated, travel burden/restrictions and COVID-19 pandemic, PI resigned (23 subjects).

- 115257
- 115266
- 115254
- 115260
- 2260
- 112264
- 2252
- 23252
- 23254
- 23255
- 43263
- 106252
- 106262
- 106254
- 2261
- 115258
- 111252
- 115262
- 120254
- 115255
- 106257
- 112251
- 112252

9.5 Results

9.5.1 Baseline Characteristics

Sixty-one subjects were treated under the Continued Access study (N=61). **Table 106** presents the subject recruitment by site for the ET002CA study.

Table 106 Subject Enrollment in ET002CA under G#120246	
Site	**Enrollment**
BWH	7
Cornell	4
OSU	10
Stanford	9
Swedish	5
UMD	13
UVA	10
UPenn	3
Total	61

The demographic data for the enrolled and treated subjects is presented in **Table 107.**

Table 107. Demographic and Baseline Characteristics of the ET002CA Treatment Group		
Characteristics		**ET002CA N=61**
Age (Yrs.)	Mean	69.5[a]
Gender	Male	41 (67%)
	Female	20 (33%)
Race	White	57 (93%)
	Hispanic	0
	Black	0
	Asian	3 (5%)
	Other	1 (2%)
Family History of ET	Yes	45 (74%)
	No	15 (25%)[b]
Years ET History	Mean	19.5
Mean Skull Density Ratio	Mean	0.54[c]
CRST Tremor Motor Score	Mean (standard deviation)	19.0 (4.9)

QUEST	Mean (standard deviation)	42.9 (17.4)
[a]Birthdate was not reported for 3 subjects. [b]Family History was not reported for 1 subject. [c]SDR was missing for 4 subjects prior to implementation of SDR.		

9.5.2 Safety Results

The investigators recorded and categorized AEs according to severity, relationship to procedure and relationship to device. All AEs were assessed for their relationship to the study device or procedure. Standard Code of Federal Regulation definitions for Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) were used in assessment of AEs.

Standard Code of Federal Regulation (CFR) definitions for Serious Adverse Events (SAEs) was used for evaluation of adverse events.

- *SAE [§803.3(aa) (1)] is an injury or illness that:*
- *causes death*
- *is life threatening, even if temporary in nature;*
- *results in permanent impairment of a body function or permanent damage to a body structure; or*
- *necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.*

Standard Code of Federal Regulation (CFR) definitions for Unanticipated Adverse Device Effects (UADEs) was used for evaluation of this type of adverse event.

> *UADE [§812.3(s)] means any serious adverse event on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.*

Tables 108 and 109 below combine all adverse events reported *since the beginning of the study*. The adverse event profile of the ET002CA cohort continues to be favorable and appears relatively benign. All events were expected. By far, most events are transient and resolved on the same day or within a few days. There were 325 total events, of which 238 (73%, 238/325) were Mild, 66 (20%, 66/325) were Moderate, and 15 (5%, 15/325) were Severe; (there were 4 (1%) Life-threatening events, two (0.6%) severity was unknown). Furthermore, 2% (1/61) of subjects experienced no adverse events.

All adverse events reported in the studies were coded in terms of relationship to the device and or procedure as follows:

- Transient Side Effects: Transient events are those events that last seconds to less than 72 hours

and resolve completely. These events are often solicited during sonications and help the physician to locate the desired ablative target.

- Procedure-Related Adverse Effects: (i.e., lasting longer than 72 hours) or are related to the procedure, such as fatigue, headache, or nausea/vomiting.
- Thalamotomy Adverse Effects: Thalamotomy side effects are events commonly reported in the literature for ablation and stimulation techniques and may include tingling/numbness, gait disturbance/imbalance, speech issues, etc.
- Unrelated Adverse Events: These 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.
- Disease Related Progression: Events that are commonly associated with worsening Essential Tremor.
- Device Related Adverse Effects: Events are caused specifically by the Exablate Neuro and cause harm to a subject, such as mistargeting or misdirection of energy. In this study there were no device related side effects.

Table 108 and **Table 109** below present ALL the AEs collected under this Continued Access (ET002CA) effort in terms of frequency, incidence, and severity.

Table 108 shows the safety profile for the continued access study is very similar to that previously reported in the PMA for the Main and Crossover groups. As shown below, nearly one third of events (100/325 = 30.8% in 42 subjects) was Transient, another third of the events (103/325=31.7% in 49 subjects was Unrelated and another third (93/325=28.6% in 46 subjects was thalamotomy related). Less than 10% (28/325 = 8.6%) in 22 subjects was procedure related and one event was related to disease progression.

The severity of events was primarily Mild (239/325 =73.5%) or Moderate (67/325 = 20.5%). Fifteen (15/325 = 4.6%) events were reported as Severe of which four events were thalamotomy-related (2 imbalance, 1 dysarthria, 1 dysmetria). Four (4/325 = 1%) events were reported as Life-threatening, but all were Unrelated to device or procedure.

Two serious adverse events were reported on study:

- Additionally, one subject with comorbid chronic inflammatory demyelinating polyneuropathy (CIDP neuropathy) was treated and developed gait imbalance and dysmetria of the upper extremities and right lower extremity which worsened over time and was determined to be related to the thalamotomy procedure.
- Another subject was treated with Exablate thalamotomy and with no prior cardiac symptoms developed a myocardial infarction post-procedure which was determined to be procedure

related. The subject was treated for the myocardial infarction and subsequently did well with tremor relief and no further cardiac issues.

Table 108. Summary of Events by grouping term and severity.

GROUPING	Frequency	Incidence	SEVERITY			
			MILD	MODERATE	SEVERE	LIFE THREATENING
TOTAL TRANSIENT	100 (30.8%)	42 (68.9%)	81	15	4	0
TOTAL UNRELATED	103 (31.7%)	49 (80.3%)	54	38	7	4
TOTAL PROCEDURE RELATED	28 (8.6%)	22 (36.1%)	24	4	0	0
TOTAL THALAMOTOMY RELATED	93 (28.6%)	46 (75.4%)	79	10	4	0
TOTAL DISEASE PROGRESSION	1 (0.3%)	1 (1.6%)	1	0	0	0
TOTAL	325 (100%)	60 (98.4%)	239	67	15	4

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
Transient	Cardiovascular	Hypertension	3 (0.9%)	3 (4.9%)	3	0	0	0
		Supraventricular Tachycardia	1 (0.3%)	1 (1.6%)	0	0	1	0
	EENT	Double Vision	1 (0.3%)	1 (1.6%)	1	0	0	0
	Gastrointestinal	Nausea/Vomiting	7 (2.2%)	7 (11.5%)	5	2	0	0
	General	Fatigue	2 (0.6%)	2 (3.3%)	0	1	1	0
	Musculoskeletal	Fall	4 (1.2%)	4 (6.6%)	3	1	0	0
		Leg Cramp	1 (0.3%)	1 (1.6%)	0	1	0	0
		Leg Pain	1 (0.3%)	1 (1.6%)	0	1	0	0
		Positional Pain	2 (0.6%)	2 (3.3%)	2	0	0	0
	Nervous	Dysarthria	1 (0.3%)	1 (1.6%)	1	0	0	0
		Imbalance	1 (0.3%)	1 (1.6%)	1	0	0	0
		Numbness/Tingling	16 (5%)	12 (19.7%)	16	0	0	0
		TIA	1 (0.3%)	1 (1.6%)	0	0	1	0
	Pain/Discomfort	Ear Pain	1 (0.3%)	1 (1.6%)	1	0	0	0
		Headache	14 (4.3%)	14 (23%)	10	4	0	0
		Pin site pain	1 (0.3%)	1 (1.6%)	0	1	0	0
		Sonication related pain	25 (7.7%)	17 (27.9%)	21	3	1	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
	Psychological	Disoriented	1 (0.3%)	1 (1.6%)	1	0	0	0
	Stereotactic Frame	Bleeding at Pin Site	2 (0.6%)	2 (3.3%)	2	0	0	0
		Drooping eyelid	1 (0.3%)	1 (1.6%)	1	0	0	0
		Pin site pain	2 (0.6%)	2 (3.3%)	2	0	0	0
	Vestibular	Dizziness	9 (2.8%)	9 (14.8%)	9	0	0	0
		Imbalance	2 (0.6%)	2 (3.3%)	2	0	0	0
		Vertigo	1 (0.3%)	1 (1.6%)	0	1	0	0
TOTAL TRANSIENT			100 (30.8%)	42 (68.9%)	81	15	4	0
Unrelated	Cardiovascular	Acute CVA	1 (0.3%)	1 (1.6%)	0	0	0	1
		Arrhythmia	1 (0.3%)	1 (1.6%)	1	0	0	0
		Atrial fibrilation	1 (0.3%)	1 (1.6%)	0	1	0	0
		Bradycardia	1 (0.3%)	1 (1.6%)	0	0	1	0
		Heart Murmur	1 (0.3%)	1 (1.6%)	0	1	0	0
		Myocardial Infarction	1 (0.3%)	1 (1.6%)	0	1	0	0
		Pulmonary embolism	1 (0.3%)	1 (1.6%)	0	1	0	0
		Syncope	1 (0.3%)	1 (1.6%)	0	1	0	0
		Thrombocytosis	1 (0.3%)	1 (1.6%)	0	1	0	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
	Death	Death	2 (0.6%)	2 (3.3%)	0	0	0	2
		Lost Tooth Implant	1 (0.3%)	1 (1.6%)	1	0	0	0
	Dental	Tooth Pain	1 (0.3%)	1 (1.6%)	0	1	0	0
	EENT	Eye Floaters	1 (0.3%)	1 (1.6%)	1	0	0	0
		Decreased vision	1 (0.3%)	1 (1.6%)	1	0	0	0
		Double Vision	1 (0.3%)	1 (1.6%)	0	1	0	0
		Hearing muffled	1 (0.3%)	1 (1.6%)	1	0	0	0
		Nosebleed	1 (0.3%)	1 (1.6%)	0	1	0	0
		Sore Throat	1 (0.3%)	1 (1.6%)	1	0	0	0
	Gastrointestinal	Cholelithiasis	1 (0.3%)	1 (1.6%)	0	0	1	0
		Hypogeusia	1 (0.3%)	1 (1.6%)	1	0	0	0
		Hyposmia	1 (0.3%)	1 (1.6%)	1	0	0	0
		Increased salivation / drooling	3 (0.9%)	3 (4.9%)	3	0	0	0
		Loose Stool	1 (0.3%)	1 (1.6%)	1	0	0	0
		Swallowing Difficulty	1 (0.3%)	1 (1.6%)	1	0	0	0
	General	Agitation	1 (0.3%)	1 (1.6%)	1	0	0	0
		Decreased Appetite	1 (0.3%)	1 (1.6%)	1	0	0	0
		Grave's Disease	1 (0.3%)	1	0	1	0	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Insomnia	1 (0.3%)	1 (1.6%)	1	0	0	0
	Infection	Bronchitis	1 (0.3%)	1 (1.6%)	0	1	0	0
		Colitis	1 (0.3%)	1 (1.6%)	0	1	0	0
		Viral Infection	1 (0.3%)	1 (1.6%)	1	0	0	0
		Hepatitis C	1 (0.3%)	1 (1.6%)	0	1	0	0
		Nasal Inflammation	1 (0.3%)	1 (1.6%)	0	1	0	0
		Pneumonia	2 (0.6%)	2 (3.3%)	0	2	0	0
		Fingernail Fungus	1 (0.3%)	1 (1.6%)	1	0	0	0
	Musculoskeletal	Arthritis	1 (0.3%)	1 (1.6%)	1	0	0	0
		Bone Fracture	3 (0.9%)	3 (4.9%)	0	2	0	0
		Carpel Tunnel	1 (0.3%)	1 (1.6%)	0	0	1	0
		Death	1 (0.3%)	1 (1.6%)	0	0	0	1
		Deconditioned Physically	1 (0.3%)	1 (1.6%)	0	1	0	0
		Gout	1 (0.3%)	1 (1.6%)	1	0	0	0
		Hand Injury	1 (0.3%)	1 (1.6%)	0	1	0	0
		Hand Swelling	1 (0.3%)	1 (1.6%)	0	1	0	0
		Hip Fracture	1 (0.3%)	1 (1.6%)	0	0	1	0
		Hip Replacement	1 (0.3%)		0	0	1	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Knee Injury	1 (0.3%)	1 (1.6%)	0	1	0	0
		Knee Problem	1 (0.3%)	1 (1.6%)	1	0	0	0
		Leg Cramp	2 (0.6%)	1 (1.6%)	0	2	0	0
		Meniscus Surgery	1 (0.3%)	1 (1.6%)	0	0	1	0
		Muscle Spasm	1 (0.3%)	1 (1.6%)	1	0	0	0
		Muscle Twitch	1 (0.3%)	1 (1.6%)	1	0	0	0
		Musculoskeletal Weakness	1 (0.3%)	1 (1.6%)	1	0	0	0
		Left Rotator Pain	1 (0.3%)	1 (1.6%)	1	0	0	0
		Planter fasciitis	1 (0.3%)	1 (1.6%)	1	0	0	0
		Rib Fracture*	1 (0.3%)	1 (1.6%)	0	1	0	0
		Shoulder Pain	1 (0.3%)	1 (1.6%)	1	0	0	0
		Tightness in the Legs	1 (0.3%)	1 (1.6%)	1	0	0	0
	Nervous	Dysmetria	1 (0.3%)	1 (1.6%)	1	0	0	0
		Dysphonia	1 (0.3%)	1 (1.6%)	1	0	0	0
		Headache	2 (0.6%)	2 (3.3%)	2	0	0	0
		Numbness/Tingling	2 (0.6%)	2 (3.3%)	1	1	0	0
		Parkinson's Disease	1 (0.3%)	1 (1.6%)	0	1	0	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Short-Term Memory Decline	1 (0.3%)	1 (1.6%)	1	0	0	0
	Pain/Discomfort	Headache	2 (0.6%)	2 (3.3%)	0	2	0	0
		Neck Pain	1 (0.3%)	1	0	1	0	0
		Other Musculoskeletal Pain	1 (0.3%)	1 (1.6%)	1	0	0	0
		Positional Pain	1 (0.3%)	1 (1.6%)	0	1	0	0
		Radiculopathy	1 (0.3%)	1	0	1	0	0
		Shoulder Pain	2 (0.6%)	2 (3.3%)	2	0	0	0
	Psychological	Anxiety Disorder	1 (0.3%)	1 (1.6%)	1	0	0	0
	Respiratory	Lung nodules	1 (0.3%)	1 (1.6%)	0	1	0	0
	Skin/Dermatologic	Basal Cell Carcinoma	1 (0.3%)	1 (1.6%)	0	1	0	0
		Erythema	2 (0.6%)	2 (3.3%)	2	0	0	0
		Itching	1 (0.3%)	1 (1.6%)	1	0	0	0
		Skin Lesion	1 (0.3%)	1 (1.6%)	1	0	0	0
		Sebaceous Cyst	1 (0.3%)	1 (1.6%)	0	1	0	0
	Stereotactic Frame	Edema	1 (0.3%)	1 (1.6%)	1	0	0	0
		Facial Edema	4 (1.2%)	4 (6.6%)	3	1	0	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Musculoskeletal Weakness	1 (0.3%)	1 (1.6%)	1	0	0	0
		Pin Site Numbness	2 (0.6%)	2 (3.3%)	2	0	0	0
		Pin site pain	2 (0.6%)	2 (3.3%)	2	0	0	0
	Urinary	Urinary Tract Infection	2 (0.6%)	2 (3.3%)	0	1	1	0
		Urinary Urgency	2 (0.6%)	2 (3.3%)	2	0	0	0
	Vestibular	Dizziness	1 (0.3%)	1 (1.6%)	1	0	0	0
		Vertigo	1 (0.3%)	1 (1.6%)	0	1	0	0
TOTAL UNRELATED			103 (31.7%)	49 (80.3%)	54	38	7	4
Procedure Related	Gastrointestinal	Nausea/Vomiting	2 (0.6%)	2 (3.3%)	1	1	0	0
	General	Fatigue	5 (1.6%)	5 (8.2%)	5	0	0	0
		Lethargy	1 (0.3%)	1 (1.6%)	1	0	0	0
	Infection	IV site Infection	1 (0.3%)	1 (1.6%)	0	1	0	0
	Nervous	Headache	1 (0.3%)	1 (1.6%)	1	0	0	0
		Imbalance	1 (0.3%)	1 (1.6%)	1	0	0	0
		Numbness/Tingling	1 (0.3%)	1 (1.6%)	1	0	0	0
	Pain/Discomfort	Headache	5 (1.6%)	5 (8.2%)	5	0	0	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Jaw Pain	1 (0.3%)	1 (1.6%)	1	0	0	0
	Unknown	Edema	1 (0.3%)	1 (1.6%)	0	1	0	0
	Vestibular	Imbalance	9 (2.8%)	9 (14.8%)	8	1	0	0
TOTAL PROCEDURE RELATED			28 (8.6%)	22 (36.1%)	24	4	0	0
Thalamotomy Related	Dental	Dysgnathia	2 (0.6%)	2 (3.3%)	2	0	0	0
	EENT	Vision Problem	2 (0.6%)	2 (3.3%)	0	2	0	0
	Musculoskeletal	Fall	1 (0.3%)	1 (1.6%)	1	0	0	0
		Hemi-body muscle weakness	1 (0.3%)	1 (1.6%)	1	0	0	0
		Imbalance	2 (0.6%)	2 (3.3%)	1	0	1	0
		Musculoskeletal Weakness	1 (0.3%)	1 (1.6%)	1	0	0	0
		Myoclonus	1 (0.3%)	1 (1.6%)	0	1	0	0
	Nervous	Ataxia	10 (3.1%)	10 (16.4%)	7	2	1	0
		Dysarthria	7 (2.2%)	7 (11.5%)	6	1	0	0
		Dysgeusia	6 (1.8%)	6 (9.8%)	5	1	0	0
		Dysmetria	9 (2.8%)	7 (11.5%)	7	1	1	0

Table 109. ET002CA Continued Access Cohort Adverse Events Coded by Frequency, Incidence and Severity

GROUPING	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	SEVERITY			
					MILD	MODERATE	SEVERE	LIFE THREATENING
		Gait Disturbance	9 (2.8%)	9 (14.8%)	8	1	0	0
		Imbalance	11 (3.4%)	11 (18%)	10	0	1	0
		Numbness/Tingling	29 (9%)	20 (32.8%)	28	1	0	0
		Slurred Speech	1 (0.3%)	1 (1.6%)	1	0	0	0
		Unclear thinking	1 (0.3%)	1 (1.6%)	1	0	0	0
TOTAL THALAMOTOMY RELATED			93 (28.6%)	46 (75.4%)	79	10	4	0
Disease Progression	Nervous	Worsening Tremor	1 (0.3%)	1 (1.6%)	1	0	0	0
TOTAL DISEASE PROGRESSION			1 (0.3%)	1 (1.6%)	1	0	0	0
TOTAL			325(100%)	60 (98.4%)	239	67	15	4

Table 110 shows the number of events experienced by study subjects. One (1) out of the 61 (2%) subjects reported no adverse events. The range of events per subject was 1-13 and five subjects experienced 10 or more over the life of the study.

Table 110. Frequency of Adverse Events per Subject

#AEs	#Subjects
0	1
1	3
2	5
3	10
4	8
5	8
6	10
7	5
8	4
9	2
≥ 10	5
Total	61

9.5.2.1 Status of procedure and Thalamotomy Related Events by Year Post Thalamotomy

The status of Thalamotomy and Procedure Related AEs annually through 5 Year follow up is detailed in **Table 111**. The status of Aes was categorized as Ongoing, Resolved or Censored in cases where the subject exited the study and the event could no longer be followed.

- 1 Year – A total of 121 Procedure (28) + and Thalamotomy (93) related (28 + 93 = 121) events in 52 subjects occurred in the first-year post-thalamotomy.
    - Sixty-three out of the 121 resolved within the first year (19 out of 28 procedure-related and 44 out of 93 thalamotomy-related events).
    - Ten events were censored for 6 subjects exiting the study and their adverse events could no longer be followed.

- Forty-eight events in 25 subjects remained ongoing at the end of the first-year post Exablate (7 procedure-related and 41 thalamotomy-related events)

- 2 Year –
  - An additional 3 events (1 procedure-related, 2 thalamotomy-related) resolved in Year 2.
  - One thalamotomy-related event was censored due to subject exit.
  - Forty-four events remained ongoing at the end of Year 2 (6 procedure-related and 38 thalamotomy-related events).
- 3 Year –
  - One procedure-related event resolved in Year 3.
  - Eleven thalamotomy-related events in five subjects were censored due to subjects exiting the study.
  - At the end pf Year 3, 32 events in 17 subjects remained ongoing.
- 4 Year –
  - One thalamotomy-related event of dysmetria resolved in Year 4.
  - Five events were censored due to the exit of 4 subjects.
  - Twenty-five events in 13 subjects were ongoing at the end of Year 4.
- 5 Year –
  - In the 5 Year visit, two procedure-related events and six thalamotomy-related events in four subjects resolved.
  - At the end of the study nineteen adverse events in 11 subjects were still ongoing.

Overall, at the end of the study, out of the 121 procedure- and thalamotomy-related events, 75 (62%) resolved, 19 (16%) were ongoing and 27 (22%) were censored due to subjects exiting the study.

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
1 Year	ONGOING	Procedure Related	General	Fatigue	2	2	2	2				
			General Total		2	2	2	2				
			Vestibular	Imbalance	5	5	5	5				
			Vestibular Total		5	5	5	5				
		Procedure Related Total			7	6	7	6				
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Musculoskeletal	Imbalance	2	2	1	1			1	1
				Myoclonus	1	1			1	1		
			Musculoskeletal Total		3	3	1	1	1	1	1	1
			Nervous	Ataxia	4	4	1	1	2	2	1	1
				Dysarthria	1	1	1	1				
				Dysgeusia	2	2	1	1	1	1		
				Dysmetria	7	4	5	4	1	1	1	1
				Gait Disturbance	5	5	4	4	1	1		
				Imbalance	4	4	3	3			1	1
				Numbness/Tingling	12	9	11	8	1	1		
				Slurred Speech	1	1	1	1				
			Nervous Total		36	21	27	18	6	5	3	2
		Thalamotomy Related Total			41	23	29	19	8	7	4	3
	ONGOING Total				48	25	36	21	8	7	4	3

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
	RESOLVED	Procedure Related	Gastrointestinal	Nausea/Vomiting	2	2	1	1	1	1		
			Gastrointestinal Total		2	2	1	1	1	1		
			General	Fatigue	3	3	3	3				
				Lethargy	1	1	1	1				
			General Total		4	4	4	4				
			Infection	IV site Infection	1	1			1	1		
			Infection Total		1	1			1	1		
			Nervous	Headache	1	1	1	1				
				Imbalance	1	1	1	1				
				Numbness/Tingling	1	1	1	1				
			Nervous Total		3	3	3	3				
			Pain/Discomfort	Headache	4	4	4	4				
			Pain/Discomfort Total		4	4	4	4				
			Unknown	Edema	1	1			1	1		
			Unknown Total		1	1			1	1		
			Vestibular	Imbalance	4	4	3	3	1	1		
			Vestibular Total		4	4	3	3	1	1		
		Procedure Related Total			19	17	15	14	4	4		
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			Musculoskeletal	Hemi-body muscle weakness	1	1	1	1				
				Musculoskeletal Weakness	1	1	1	1				
			Musculoskeletal Total		2	2	2	2				
			Nervous	Ataxia	4	4	4	4				

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
				Dysarthria	4	4	4	4				
				Dysgeusia	4	4	4	4				
				Dysmetria	3	3	2	2	1	1		
				Gait Disturbance	4	4	4	4				
				Imbalance	5	5	5	5				
				Numbness/Tingling	16	11	16	11				
				Unclear thinking	1	1	1	1				
			Nervous Total		41	25	40	25	1	1		
		Thalamotomy Related Total			44	26	43	26	1	1		
	RESOLVED Total				63	34	58	33	5	5		
	CENSORED	Procedure Related	Pain/Discomfort	Headache	1	1	1	1				
				Jaw Pain	1	1	1	1				
			Pain/Discomfort Total		2	1	2	1				
		Procedure Related Total			2	1	2	1				
		Thalamotomy Related	EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Nervous	Ataxia	2	2	2	2				
				Dysarthria	2	2	2	2				
				Imbalance	2	2	2	2				
				Numbness/Tingling	1	1	1	1				
			Nervous Total		7	5	7	5				
		Thalamotomy Related Total			8	5	7	5	1	1		
	CENSORED Total				10	6	9	6	1	1		

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
1 Year Total					121	52	103	48	14	13	4	3
2 Year	ONGOING	Procedure Related	General	Fatigue	2	2	2	2				
			General Total		2	2	2	2				
			Vestibular	Imbalance	4	4	4	4				
			Vestibular Total		4	4	4	4				
		Procedure Related Total			6	5	6	5				
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Musculoskeletal	Imbalance	1	1	1	1				
				Myoclonus	1	1			1	1		
			Musculoskeletal Total		2	2	1	1	1	1		
			Nervous	Ataxia	4	4	1	1	2	2	1	1
				Dysarthria	1	1	1	1				
				Dysgeusia	2	2	1	1	1	1		
				Dysmetria	7	4	5	4	1	1	1	1
				Gait Disturbance	5	5	4	4	1	1		
				Imbalance	4	4	3	3			1	1
				Numbness/Tingling	10	8	9	7	1	1		
				Slurred Speech	1	1	1	1				
			Nervous Total		34	20	25	17	6	5	3	2
		Thalamotomy Related Total			38	21	27	18	8	7	3	2

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
	ONGOING Total				44	22	33	19	8	7	3	2
	RESOLVED	Procedure Related	Vestibular	Imbalance	1	1	1	1				
			Vestibular Total		1	1	1	1				
		Procedure Related Total			1	1	1	1				
		Thalamotomy Related	Nervous	Numbness/Tingling	2	2	2	2				
			Nervous Total		2	2	2	2				
		Thalamotomy Related Total			2	2	2	2				
	RESOLVED Total				3	3	3	3				
	CENSORED	Thalamotomy Related	Musculoskeletal	Imbalance	1	1					1	1
			Musculoskeletal Total		1	1					1	1
		Thalamotomy Related Total			1	1					1	1
	CENSORED Total				1	1					1	1
2 Year Total					48	25	36	21	8	7	4	3
3 Year	ONGOING	Procedure Related	General	Fatigue	1	1	1	1				
			General Total		1	1	1	1				
			Vestibular	Imbalance	4	4	4	4				
			Vestibular Total		4	4	4	4				
		Procedure Related Total			5	5	5	5				

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Musculoskeletal	Imbalance	1	1	1	1				
				Myoclonus	1	1			1	1		
			Musculoskeletal Total		2	2	1	1	1	1		
			Nervous	Ataxia	1	1	1	1				
				Dysarthria	1	1	1	1				
				Dysgeusia	2	2	1	1	1	1		
				Dysmetria	5	3	4	3			1	1
				Gait Disturbance	2	2	2	2				
				Imbalance	3	3	2	2			1	1
				Numbness/Tingling	9	7	8	6	1	1		
			Nervous Total		23	15	19	14	2	2	2	1
		Thalamotomy Related Total			27	16	21	15	4	4	2	1
	ONGOING Total				32	17	26	16	4	4	2	1
	RESOLVED	Procedure Related	General	Fatigue	1	1	1	1				
			General Total		1	1	1	1				
		Procedure Related Total			1	1	1	1				
	RESOLVED Total				1	1	1	1				

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
	CENSORED	Thalamotomy Related	Nervous	Ataxia	3	3			2	2	1	1
				Dysmetria	2	1	1	1	1	1		
				Gait Disturbance	3	3	2	2	1	1		
				Imbalance	1	1	1	1				
				Numbness/Tingling	1	1	1	1				
				Slurred Speech	1	1	1	1				
			Nervous Total		11	5	6	3	4	3	1	1
		Thalamotomy Related Total			11	5	6	3	4	3	1	1
	CENSORED Total				11	5	6	3	4	3	1	1
3 Year Total					44	22	33	19	8	7	3	2
4 Year	ONGOING	Procedure Related	General	Fatigue	1	1	1	1				
			General Total		1	1	1	1				
			Vestibular	Imbalance	2	2	2	2				
			Vestibular Total		2	2	2	2				
		Procedure Related Total			3	3	3	3				
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Musculoskeletal	Imbalance	1	1	1	1				
				Myoclonus	1	1			1	1		

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
			Musculoskeletal Total		2	2	1	1	1	1		
			Nervous	Ataxia	1	1	1	1				
				Dysgeusia	2	2	1	1	1	1		
				Dysmetria	3	3	2	2			1	1
				Gait Disturbance	2	2	2	2				
				Imbalance	3	3	2	2			1	1
				Numbness/Tingling	7	5	6	4	1	1		
			Nervous Total		18	12	14	10	2	2	2	1
		Thalamotomy Related Total			22	13	16	11	4	4	2	1
		ONGOING Total			25	13	19	11	4	4	2	1
	RESOLVED	Thalamotomy Related	Nervous	Dysmetria	2	1	2	1				
			Nervous Total		2	1	2	1				
		Thalamotomy Related Total			2	1	2	1				
		RESOLVED Total			2	1	2	1				
	CENSORED	Procedure Related	Vestibular	Imbalance	2	2	2	2				
			Vestibular Total		2	2	2	2				
		Procedure Related Total			2	2	2	2				
		Thalamotomy Related	Nervous	Dysarthria	1	1	1	1				
				Numbness/Tingling	2	2	2	2				
			Nervous Total		3	3	3	3				
		Thalamotomy Related Total			3	3	3	3				

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
	CENSORED Total				5	4	5	4				
4 Year Total					32	17	26	16	4	4	2	1
9	ONGOING	Procedure Related	General	Fatigue	1	1	1	1				
			General Total		1	1	1	1				
		Procedure Related Total			1	1	1	1				
		Thalamotomy Related	Dental	Dysgnathia	1	1	1	1				
			Dental Total		1	1	1	1				
			EENT	Vision Problem	1	1			1	1		
			EENT Total		1	1			1	1		
			Musculoskeletal	Imbalance	1	1	1	1				
				Myoclonus	1	1			1	1		
			Musculoskeletal Total		2	2	1	1	1	1		
			Nervous	Ataxia	1	1	1	1				
				Dysgeusia	2	2	1	1	1	1		
				Dysmetria	3	3	2	2			1	1
				Gait Disturbance	1	1	1	1				
				Imbalance	2	2	1	1			1	1
				Numbness/Tingling	5	4	4	3	1	1		
			Nervous Total		14	10	10	8	2	2	2	1
		Thalamotomy Related Total			18	11	12	9	4	4	2	1
	ONGOING Total				19	11	13	9	4	4	2	1

Table 111. Status of Thalamotomy and Procedure Related Adverse Events Following Exablate Thalamotomy by Year							AE severity					
							Mild		Moderate		Severe	
Visit	AE STATUS	GROUPING TERM	CODED BODY SYSTEM	CODED AE TERM	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence	Frequency	Incidence
	RESOLVED	Procedure Related	Vestibular	Imbalance	2	2	2	2				
			Vestibular Total		2	2	2	2				
		Procedure Related Total			2	2	2	2				
		Thalamotomy Related	Nervous	Gait Disturbance	1	1	1	1				
				Imbalance	1	1	1	1				
				Numbness/Tingling	2	2	2	2				
			Nervous Total		4	4	4	4				
		Thalamotomy Related Total			4	4	4	4				
	RESOLVED Total				6	4	6	4				
9 Year Total					25	13	19	11	4	4	2	1

9.5.2.2 Summary of Safety

The safety profile of the Exablate thalamotomy procedure in the Exablate Continued Access Cohort is no different from the original study cohort :

- Approximately two-thirds of the adverse events are either transient, resolving in less than 72 hours or unrelated to the device and procedure. Ninety-four percent of the adverse events were mild or moderate in severity, mostly mild (74%).

9.5.3 Effectiveness Results

The Continued Access study endpoints were computed in the same manner as the original IDE study. The effectiveness data is presented graphically in a bar chart to demonstrate that the effect is durable over time.

9.5.3.1 Primary Endpoint – Tremor / Motor Function

For this report, we used the site assessor scoring across all time points for consistency through long-term follow-up visits. All available endpoints data is included in the analyses and figures presented below. The ET002CA analyses were prepared using observed data only.

The primary analysis that was presented in the PMA is Mean Score of the "CRST Part A treated arm tremor plus the Part B Tremor/Motor Function Scores" which is shown for ET002CA in **Figure 82** and **Table 112**. Percent change from Baseline is presented below in **Figure 83**. As the figures show, the Exablate thalamotomy effect is of similar magnitude and improved from the Baseline values as was expected based on the PMA pivotal results.

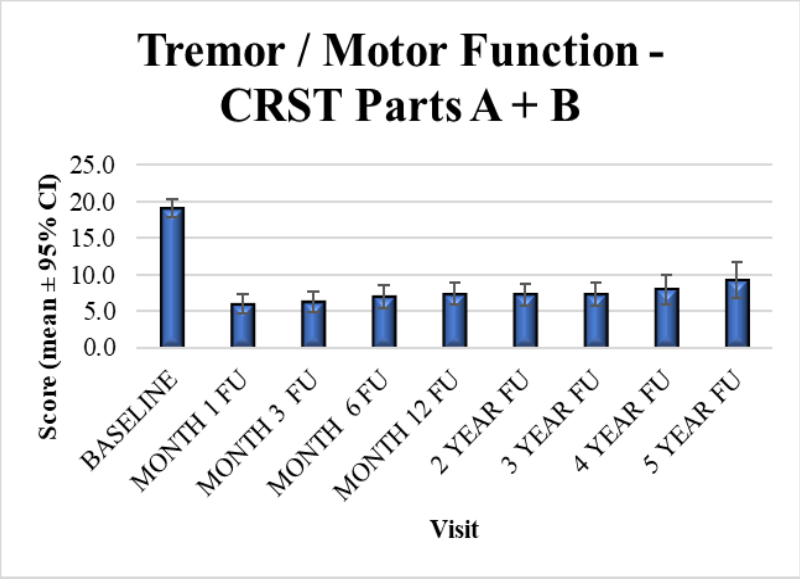


Figure 82. Tremor/Motor Function Scores for Part A Treated Upper Arm Tremor plus Part B Function. Lower scores indicate improvement in tremor.

Table 112 ET002CA Motor/Function Tremor by Visit.

TM Scores	BASELINE	MONTH 1 FU	MONTH 3 FU	MONTH 6 FU	MONTH 12 FU	2 YEAR FU	3 YEAR FU	4 YEAR FU	5 YEAR FU
mean	19.0	6.0	6.3	7.0	7.4	7.3	7.3	7.9	9.2
s.d.	4.90	5.08	5.34	5.94	5.73	5.10	4.91	5.73	6.16
n	61	60	55	55	53	45	35	31	23
95% CI	1.23	1.29	1.41	1.57	1.54	1.49	1.63	2.02	2.52
95% UL	20.26	7.24	7.70	8.57	8.90	8.78	8.91	9.95	11.73
95% LL	17.80	4.66	4.88	5.43	5.81	5.80	5.66	5.92	6.70

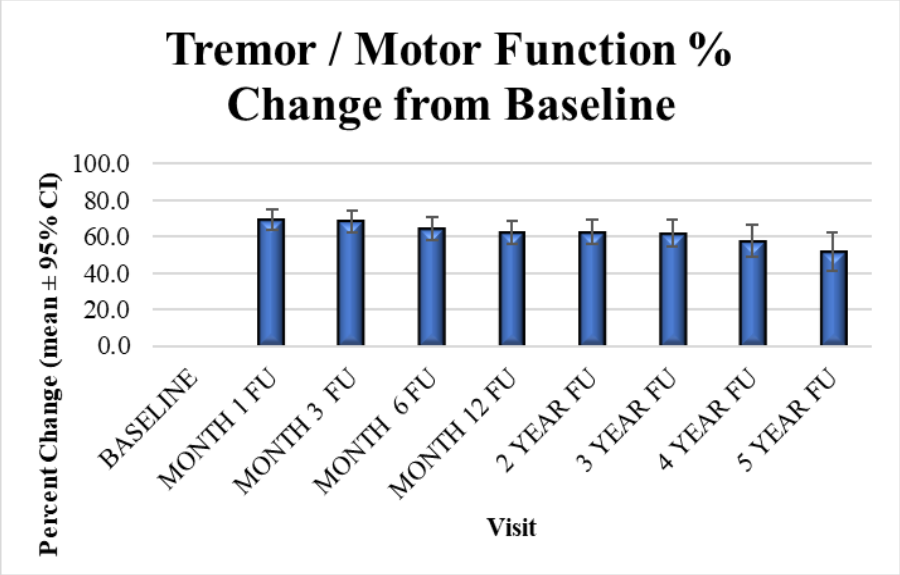


Figure 83. Percent Change from Baseline of Primary Endpoint – CRST Motor/Function Tremor for the Treated Arm Across Visits.

Figure-83 shows the %-change (improvement) from baseline of the Tremor/Motor Function component by study visit. The data shows a stable outcome across visits.

9.5.3.2 Secondary Endpoints – DRST Part A Posture

In **Figure 84** and **Table 113** below, the Posture score (the posture component of the CRST Part A treated arm) was also presented in the PMA. A lower score represents improvement. This measure also shows similar outcomes of improvement from Baseline across all time points. Percent change from Baseline in the Part A Posture scores is consistent at 70% improvement across time as presented below in **Figure 85**.

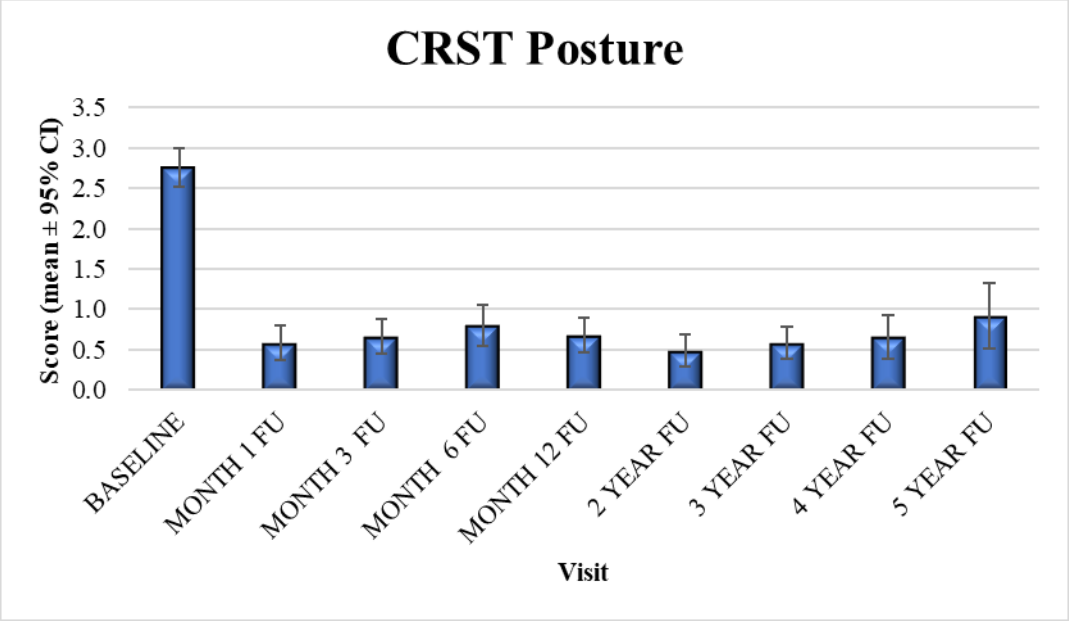


Figure 84. CRST Posture Component of the Treated Upper Arm by Study Visit. Lower scores indicate improvement in tremor

Table 113 Posture Score by Study Visit

Posture Scores	BASELINE	MONTH 1 FU	MONTH 3 FU	MONTH 6 FU	MONTH 12 FU	2 YEAR FU	3 YEAR FU	4 YEAR FU	5 YEAR FU
mean	2.8	0.6	0.7	0.8	0.7	0.5	0.6	0.7	0.9
s.d.	0.94	0.83	0.84	0.98	0.80	0.69	0.60	0.79	1.00
n	61	60	56	56	53	45	36	32	23
95% CI	0.24	0.21	0.22	0.26	0.22	0.20	0.20	0.27	0.41
95% UL	3.01	0.79	0.88	1.06	0.90	0.69	0.78	0.93	1.32
95% LL	2.54	0.37	0.44	0.55	0.46	0.29	0.39	0.38	0.51

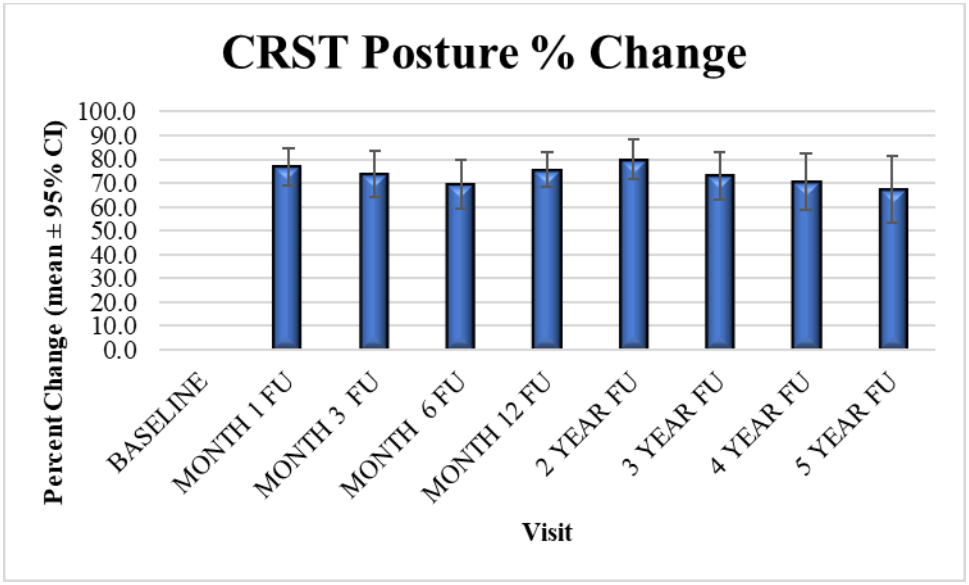


Figure 85. Percent change from baseline of CRST Posture Component of the Treated Upper Arm by by Study Visit

Figure-85 shows the %-change (improvement) from baseline of the CRST Posture component of the treated upper arm by study visit. The data shows a stable outcome across visits.

9.4.3.3 Secondary Endpoints – CRST Part C Activities of Daily Living

In **Figure 86** and **Table 114**, the CRST Part C Activities of Daily Living Scores showed a similar and repeated trend of improvement that was similar across all visits. A lower score is better than a higher score. Percent change from Baseline scores are presented below in **Figure 87**.

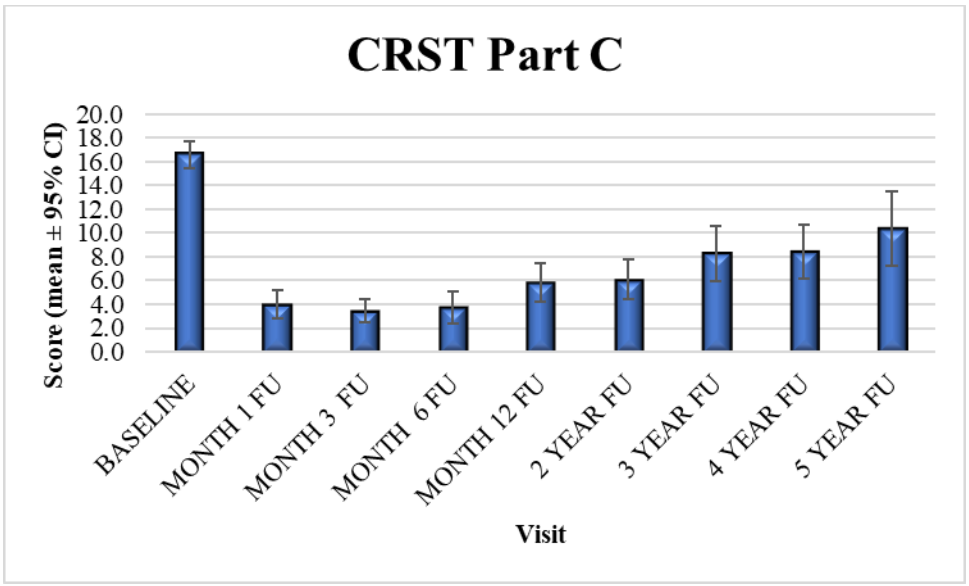


Figure 86. CRST Part C Activities of Daily Living.

Table 114 CRST Part C Score – Activities of Daily Living by Visit.

Part C Scores	BASELINE	MONTH 1 FU	MONTH 3 FU	MONTH 6 FU	MONTH 12 FU	2 YEAR FU	3 YEAR FU	4 YEAR FU	5 YEAR FU
mean	16.7	4.0	3.5	3.8	5.8	6.1	8.3	8.4	10.4
s.d.	4.87	4.66	3.81	5.13	6.07	5.73	7.05	6.61	7.66
n	61	60	56	56	53	45	35	32	23
95% CI	1.22	1.18	1.00	1.34	1.63	1.67	2.34	2.29	3.13
95% UL	17.91	5.19	4.46	5.09	7.46	7.74	10.62	10.70	13.52
95% LL	15.47	2.84	2.47	2.41	4.20	4.39	5.95	6.12	7.26

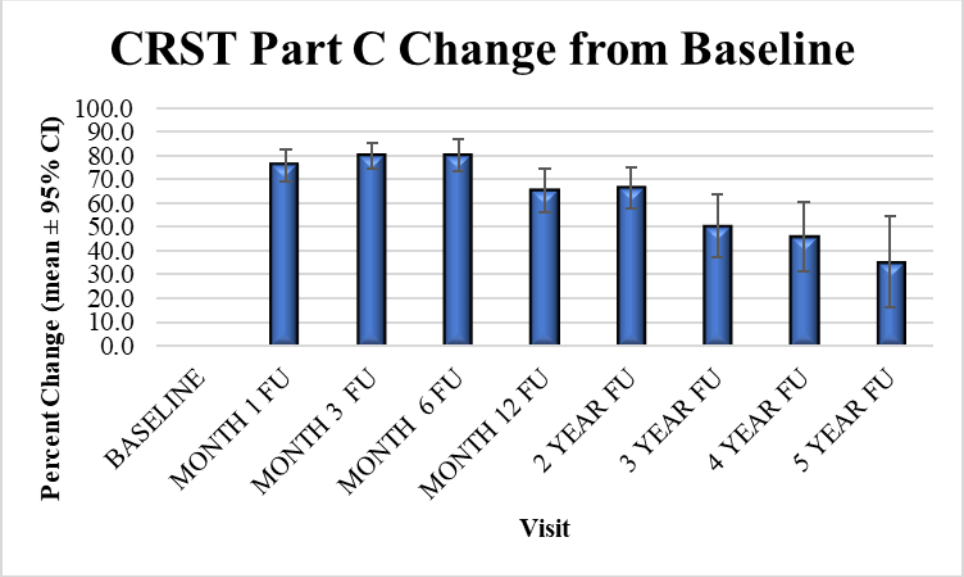


Figure 87. Percent-Change of CRST Part C Activities of Daily Living.

Figure-87 shows the %-change (improvements) from baseline of the CRST Part C by study visit. The graph shows the result across time.

9.5.3.4 Secondary Endpoints – Quality of Life in Essential Tremor (Quest)

In **Figures 88** and 89, and **Table 115**, the Quality of Life in Essential Tremor (QUEST) measure showed a similar trend of improvement in the quality of life as compared to the Pivotal trial cohorts.

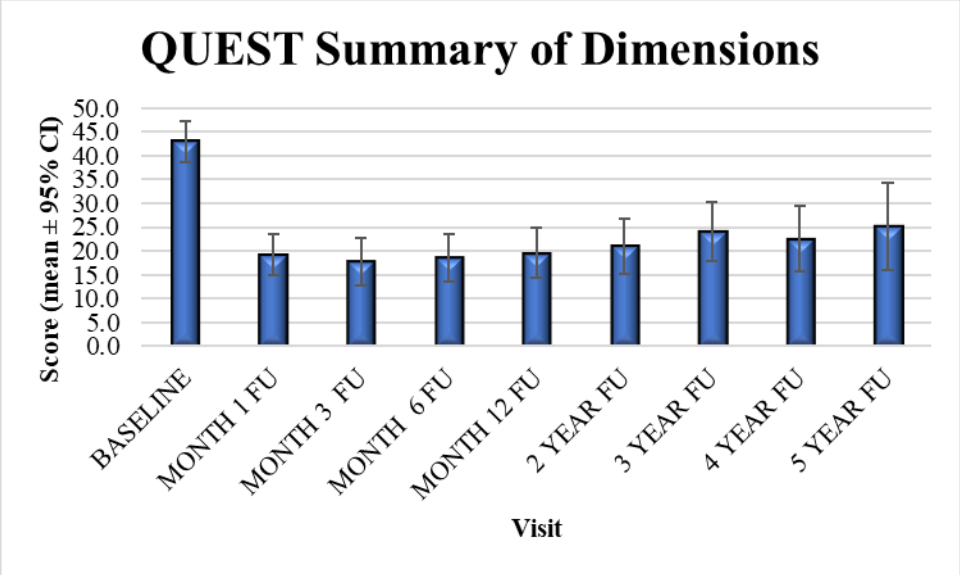


Figure 88. Quality of Life in Essential Tremor Summary of Dimensions across all visits. Lower score show improvement.

Table 115 QUEST Summary of Dimensions Total Scores

	BASELINE	MONTH 1 FU	MONTH 3 FU	MONTH 6 FU	MONTH 12 FU	2 YEAR FU	3 YEAR FU	4 YEAR FU	5 YEAR FU
mean	42.9	19.2	17.8	18.6	19.6	21.0	24.0	22.5	25.1
s.d.	17.40	17.18	18.91	19.03	19.79	19.85	18.74	19.68	21.92
n	61	59	56	57	53	45	35	31	22
95% CI	4.37	4.38	4.95	4.94	5.33	5.80	6.21	6.93	9.16
95% UL	47.25	23.57	22.71	23.52	24.88	26.84	30.17	29.44	34.30
95% LL	38.51	14.80	12.81	13.64	14.22	15.24	17.75	15.59	15.98

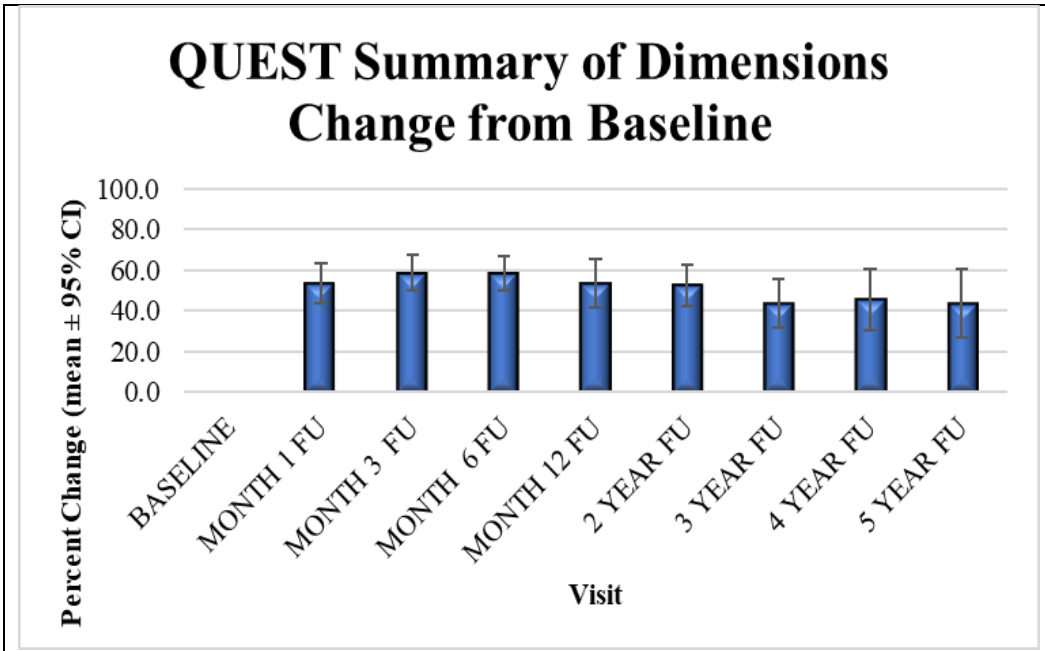


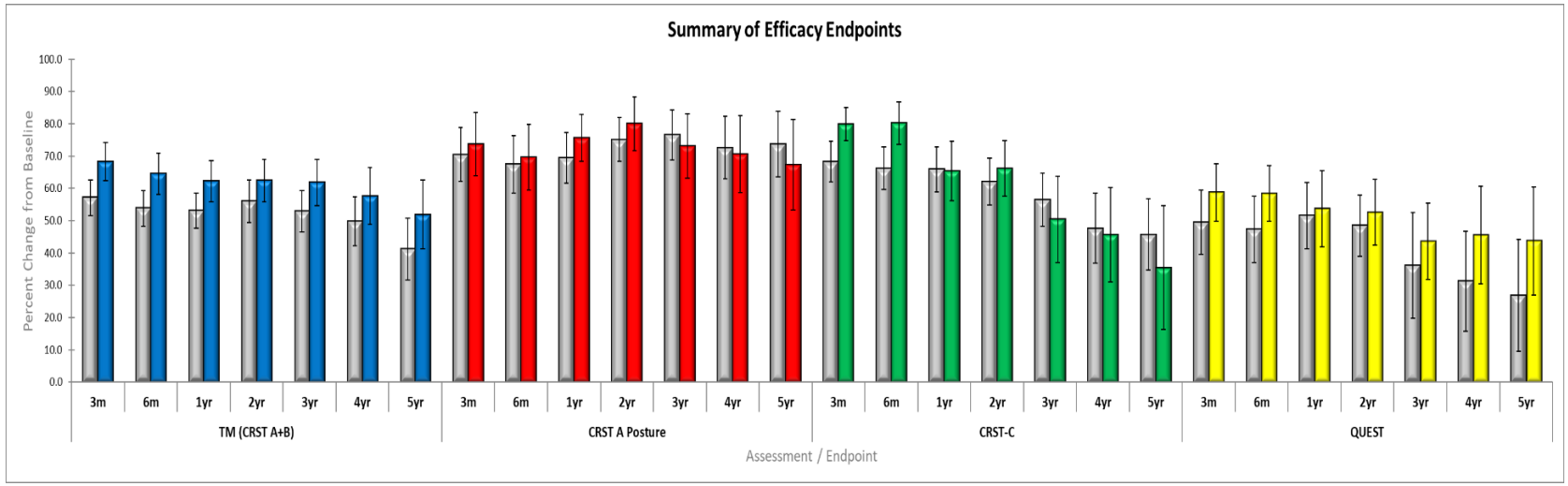
Figure 89. Percent-change of Quality of Life in Essential Tremor (QUEST).

Figure-89 shows the %-change (improvement) from baseline of the QUEST by study visit. The data shows a very stable outcome across visits, especially considering that the QUEST is a general assessment not focused on unilateral tremor.

9.5.3.5 Efficacy Conclusion

Improvement was maintained through the 5 years of follow-up. Mean Tremor Motor scores changed from 6 at the 3 Month visit to 9 at the 5 Year visit. Likewise, Posture scores averaged 0.6 at the 3 Month and 0.9 at the 5 Year visit. These outcome measures were consistent over time. Similarly, measures including social and functional dimensions continued to show an effect over the 5 years of the study. Mean CRST Part C changed from 3.5 at the 3 Months to 10.4 at the 5 Year visit and the Quest Total changed from 17.8 at 3 Month to 25 at the 5 Year visit. By comparison, the Baseline CRST Part C averaged 17 and the Baseline QUEST averaged 43. All these outcome measures show improvement when compared to Baseline through year-5. Furthermore, the outcomes in the ET002CA track those of the original ET002 pivotal trial (P150038). (**Figure 90**).

Figure 90. Comparison of percent change from Baseline between ET002CA (Continued Access, colored bars) and ET002 (PMA Pivotal Trial, gray bars).



9.6 Conclusions Drawn from the Study

For this population of subjects diagnosed with idiopathic ET with medication-refractory tremor, the Exablate Neuro treatment is a safe and effective treatment for their Essential Tremor. The result from the pivotal study showed that the treatment is efficacious and safe; most of the adverse events were mild or moderate in severity. Similarly, the data from the Continued Access study with 5-year long-term follow-up results continues to support the reasonable assurance of device safety and effectiveness when used in accordance with the indications for use.

9.7 Strengths and Weakness of the PAS Study

The main strength of this Continued Access PAS is the 5-year follow-up duration including more than 95% of the original population at the 12 Month visit. Twenty-six subjects completed the 5 Year visit despite COVID-19 pandemic. With respect to effectiveness, the duration of tremor/motor function, posture and activities of daily living were sustained through year 5.

Regarding safety, no new adverse events were observed during long term follow-up that were related to the device, procedure or thalamotomy. Furthermore, some of the unresolved events at the end of 12 Month follow-up continued to resolve with time. All events were followed using the worst severity ever reported during the study.

With respect to weaknesses of the study, the continued access study was performed using the original independent comparator. However, the study design was the same as the pivotal trial with respect to the test arm and the results were similar (**Figure 90**).

Additionally, the study was performed as a unilateral procedure and was performed on the subject's tremor dominant arm. While some patients might benefit from bilateral treatment, clinically meaningful improvements were observed in the unilateral side that permitted subjects to show improvement in their long-term activities of daily living.

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

10. Men and women, age 30 years and older, desiring bilateral treatment option.
11. Diagnosis of idiopathic PD by UK Brain Bank Criteria.
12. Levodopa responsive (≥ 30% reduction in MDS-UPDRS motor subscale in the ON vs OFF medication state).
13. MDS-UPDRS ≥ 30 in the meds OFF state.
14. 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

24. ≥ 3 on the PULL test.
25. Severe premorbid risks per MDS-UPDRS Part II aspects of experiences of daily living (speech, chewing and swallowing, saliva and drooling).
26. Significant cognitive impairment as determined by neuropsychologist.
27. Unstable psychiatric disease.
28. History of abnormal bleeding, hemorrhage, or coagulopathy.
29. Any illness that in the investigator's opinion preclude participation in this study.
30. Contraindications for MR imaging (e.g. implanted metallic devices).
31. 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 116** is shown below:

Table 116. 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 116. 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 116. 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.

2) **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.

3) **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 91**). 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).

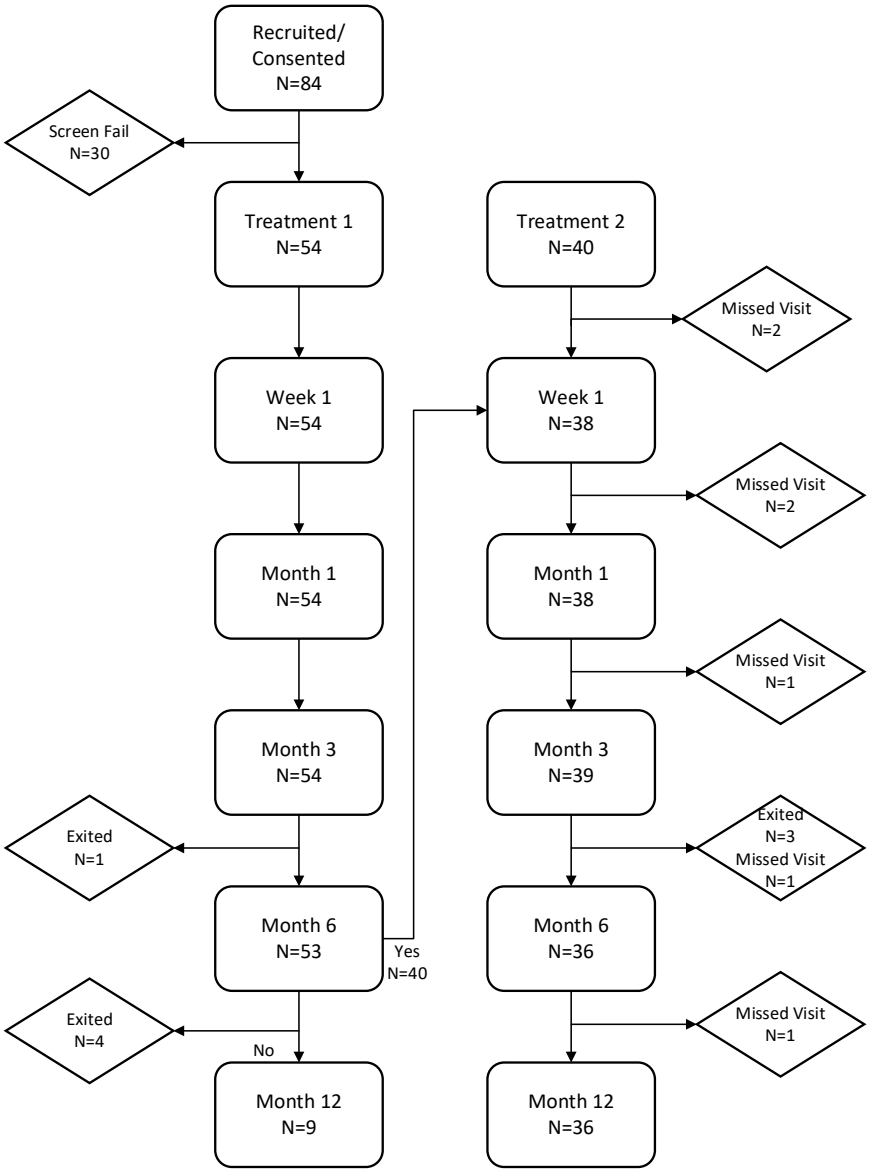


Figure 91 Subject Disposition Flow Chart

Subject accountability for this study is presented in **Table 117** (Unilateral) and in **Table 118** (Bilateral).

Table 117. 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 118. 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 119**. 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 119 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 119 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 120**. The most common reason was that sufficient relief was already obtained with the first treatment.

Table 120. 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 121**. 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 121. 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 122**. 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 122. 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 123**.

Table 123. 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 124**. 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 124. 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 125** 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 125. 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 126 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 126. 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 126. 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 126. 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 126. 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 126. 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 126. 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 126. 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 127 below presents a full listing of all adverse events from T1 through Month 12 post T2.

Table 127. 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)

Table 127. 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 ($\%_S$)
		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)
		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)

Table 127. 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 (%$_S$)
		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)
		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)

Table 127. 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 ($\%_S$)
		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)
		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)**

Table 127. 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 (%$_S$)
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)
	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)

Table 127. 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 (%$_S$)
		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)
	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)

Table 127. 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 ($\%_S$)
	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)**
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)

Table 127. 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 ($\%_S$)
		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)
		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)

Table 127. 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 ($\%_S$)
		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)
	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)

Table 127. 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 (%$_S$)
	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)
		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)

Table 127. 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 ($\%_S$)
		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)
	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 128**. 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 128. 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 129**.

Table 129. 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 129. 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 129** 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 126** above.

Overall, a total of 19 speech events in 15 of the 40 subjects were reported in this study (see **Table 126** 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 130** and **Figure 92**, 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 130. 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 130. 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.				

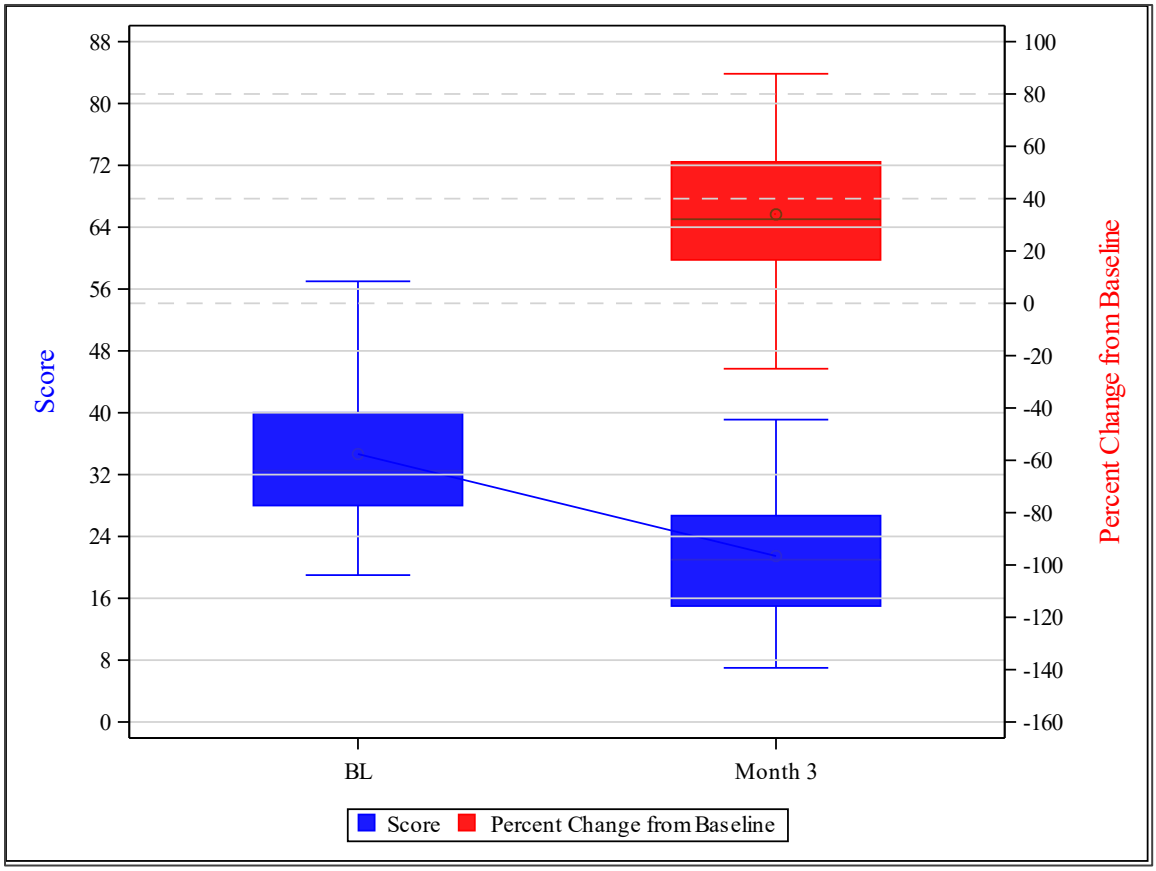


Figure 92. Primary Endpoint – MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score for Both Treated Side – Score and Percent Change from Baseline (Bilateral mITT).

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 131** and **Figure 93.** 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 131. 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 131. 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.				

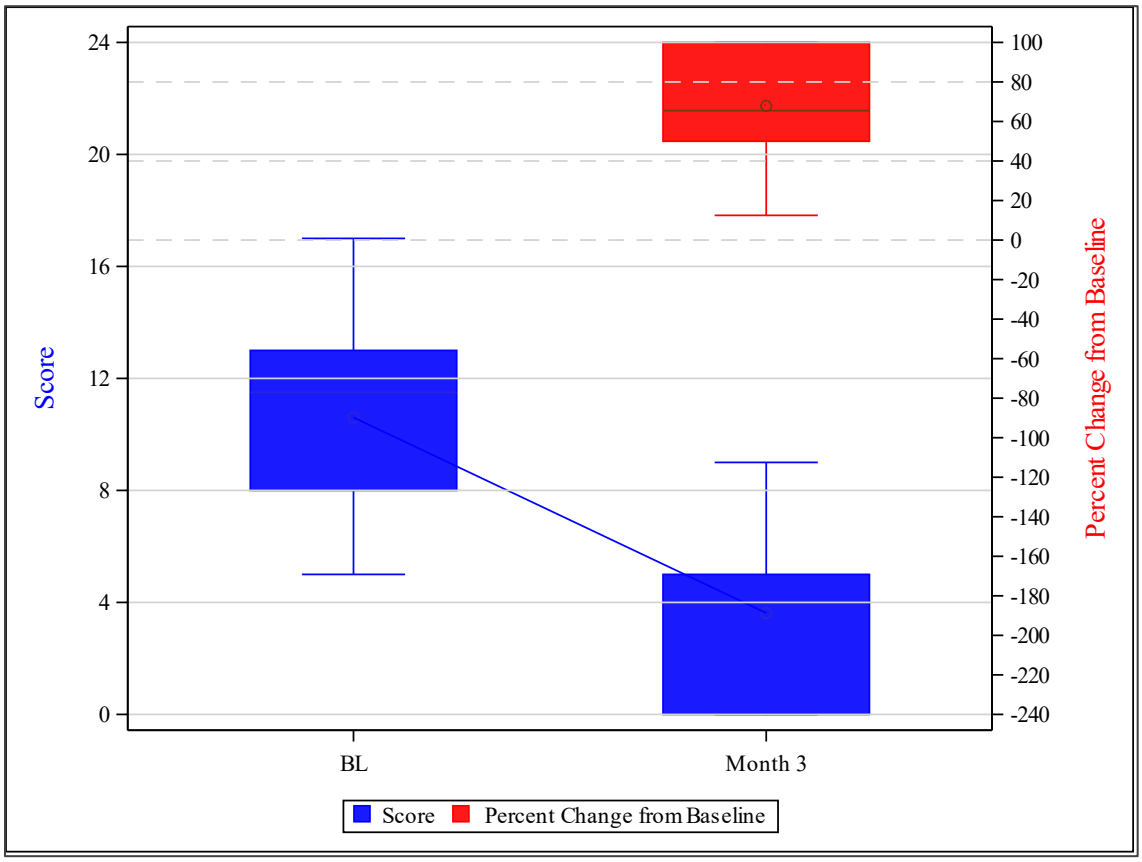


Figure 93. Confirmatory Endpoint 1:MDS-UPDRS Part IV Score and Percent Change from Baseline (Bilateral mITT)

Confirmatory Endpoint 2:

A second confirmatory endpoint was also performed that assessed the MDS-UPDRS Part III Total Score OFF medication, see **Table 132** and **Figure 94**. 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 132. 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.				

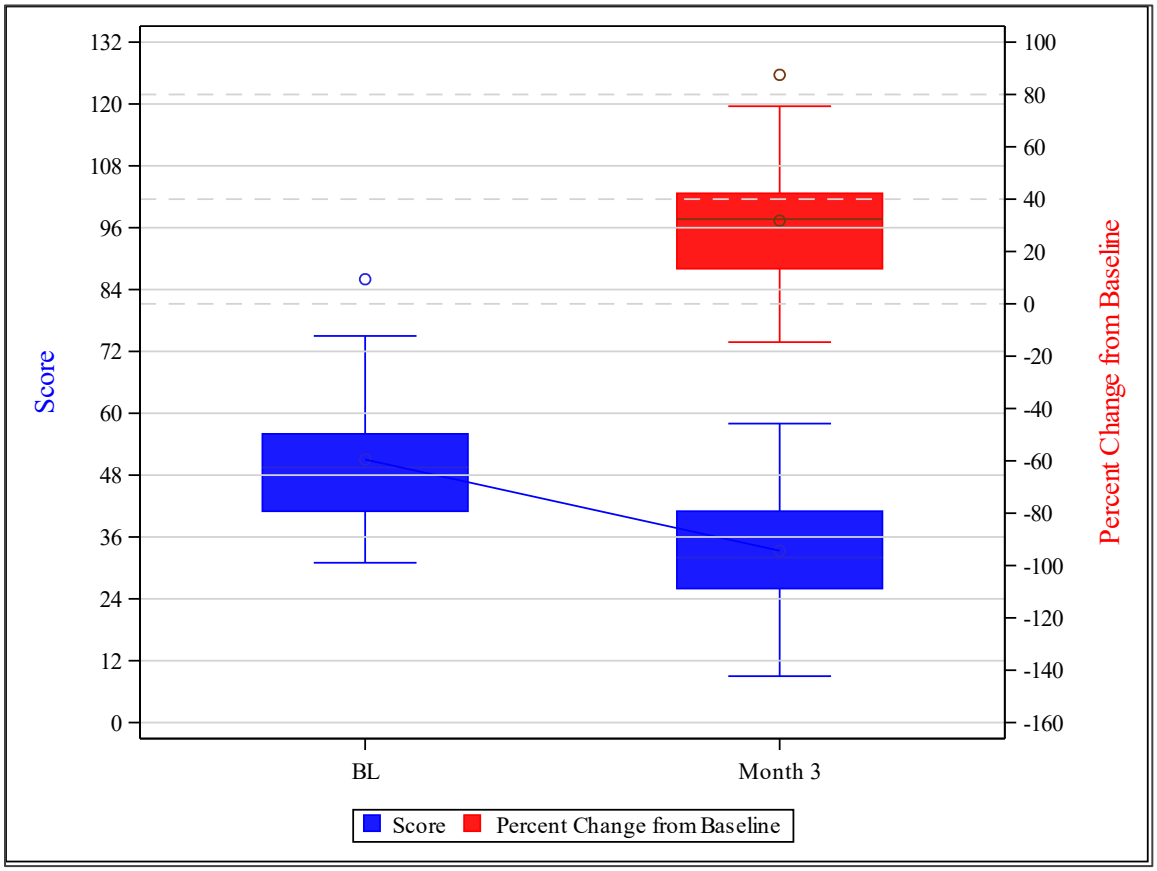


Figure 94. Confirmatory Endpoint 2: MDS-UPDRS Part III Total Score – Score and Percent Change from Baseline (Bilateral mITT)

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 133** and **Figure 95**. 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 133. 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 133. 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.				

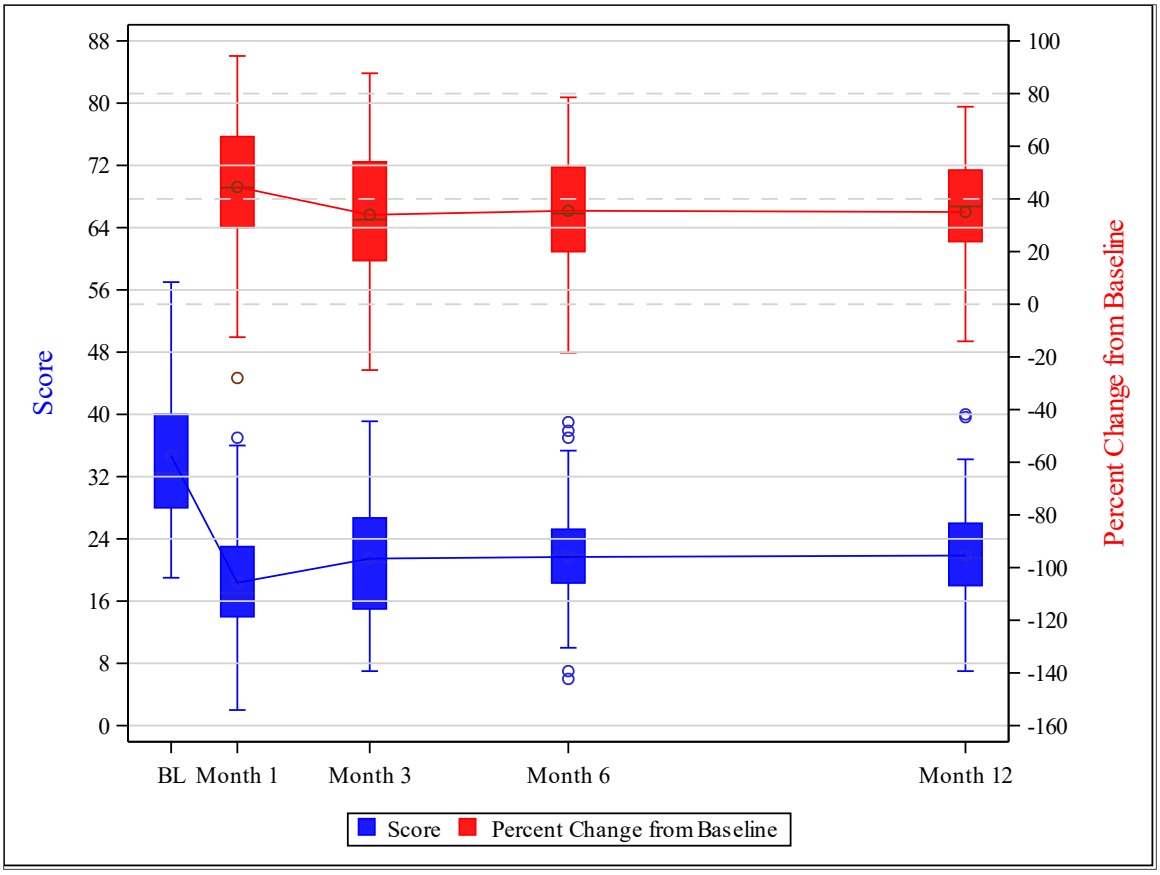


Figure 95. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Bilateral Effect – Score and Percent Change from Baseline (Bilateral mITT)

MDS-UPDRS Part IV

Change as compared to baseline for MDS-UPDRS Part IV – Motor Complications through Month 12 is shown in **Table 134** and **Figure 96**. 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 134. 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 134. 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.				

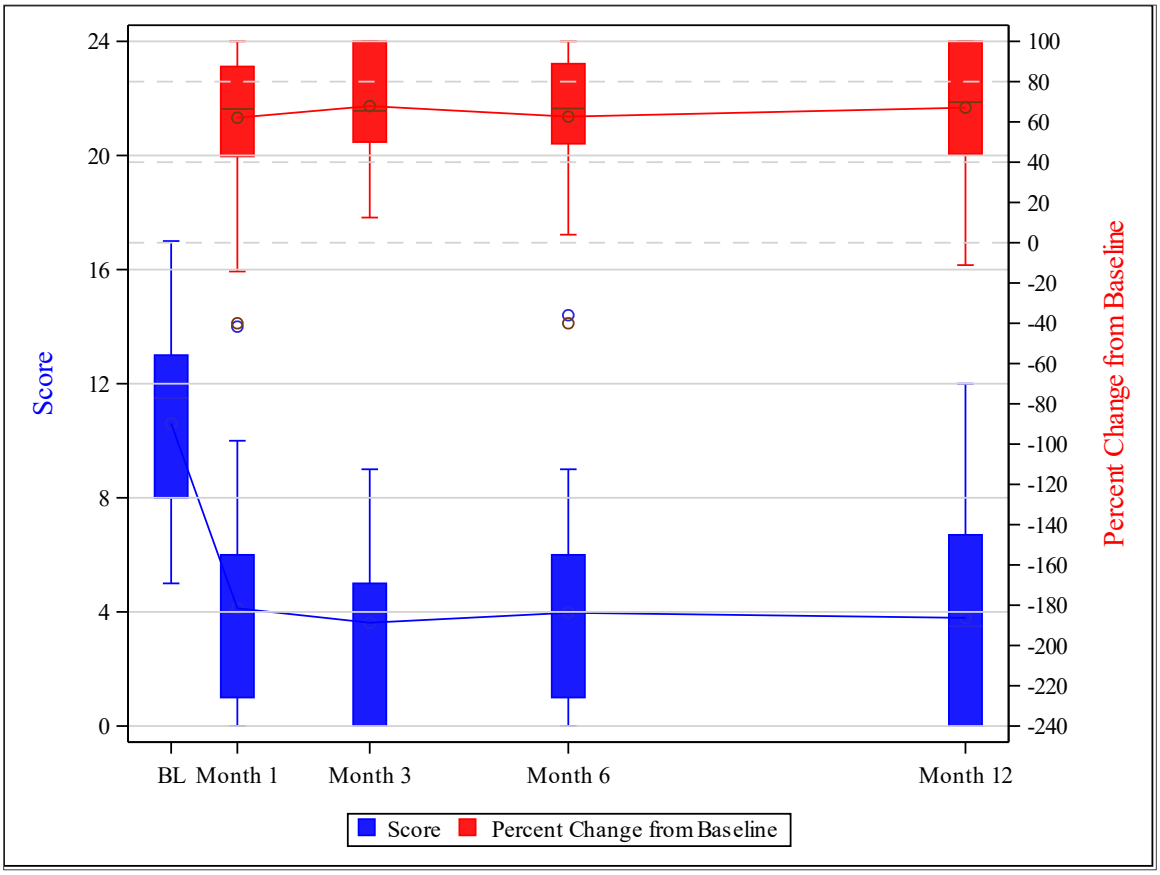


Figure 96. Secondary Endpoint 2: MDS-UPDRS Part IV – Score and Percent Change from Baseline (Bilateral mITT)

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 135** and **Figure 97**. 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 135. 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 135. 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 135. 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.				

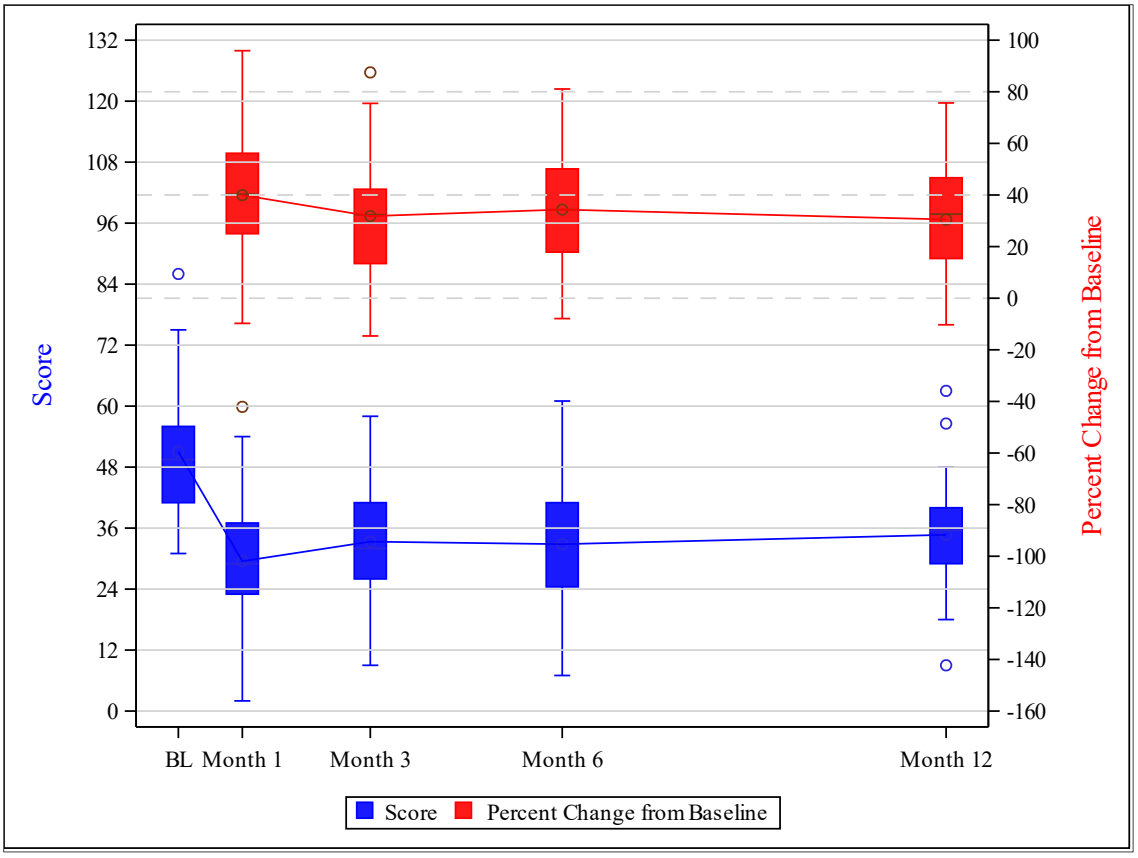


Figure 97. Secondary Endpoint 3: MDS-UPDRS Part III OFF Med Total Score – Score across Visits and Percent Change from Baseline (Bilateral mITT)

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 98**) 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 136** below.

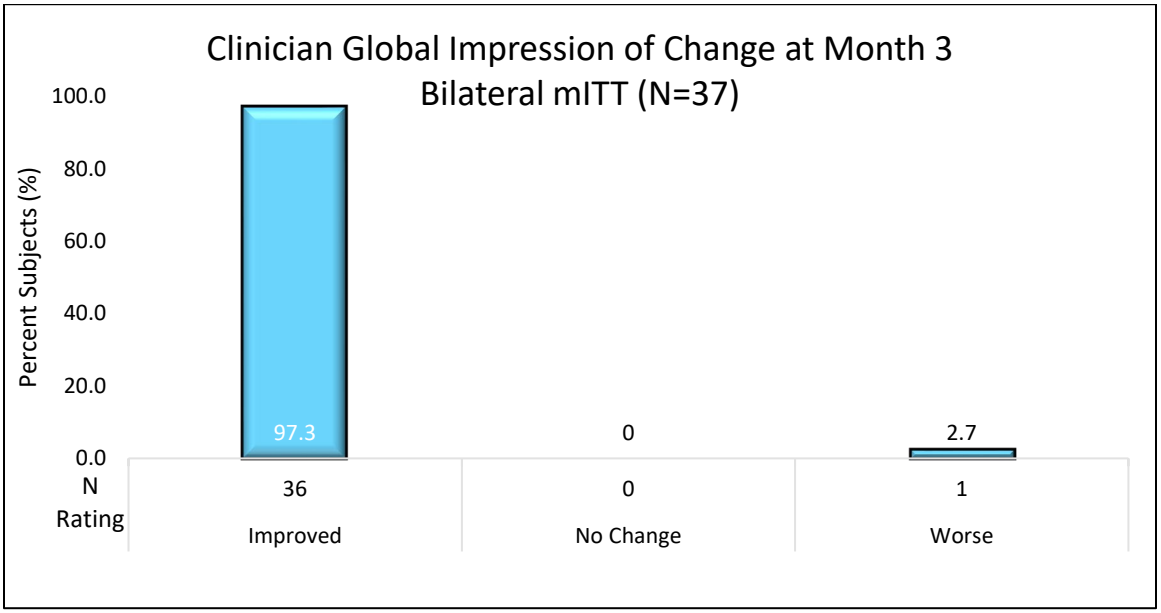


Figure 98: Clinician Global Impression of Change at Month-3 in the Bilateral mITT population with available data

Table 136. 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 99)** 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 137** below.

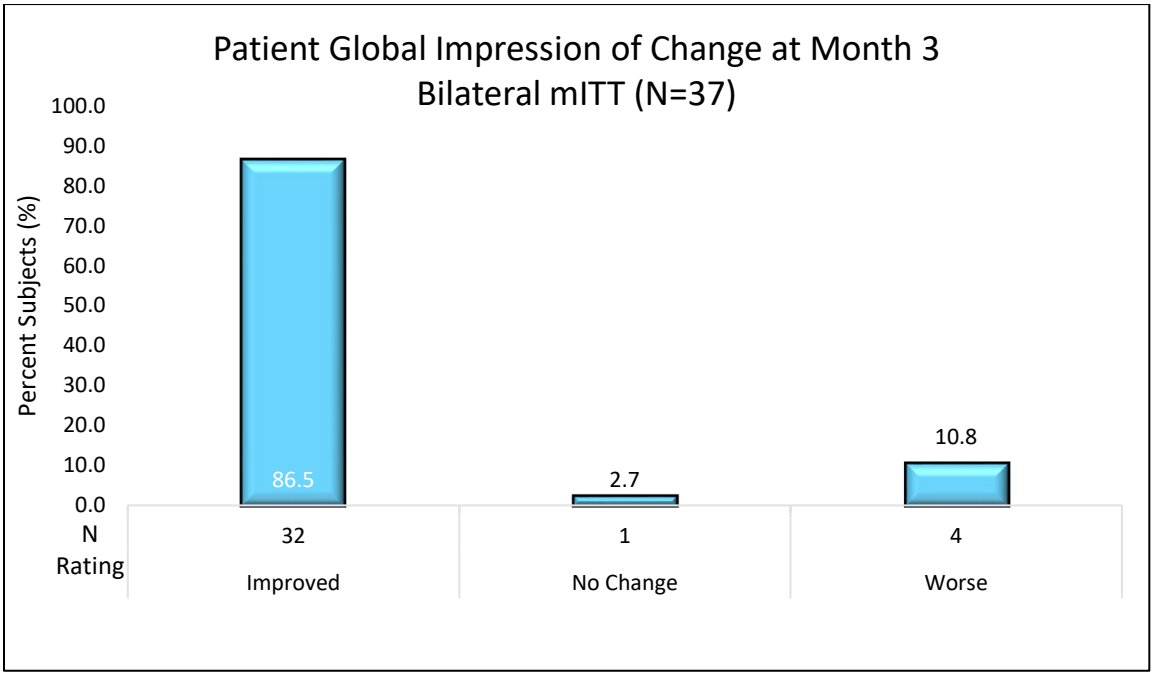


Figure 99: Patient Global Impression of Changes at Month-3 in the Bilateral mITT population with available data

Table 137. 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 100**) 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.

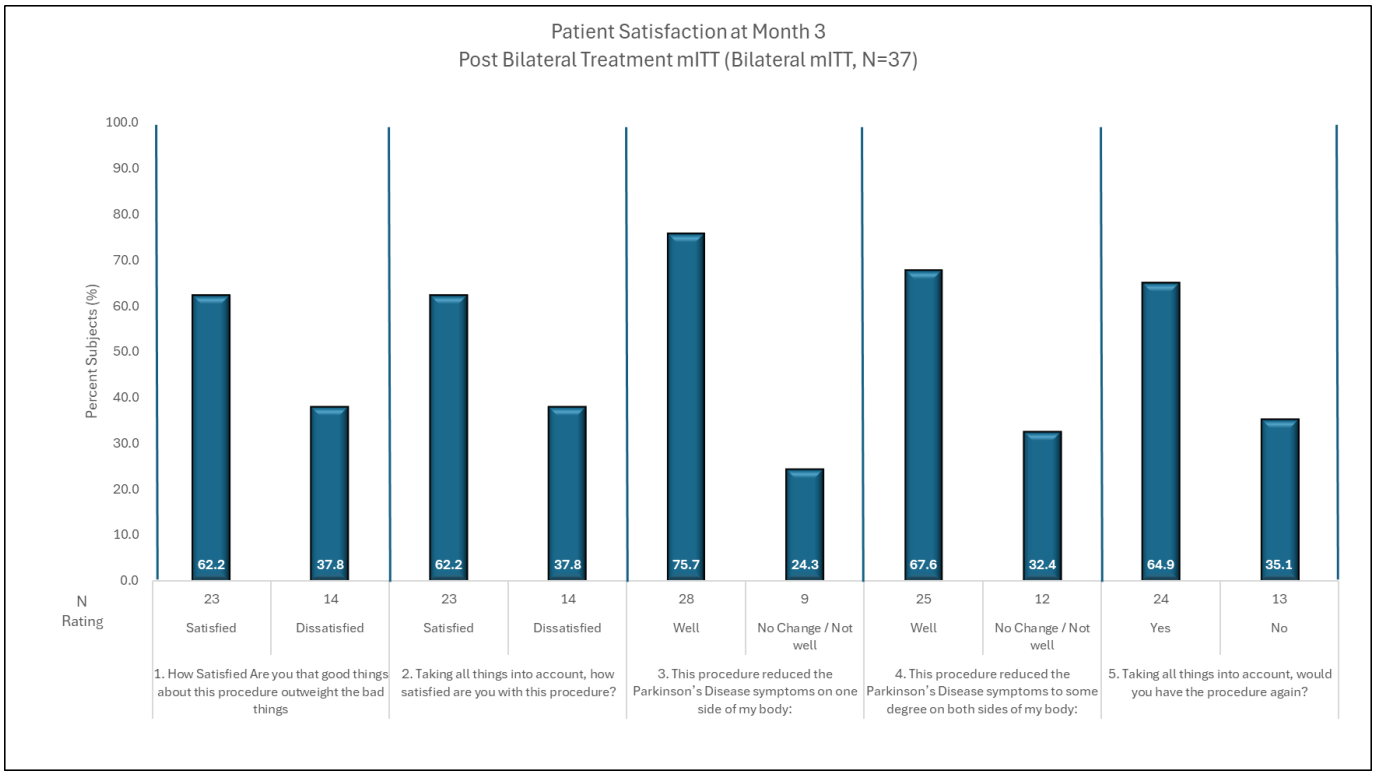


Figure 100 Patient Satisfaction Assessments at Month-3 in the Bilateral mITT population with available data

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 138** and for percent change (Figure 101) and score change (Figure 102). 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 101) and change in score (Figure 102) 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 138**.

Table 138. 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 138. 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.							

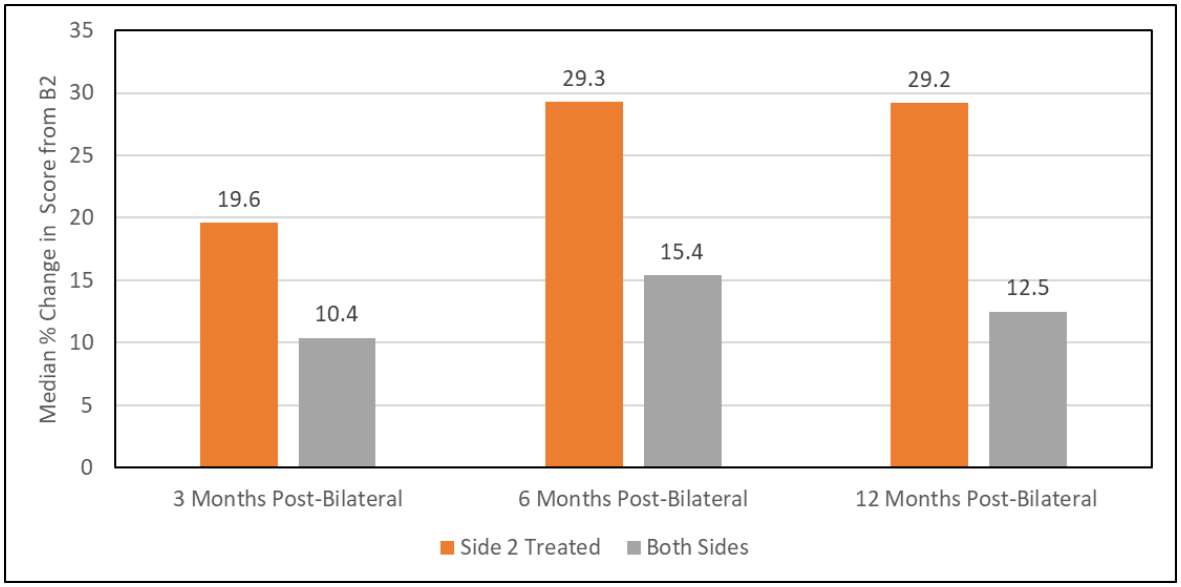


Figure 101: Percent change in Median MDS-UPDRS Part III Off Medication Upper and Lower Extremity Scores with respect to median score at B2 for first side treated, second side treated, and both sides. Baseline is defined as B2 (6-month post-unilateral timepoint).

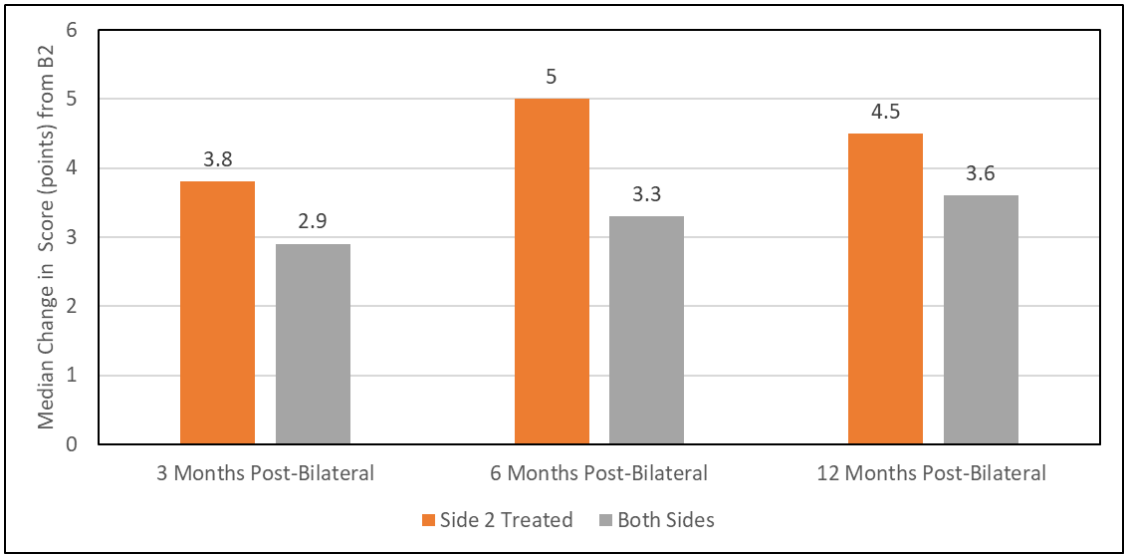


Figure 102: Median improvement in MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score after T2 with respect to median score at B2 for second side treated and both sides. Baseline is defined as score at B2 (6-month post-unilateral timepoint). Positive values indicate reduction in score (improvement).

(Figure 103) 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 103demonstrates 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.

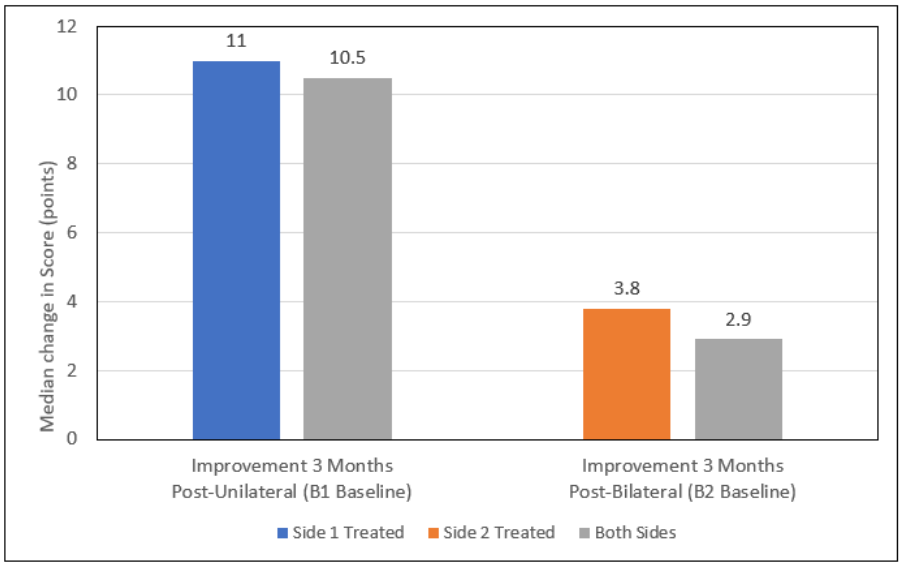


Figure 103: Median improvement in MDS-UPDRS Part III Off Medication Upper and Lower Extremity Score for the side treated and both sides 3 months after unilateral and bilateral procedures. Scores at B1 and B2 were used as baseline scores for the unilateral and bilateral procedures, respectively.

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 139** , 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 139. 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 140** 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 140. 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 141 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 141. 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 141. 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 142 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 142. 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 142. 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 142. 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 142. 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 142. 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 142. 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 142. 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 142. 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 143**. 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 143. 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 144**. 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 104**. 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 144. 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.				

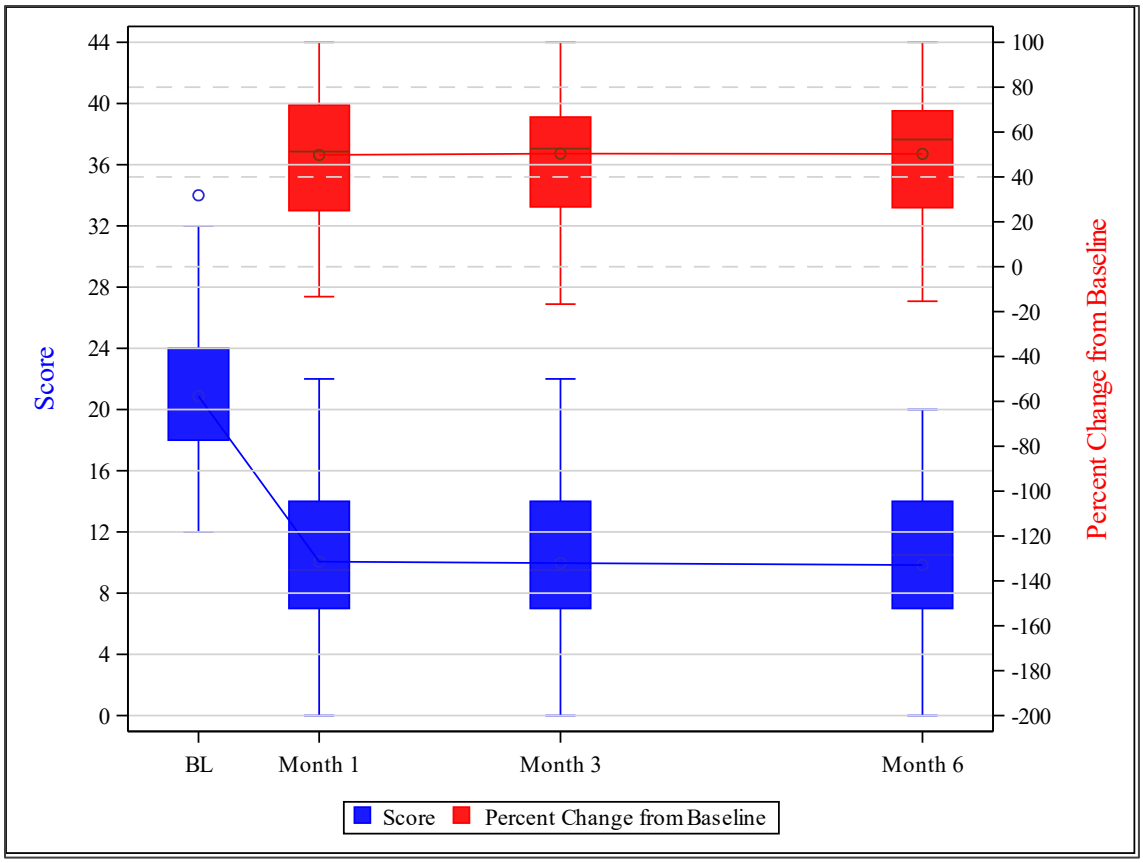


Figure 104. Secondary Endpoint 1: MDS-UPDRS Part III OFF Med Upper and Lower Extremity Score Treated Side – Score across visits and Percent Change from Baseline (Unilateral mITT)

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 145**. 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 105**. 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 145. 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.

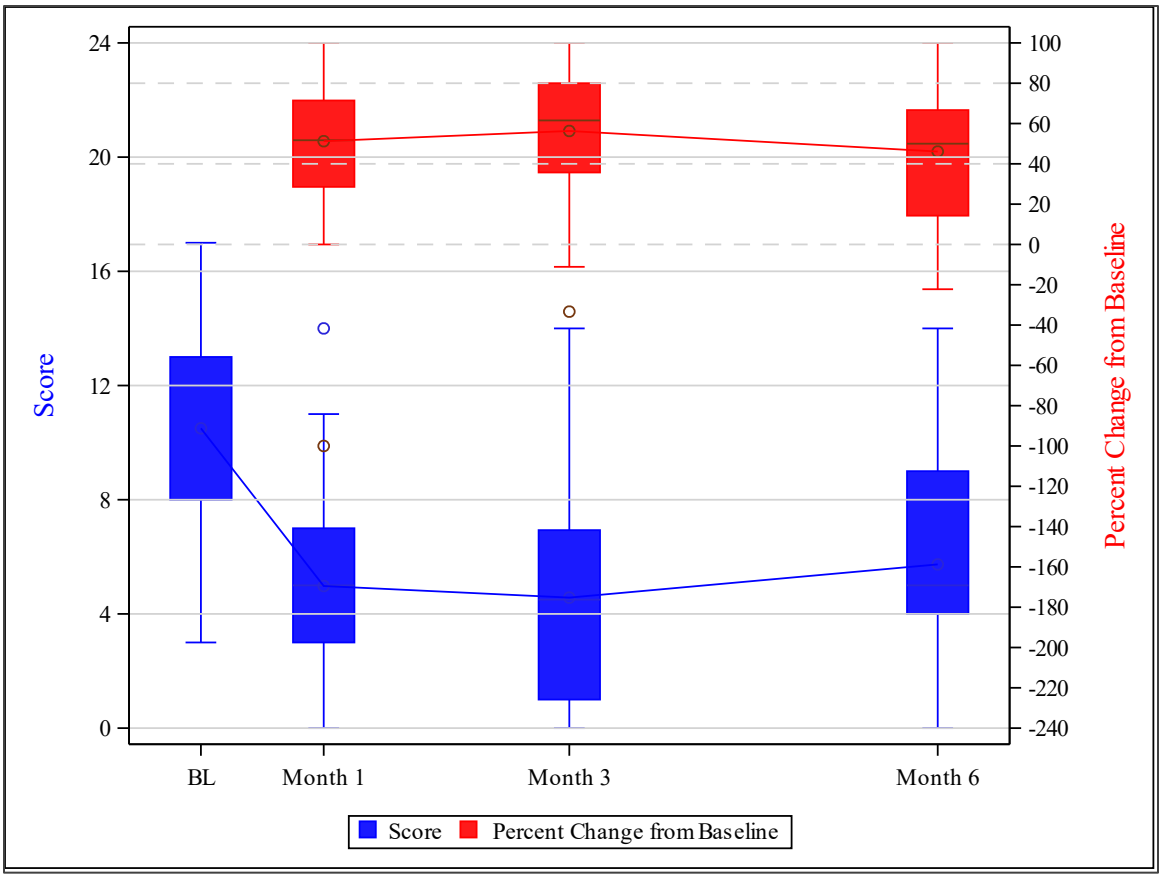


Figure 105. Secondary Endpoint 2: MDS-UPDRS Part IV – Score and Percent Change from Baseline (Unilateral mITT)

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 146.**

Table 146. 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 146. 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 - 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 147**.

Table 147. 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 147. 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 148**.

Table 148. 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 149**. 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 149 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.