# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Magnetic Resonance (MR)-Guided Focused Ultrasound System

Device Trade Name: Exablate Model 4000 Type 1.0 & 1.1 System ("Exablate Neuro")

Device Procode: POH

Applicant's Name and Address: INSIGHTEC, Inc.
4851 LBJ Freeway, Suite 400
Dallas, Texas 75244

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150038/S014

Date of FDA Notice of Approval: October 29, 2021

The original PMA P150038 was approved on July 11, 2016, and is indicated for use in the unilateral thalamotomy treatment of idiopathic essential tremor patients with medication-refractory tremor. 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. The indications for use of the Exablate Neuro was expanded in a panel-track PMA supplement, P150038/S006, that was approved on December 16, 2018, for the unilateral thalamotomy (*ventralis intermedius*) treatment of tremor-dominant Parkinson's disease with medication-refractory tremor. Patients must be at least age 30. The SSED to support the indications for use is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Exablate Neuro for use 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 (also see patient selection criteria from the pivotal study in Section X.A.).

## II. INDICATIONS FOR USE

The Exablate Neuro is indicated for use 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.

## III. CONTRAINDICATIONS

The Exablate Neuro treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging, such as non-magnetic resonance imaging (MRI) compatible implanted metallic devices including cardiac pacemakers, size limitations, 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 hours (hrs) (min: 0.48 hrs, max: 5:54 hrs).
- Patients who have an overall skull density ratio of 0.45 (± 0.05) or less as calculated from the screening computed tomography (CT).
- Parkinson's disease patients with unstable psychiatric disease, uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Exablate Neuro labeling.

## V. DEVICE DESCRIPTION

The Exablate Model 4000 Type 1.0 & 1.1 System ("Exablate Neuro") is a transcranial MR image-guided focused ultrasound system that combines a multi-channel phased-array focused ultrasound transducer and magnetic resonance imaging (MRI) in a closed-loop procedure for the thermal treatment of brain tissue. The Exablate Model 4000 Type 1.0 & 1.1 System uses software version 7.33 in conjunction with GE Medical Systems ("GE") and Siemens 3 Tesla (T) MRI scanners or GE 1.5 T MRI scanners with a dedicated Exablate Neuro 1.5 T MR Head Coil. The device operates by guiding the focus of the ultrasound energy to the target region in the brain. The energy is then repeatedly transmitted to the target until the desired outcome is achieved. The targeted area is defined based on MR images taken during the procedure. The treatment procedure is constantly monitored by real-time closed-loop thermal feedback. Once targeting is complete, the treatment outcome is confirmed with adequate post-treatment MRI sequences.

The Exablate Model 4000 Type 1.0 & 1.1 System is comprised of three main components:

1. Exablate Neuro Treatment Table and Transducer Helmet (for Type 1.0) or Transducer Helmet with Cart for storage/transport (for Type 1.1), which contains the actual transducer and its supporting hardware and electronics and the stabilization system (see Figure 1).

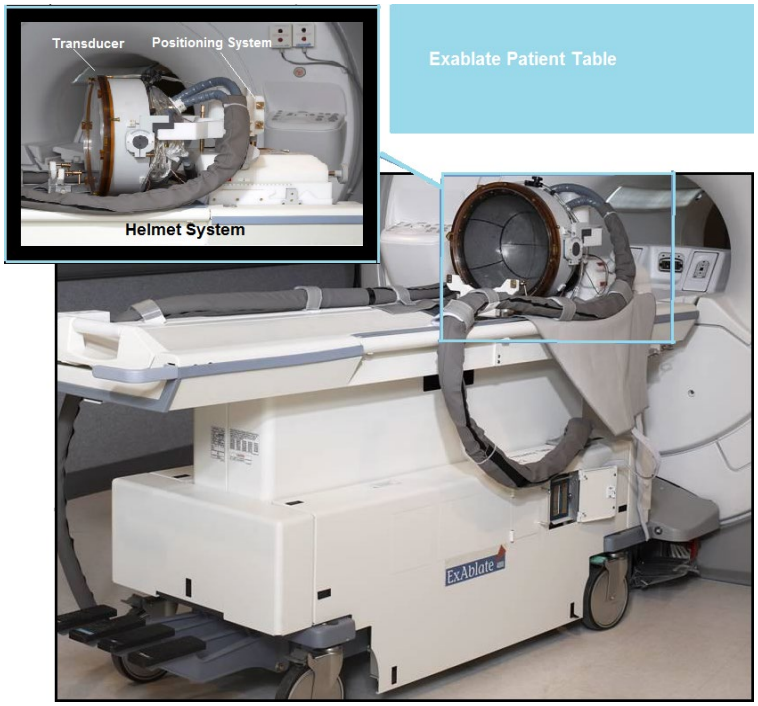



**Figure 1: Exablate Neuro Patient Table**

2. Exablate Neuro Operator Console/Workstation (WS) is a personal computer (PC) that allows the clinical user to run the device system through the clinical application software.
3. Exablate Neuro Equipment, including:
    a. Equipment Cabinet contains the control PC, power supplies, and control and data acquisition electronics.
    b. Front-End (FE) Unit contains the power amplifiers that drive the focused ultrasound transducer, as well as the control and monitoring electronics.
    c. Water System contains equipment to cool and degas the water that is used as the interface between the transducer and the patient's head in order to remove excess heat deposited in the skull by the ultrasound energy.

A more detailed device description can be found in the Exablate Neuro labeling.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of medication-refractory moderate to severe motor complications in patients with idiopathic Parkinson's disease, including medication, surgical resection of the area in the brain responsible for the motor

complications, radiofrequency pallidotomy or thalamotomy, and implantation of a deep brain stimulator. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

The Exablate Neuro is approved for marketing in the following countries: Australia, Brazil, Canada, Chile, China, Germany, India, Israel, Italy, Japan, Korea, Mexico, Russia, Spain, Switzerland, Taiwan, United Kingdom, and United States.

The Exablate Neuro has not been withdrawn from the market outside of the United States for safety or effectiveness reasons.

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

Below is a list of the potential adverse effects and complications associated with the use of the device.

Adverse effects for the Exablate Neuro can include numbness or tingling of the fingers, imbalance or unsteadiness, ataxia or gait disturbance, pain, and headache.

In addition, the following adverse effects have been identified as possible treatment-related complications of Exablate Neuro treatment. These can be classified into non-significant and significant adverse effects based on their severity, additional treatment required and long-term consequences.

Non-serious adverse effects that resolve without sequelae within 10-14 days after treatment include:

- Transient fever.
- Oral temperature greater than 100.4 °F or 38 °C.
- Transient skin pain.
- First and second degree skin burns less than 2 cm in diameter.
- Pain during the sonication treatment.

Serious anticipated treatment adverse effects of the Exablate Neuro are those which may require medical treatment, may have sequelae, and for which time of resolution is not defined:

- Tissue damage in area other than the treatment area.
- Hemorrhage in the treated brain area requiring emergency treatment.
- Skin burns with ulceration of the skin.
- Skin retraction and scar formation.
- Venous thromboembolic events.

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

## IX. SUMMARY OF NONCLINICAL STUDIES

The Exablate Neuro was first approved in P150038 on July 11, 2016, for use in the unilateral thalamotomy treatment of idiopathic essential tremor patients with medication-refractory tremor. No additional non-clinical performance testing was conducted to support the current PMA supplement. A summary of the non-clinical studies conducted on the Exablate Neuro can be found in the Summary of Safety and Effectiveness Data (SSED) for P150038 at the following location: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150038B.pdf.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of unilateral pallidotomy with the Exablate Neuro in patients with advanced, idiopathic Parkinson's disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson's disease medication treatment in the US, Canada, Israel, Italy, Korea, Spain, Taiwan, and United Kingdom under IDE # G170237. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

Patients were treated between March 26, 2018, and January 31, 2020. The database for this Panel Track Supplement reflected data collected through January 13, 2021, and included 94 randomized patients. There were 19 investigational sites with 11 sites in the US and 8 sites outside the US.

The study was a prospective, multi-center, two-arm, randomized (3:1), sham-controlled, double-blinded clinical study titled "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease with Unilateral Lesioning of the Globus Pallidum using the Exablate Neuro System (PD006)." Both patients and neurologists conducting the 3-month effectiveness outcome assessments were blinded to the treatment assignment. Treating physicians were not blind to the treatment assignment. The primary outcome was evaluated at 3-months post-procedure with follow-up visits scheduled at 1 week, 1 month, 3 months, 6 months, and 12 months after the Exablate Neuro procedure.

The control group treatment was an active sham where all patients received the same pre-treatment testing, post-treatment MRI scans, and went through the same set-up procedures as the patients randomized to the investigational Exablate Neuro arm. Patients in both study groups underwent unilateral pallidotomy to the symptom-dominant side of the GPi. For patients who had bilateral PD where both sides met study selection criteria, usually the dominant side was treated. Patients in the sham

control arm received pantomimed sonications for the same duration as the Exablate Neuro treatment protocol. The sham control patients were followed through the 3-month follow-up visit to evaluate the effectiveness outcomes and received the same assessments as the patients in the investigational Exablate Neuro arm of the study. At the conclusion of the 3-month follow-up visit, the patients and neurologists were unblinded and the patients that received the investigational Exablate Neuro treatment continued follow-up at 6 months and 12 months post-procedure. After the unblinding occurred after the 3-month follow-up visit, the sham control patients were permitted to crossover to receive the Exablate Neuro treatment as long as they met the study selection criteria and these patients followed the same follow-up schedule as the patients in the investigational arm.

The statistical analysis was based on a responder analysis for the primary effectiveness outcome tested using the following hypothesis and analyzed using logistic regression on each imputed data set:

$H_0$: Response Rate Exablate ≤ Response Rate Sham
$H_1$: Response Rate Exablate > Response Rate Sham

The sample size calculation was based on a minimum of 92 and maximum of 107 randomized patients in a 3:1 (Exablate Neuro: Sham) ratio. The minimum sample size of 92 patients accounted for a 15% increase due to the potential for patient drop-out. A response rate of 70% in the Exablate Neuro arm and 20% in the sham control arm was expected.

The analysis populations for the pivotal study were defined as follows with the modified intent-to-treat (mITT) population used to analyze the primary and secondary confirmatory effectiveness outcomes:

- The intent-to-treat (ITT) population includes all patients who signed the informed consent document and were randomized.
- The safety analysis population includes all randomized patients with at least one sonication (Exablate Neuro or Sham) in the main stage of the study.
- The mITT population includes all safety patients receiving at least one sonication for whom there exists primary effectiveness data at baseline and at least one post-baseline assessment sufficiently to determine the primary effectiveness outcome (i.e., data for both Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Unified Dyskinesia Rating Scale (UDysRS)).
- The per protocol (PP) population includes all mITT patients who have observed primary effectiveness data at baseline and the 3-month follow-up visit, observed lesion on post-operative imaging, and have no major protocol violations likely to affect the outcome.

The clinical study included a Data Safety Monitoring Board (DSMB) that reviewed all adverse events and adjudicated the serious adverse events (SAEs) for their relationship to the investigational device or procedure. The role of the DSMB was to

monitor the safety of the clinical study and make recommendations for study continuation or stoppage. The study also included blinded neurologists who conducted all of the primary and secondary confirmatory effectiveness outcome assessments.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease with Unilateral Lesioning of the Globus Pallidum using the Exablate Neuro System (PD006)" study was limited to patients who met the following inclusion criteria:

   - Men and women, age 30 years and older.
   - Subjects who are able and willing to give informed consent and able to attend all study visits through 12 months.
   - Subjects with a diagnosis of idiopathic Parkinson's disease (PD) by United Kingdom (UK) Brain Bank Criteria as confirmed by a movement disorder neurologist at the site.
   - Levodopa responsive as defined by at least a 30% reduction in MDS-UPDRS motor subscale in the ON vs. OFF medication state.
   - 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).
   - 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.
   - Subject is able to communicate sensations during the Exablate procedure.
   - Globus pallidus internus nucleus can be targeted by the Exablate device.
   - Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
   - 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).

   Patients were not permitted to enroll in the "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease with Unilateral Lesioning of the Globus Pallidum using the Exablate Neuro System (PD006)" study if they met any of the following exclusion criteria:

   - Hoehn and Yahr stage in the ON medication state of 3 or greater.

- 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.
- Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications.
- Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia.
- Presence of significant cognitive impairment using Mini-Mental State Exam (MMSE) ≤ 24.
- 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:
    - Significant or active mood disorders requiring cognitive behaviorial therapy, transcranial magnetic stimulation, electroconvulsive therapy, or has been hospitalized within 12 months or screening.
    - Depression with a score of 19 or greater on Beck Depression Inventory.
    - 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.
- Subjects with an active alcohol or drug dependency or history of drug/alcohol abuse within the past year prior to screening as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for substance or alcohol use disorders.
- 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.
- Severe hypertension (diastolic blood pressure (BP) > 100 on medication).
- Current medical condition resulting in abnormal bleeding and/or coagulopathy.
- Receiving anticoagulant (e.g., warfarin) or antiplatelet (e.g., aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk of hemorrhage (e.g., Avastin) within one month of focused ultrasound procedure.
- 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 international normalized ratio (INR) coagulation studies exceeding the institution's laboratory standard.

- Patient with severely impaired renal function with estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$ (or per local standards should that be more restrictive) and/or who is on dialysis.
- 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.
- Significant claustrophobia that cannot be managed with mild medication.
- Subjects who weigh more than the upper weight limit of the MR scanner table and who cannot fit into the MR scanner.
- Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment.
- History of intracranial hemorrhage, multiple strokes, or a stroke within past 6 months.
- Subjects with a history of seizures within the past year.
- Subjects with brain tumors.
- Subjects with intracranial aneurysms requiring treatment or arterial venous malformations (AVMs) requiring treatment.
- Are participating or have participated in another clinical trial in the last 30 days.
- Any illness that in the investigator's opinion preclude participation in this study.
- Subjects unable to communicate with the investigator and staff.
- Pregnancy or lactation.
- Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: human immunodeficiency virus (HIV), liver failure, blood dyscrasias.
- 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.
- Subjects who have an overall skull density ratio of less than 0.40 as calculated from the screening computed tomography (CT).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1-week, 1-month, 3-months, 6-months, and 12-months, postoperatively. The PD006 clinical study also consented patients to be followed up to 5-years postoperatively. The study's primary effectiveness outcome was evaluated at 3-months postoperative, at which time all patients were unblinded. After unblinding, the sham control patients were given an opportunity to crossover to the Exablate Neuro treatment. Sham control patients who crossed over to the Exablate Neuro treatment were scheduled to return for follow-up examinations at 1-week, 1-month, 3-months, 6-months, and 12-months, postoperatively.

Preoperatively, patients underwent a review of their medical history and medications, and laboratory, imaging (CT and MRI), general physical, neurological, visual field, gait, MDS-UPDRS, UDysRS, and neuropsychological assessments. Postoperatively, the objective parameters measured during the study included a review of concomitant medications, MRI, general physical, neurological, visual field, gait, MDS-UPDRS, UDysRS, neurophychological, blinding, patient and physician global impression of change, and patient satisfaction questionnaire assessments (see Table 1). Adverse events and complications were recorded at all visits.

**Table 1. 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 months)** |
|---|---|---|---|---|---|---|---|---|
| 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 [Timed Get-Up-and-Go (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 |

| Table 1. 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 months)** |
| 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 |
| 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<br><br>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 key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Outcomes

With regards to safety, the incidence and severity of device- and procedure-related adverse events from the first treatment day visit through the 12-month follow-up visit was be evaluated.

With regards to effectiveness, the response to treatment is evaluated by whether a patient improved on either MDS-UPDRS Part III (OFF medication motor exam on the treated side) or UDysRS Objective Impairment (ON medication) without worsening on the other assessment. Clinical outcome in the PD006 clinical study is defined as follows:

- MDS-UPDRS Part III (OFF medication motor exam) on the treated side:
    - Improvement is defined as a reduction of more than 3 points at the 3-month follow-up visit compared to baseline.
    - Worsening is defined as an increase of 4 points or more at the 3-months follow-up visit compared to baseline.
- UDysRS (ON medication):
    - Improvement is defined as a reduction of more than 3 points at the 3-months follow-up visit compared to baseline.
    - Worsening is defined as an increase of more than 3 points at the 3-month follow-up visit compared to baseline.

The PD006 clinical study was also designed with confirmatory secondary outcomes to assess the percent change improvement from baseline to the 3-month follow-up visit on the following assessments:

- MDS-UPDRS Part IV
- MDS-UPDRS Part III OFF Medication, Treated Side Extremities
- MDS-UPDRS Part II

The PD006 clinical study also evaluated the following assessments through the 12-month follow-up visit as secondary and additional effectiveness outcomes:

- MDS-UPDRS Part III OFF Medication, Treated Side Extremities
- MDS-UPDRS Part II
- MDS-UPDRS Part IV
- UDysRS Part III Objective Impairment
- Historical and Objective UDysRS sub-scores at all visits as well at the Total UDysRS score
- MDS-UPDRS: Total of Parts I, II, III OFF Medication (Treated Side), and IV ON Medication
- Clinician Global Impression of Change (CGIC): A 7-point scale requiring the physician to rate the severity of the patient's condition at the time of assessment, relative to before Exablate Neuro treatment.
- Patient Global Impression of Change (PGIC): A 7-point scale requiring the patient to rate the severity of their condition at the time of assessment, relative to before Exablate Neuro treatment.
- Patient Satisfaction Questionnaire that comprises of 5 questions assessing patient treatment satisfaction.

With regard to success criteria, the responder rate in both the Exablate Neuro treatment arm and the sham control arm were compared and tested for the following hypothesis:

$H_0$: Response Rate Exablate Neuro ≤ Response Rate Sham
$H_1$: Response Rate Exablate Neuro > Response Rate Sham

A responder was defined as a patient that improved on the MDS-UPDRS Part III (OFF medication motor exam on the treated side) and no worsening on the UDysRS Impairment (ON medication) OR a patient that improved on the UDysRS Impairment (ON medication) and no worsening on the MDS-UPDRS Part III (OFF medication motor exam on the treated side). A non-responder was a patient that did not meet the definition for a responder. The responder and non-responder definitions for improvement or worsening of the clinical outcome in the PD006 clinical study is defined as follows:

- MDS-UPDRS Part III (OFF medication motor exam) on the treated side:
  - Improvement is defined as a reduction of more than 3 points at the 3-month follow-up visit compared to baseline.
  - Worsening is defined as an increase of 4 points or more at the 3-months follow-up visit compared to baseline.
- UDysRS (ON medication):
  - Improvement is defined as a reduction of more than 3 points at the 3-months follow-up visit compared to baseline.
  - Worsening is defined as an increase of more than 3 points at the 3-month follow-up visit compared to baseline.

## B. Accountability of PMA Cohort

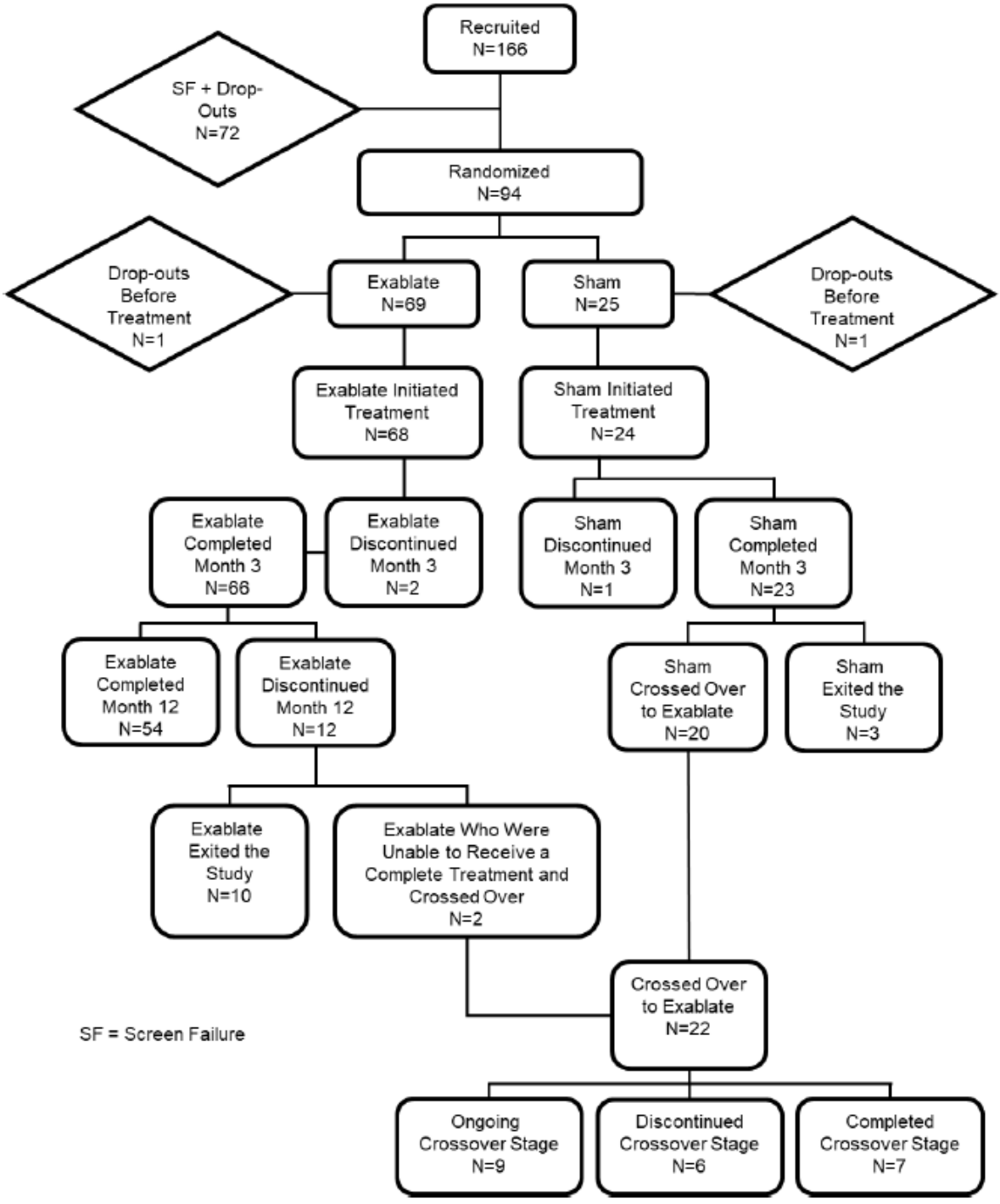
At the time of database lock, of 166 patients enrolled in the PMA study, 54.8% (91) patients (67 patients in the Exablate Neuro group and 24 patients in the sham control group) are available for analysis at the completion of the study, the 3 month post-operative visit. This also comprises the mITT population used to analyze the primary effectiveness endpoint. The disposition of the patients in the PD006 clinical study is described in Figure 2 and Table 2 shows the number of patients in the analysis populations.

**Table 2:** Analysis Populations used in the PD006 Study

| Analysis Populations | Treatment Group | | | | Total | |
|---|---|---|---|---|---|---|
| | Exablate | | Sham | | | |
| | N | % | N | % | N | % |
| ITT | 69 | 73.4 | 25 | 26.6 | 94 | 100.0 |
| Safety[1] | 68 | 73.9 | 24 | 26.1 | 92 | 100.0 |
| mITT[2] | 67 | 73.6 | 24 | 26.4 | 91 | 100.0 |
| PP[3] | 63 | 74.1 | 22 | 25.9 | 85 | 100.0 |

[1] One subject in each treatment arm did not proceed to treatment when COVID-19 pandemic occurred. [2] One subject in the treatment arm did not return for any follow-up visits and could not be included in the mITT analyses. [3] Six subjects (4 Exablate and 2 Sham) had observed primary efficacy data at Month3, and no major protocol deviations.

**Figure 2:** Patient Disposition Flow Chart for PD006 Study




## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a Parkinson's disease study performed in the US.

| Table 3. Demographic Characteristics | | | |
|---|---|---|---|
| **Demographic Characteristics** | | **Treatment Group** | |
| | | **Exablate Neuro** | **Sham** |
| Age [Years] | Mean | 64.2 | 63.3 |
| | N | 68 | 24 |
| Body Mass Index (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%) | 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 (100.0%)* |
| Ethnicity | Hispanic | 2 (3.0%) | 2 (9.1%) |
| | Non-Hispanic | 64 (97.0%) | 20 (90.9%) |
| | Total | 66 (100.0%)* | 22 (100.0%)* |
| Time from Initial PD Symptoms [Years] | Mean | 10.5 | 11.1 |
| | 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 |

*N is based on observed data available.

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the safety cohort of 68 patients in the Exablate Neuro group and 24 patients in the sham control group. The safety data for the 68 patients in the Exablate Neuro group available for the 12 month evaluation were analyzed. The safety data for the sham control group was only collected through the 3-month follow-up visit at which time all sham control patients could cross over to the Exablate Neuro treatment or exist the study. Serious adverse effects and all adverse effects are reported in Tables 4 and 5. The key safety outcomes for this study are presented below in Tables 6 to 8. All of the adjudication of the relatedness and severity of the adverse events were made by the DSMB.

**Adverse effects that occurred in the PMA clinical study:**

Table 4 presents all of the serious adverse events (SAEs) reported in the PD006 clinical study. There were 10 patients (14.7%) in the Exablate Neuro group with 15 SAEs and 1 (5.6%) patient in the sham group with 1 SAE. Pulmonary embolism was the only SAE categorized by the DSMB as related to the Exablate Neuro treatment. The patient developed a pulmonary embolism that was observed during the 1-week follow-up visit. The majority of the patients who experienced neurological SAEs appear to have been responders to the Exablate Neuro treatment and the SAEs were ultimately resolved.

**Table 4:** All Serious Adverse Events Observed in the PD006 Study

| Serious Adverse Events | Exablate | | Sham | | AE Onset From Treatment (Days) | AE Duration (Days) | Responder or Non-Responder |
|---|---|---|---|---|---|---|---|
| | Frequency (N=131) | Incidence (N=68) | Frequency (N=18) | Incidence (N=24) | | | |
| Pulmonary Embolism | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 5 | 1 | Non-Responder |
| Cholecystitis | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 8 | 1 | Responder |
| Hernia | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 13 | 1 | Responder |
| Subdural Hematoma | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 18 | 53 | Responder |
| Subdural Hemorrhage | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 361 | 28 | Responder |
| Stroke | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 354 | 10 | Responder |
| Fall | 2 (1.5%) | 2 (2.9%) | 0 (0%) | 0 (0%) | 19 and 287 | 70 and 220 | Responder and Non-Responder |
| Deep Vein Thrombosis | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 26 | 79 | Non-Responder |
| Metastatic Endometrial Cancer | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 59 | Ongoing | Non-Responder |
| Laminectomy | 0 (0%) | 0 (0%) | 1 (5.6%) | 1 (4.2%) | 75 | 324 | Non-Responder |
| Leg Fracture | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 83 | 129 | Responder |
| Myocardial Infarction | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 148 | 0 | Responder |
| Diverticulitis | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 287 | 92 | Non-Responder |
| Interstitial Pneumonia | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 313 | 16 | Responder |
| Cytomeglovirus | 1 (0.8%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 406 | Ongoing | Responder |
| **Total SAEs** | **15 (11.5%)** | **10* (14.7%)** | **1 (5.6%)** | **1 (4.2%)** | | | |

*Some patients experienced more than one SAE.

**Table 5. Frequency and Incidence of Adverse Events by Treatment Group**

| **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%) |

| Table 5. Frequency and Incidence of Adverse Events by Treatment Group | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| | | 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%) |
| | 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%) |

| Table 5. Frequency and Incidence of Adverse Events by Treatment Group | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| | 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%) |
| | 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%) |
| | | 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%) |

| Table 5. Frequency and Incidence of Adverse Events by Treatment Group | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| | | 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%) |
| | | 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%) |

| Table 5. Frequency and Incidence of Adverse Events by Treatment Group | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| | | 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%) |
| | | 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%) |
| | | 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%) |

| Table 5. Frequency and Incidence of Adverse Events by Treatment Group | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| | | 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) |

There were a total of 149 adverse events (AEs) that occurred in the clinical study with 131 AEs that occurred in the Exablate Neuro group and 18 AEs in the sham control group. Table 6 shows the number of patients in the Exablate Neuro and sham control arms of the study who experienced at least one AE during the trial.

| Table 6. Patients With and Without Adverse Event | | | | |
|---|---|---|---|---|
| **Experience of at Least One Adverse Event** | **Treatment Group** | | | |
| | **Exablate Neuro** | | **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 7 presents all AEs observed during the PD006 clinical study based on severity and Table 8 shows the onset of the AE and whether the AE was resolved or not for both study groups.

| Table 7. Severity of Adverse Events | | | | |
|---|---|---|---|---|
| | 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** | 2 (1.5%) | 3 (4.4%) | 0 (0%) | 0 (0%) |
| **Total** | 131 (100.0%) | 43 (63.2%) | 18 (100.0%) | 12 (50.0%) |

**Table 8:** Adverse Event Onset vs. 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%)** |

2. Effectiveness Results

The analysis of effectiveness was based on the 67 and 24 evaluable patients in the Exablate Neuro and sham control groups, respectively, at the 3-month time point (mITT population). Key effectiveness outcomes are presented in Tables 9 to 13.

As stated above, each patient was defined as a "Responder" or "Non-Responder" based on whether the patient improved on the MDS-UPDRS Part III (OFF medication motor exam on the treated side) and had no worsening on the UDysRS Impairment (ON medication) OR the patient improved on the UDysRS Impairment (ON medication) and had no worsening on the MDS-UPDRS Part III (OFF medication motor exam on the treated side). The "Responder" and "Non-Responder" definitions for improvement or worsening of the clinical outcome in the PD006 clinical study is defined as follows:

- MDS-UPDRS Part III (OFF medication motor exam) on the treated side:
  - Improvement is defined as a reduction of more than 3 points at the 3-month follow-up visit compared to baseline.
  - Worsening is defined as an increase of 4 points or more at the 3-months follow-up visit compared to baseline.
- UDysRS (ON medication):
  - Improvement is defined as a reduction of more than 3 points at the 3-months follow-up visit compared to baseline.
  - Worsening is defined as an increase of more than 3 points at the 3-month follow-up visit compared to baseline.

Out of 67 mITT patients randomized to the Exablate Neuro group, 65 completed the 3-month follow-up visit and had an observed primary outcome. Out of 24 mITT patients randomized to the Sham group, 23 completed the 3-month follow-up visit and had an observed primary outcome. The primary outcome shown in Table 9 was imputed using multiple imputation (as defined in the statistical analysis plan (SAP)) for the 3 missing patients: 2 Exablate Neuro patients and one sham patient.

The mean number of responders was 68.6% (46/67) of patients in the Exablate Neuro study arm compared to 33.3% (8/24) of patients in the sham study arm. Using the imputation analyses, the results yielded the odds ratio between groups of 4.4. The p-value is 0.005. The null hypothesis was rejected.

| Table 91. Primary Effectiveness Outcome - 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% Confidence Limit (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** | | |

Tables 10-12 shows the results of the confirmatory secondary effectiveness outcomes to assess the percent change improvement from baseline to the 3-month follow-up visit on the following assessments for both the Exablate Neuro and sham control groups:

- MDS-UPDRS Part IV;
- MDS-UPDRS Part III OFF Medication, Treated Side Extremities;
- MDS-UPDRS Part II.

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. An individual's score is the sum of the items in the MDS-UPDRS Part IV ON Medication. As shown in Table 10, the results demonstrate a 46% improvement compared to baseline in the Exablate Neuro study arm while there was no improvement in the sham control group. The difference between treatment groups was significant with a p-value of $< 0.001$.

**Table 10:** Confirmatory Secondary Effectiveness Outcome Analysis – MDS-UPDRS Part IV (mITT Population)

| Visit / Statistics | | MDS-UPDRS Part IV- Motor Complication | | | | | |
|---|---|---|---|---|---|---|---|
| | | 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 study arm had a baseline score of "0," and % change from baseline cannot be calculated for patients who have a baseline score of "0."

The effect of the Exablate Neuro unilateral pallidotomy on motor complications as measured by the MDS-UPDRS Part III OFF Medication was assessed by the movement disorders specialist. All measurements are taken in the OFF medication condition for the treated side only and have a maximum total score of 44 points. The 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 11 below, the study data demonstrated a mean 26% improvement compared to baseline in the Exablate Neuro group and 6% in the Sham group (p=0.015).

**Table 11:** Confirmatory Secondary Effectiveness Outcome Analysis – MDS-UPDRS Part III OFF Medication Treated Side Motor Score (mITT Population)

| | | 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 | | | | | |

The MDS-UPDRS Part II focuses on the effect of PD symptoms on motor aspects of daily living. Patient's daily routine activities evaluated include: 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. The individual's score is the sum of items in the MDS-UPDRS Part II.

As shown in Table 12 below, the study data demonstrated a 16% improvement compared to baseline for the Exablate Neuro group, while the sham group demonstrated a 30% worsening compared to baseline. The difference between treatment groups was highly significant with a p-value of 0.013.

**Table 12:** Confirmatory Secondary Effectiveness Outcome Analysis – MDS-UPDRS Part II Daily Living Score (mITT Population)

| | | 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 | | | | | |

A sensitivity analysis evaluated the robustness of the primary study outcome following data imputation that was performed on the mITT population in worst-case and best-case imputations. Under the best-case scenario, all patients that had missing data for the primary outcome analysis were imputed as "Responders". Under the worst-case scenario, all patients that had missing data for the primary outcome analysis were imputed as "Non-Responders". Table 13 presents the results of the primary outcome analysis with worst-case and best-case imputation scenarios. Under the best-case imputation, 70.1% and 29.2% of the Exablate Neuro and sham patients were "Responders," respectively. Under the worst-case imputation, the primary outcome remained statistically significant (p=0.013) with 67.2% and 37.5% of patients in the Exablate Neuro and sham arms, respectively, being "Responders."

Additional analyses of the primary outcome were conducted using the PP and ITT populations. The results showed that the primary effectiveness and confirmatory secondary effectiveness outcomes were statistically significant (p-value < 0.05) between the number of responders in the Exablate Neuro and sham study arms.

| Table 13. Sensitivity Analysis of Primary Outcome | | | | |
|---|---|---|---|---|
| | Worst-Case | | Best-Case | |
| Statistics | Exablate | Sham | Exablate | Sham |
| Total N | 67 | 24 | 67 | 24 |
| Responder | 45 | 9 | 47 | 7 |
| Responder Rate | 67.2 | 37.5 | 70.1 | 29.2 |
| Lower 95% CL | 54.6 | 18.7 | 57.7 | 12.6 |
| Upper 95% CL | 78.2 | 59.5 | 80.8 | 51.1 |
| CL Interval | 23.6 | 40.8 | 23.1 | 38.5 |
| P-Value | 0.013 | | < 0.001 | |

3. Subgroup Analyses

No subgroup analyses were conducted based on any preoperative characteristics, such as sex/gender, site, age, race or ethnicity, to evaluate for potential association with outcomes.

4. Pediatric Extrapolation

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

### E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 20 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The PD006 clinical study was designed with the following four secondary effectiveness outcome analyses based on data collected through 12-months post-procedure for the Exablate Neuro study arm and 3-month follow-up data for the sham control arm to assess the durability of the Exablate Neuro treatment up to 1-year post-procedure:

- MDS-UPDRS Part III OFF Medication, Treated Side Extremities;
- MDS-UPDRS Part II;

- MDS-UPDRS Part IV;
- UDysRS Part III Objective Impairment.

Table 14 shows the MDS-UPDRS Part III OFF Medication analysis for both study groups and showed that the percent change from baseline for the Exablate Neuro arm was stable through the 12-month follow-up visit: 20% at 1-month, 26% at 3-months, 26% at 6-months, and 22% at 12-months follow-up.

**Table 14. Secondary Outcome - MDS-UPDRS Part III OFF Medication - Treated Side Motor Score through Month 12 (mITT)**

| | | OFF Medication MDS-UPDRS Part III Motor Score | | | | | |
|---|---|---|---|---|---|---|---|
| **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 | |
| | 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 | |

| Table 14. Secondary Outcome - MDS-UPDRS Part III OFF Medication - Treated Side Motor Score through Month 12 (mITT) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | OFF Medication MDS-UPDRS Part III Motor Score | | | | | |
| Visit / Statistics | | Calculated Score | | Change from Baseline | | Percent Change from Baseline | |
| | | Exablate | Sham | Exablate | Sham | Exablate | Sham |
| | N | 67 | | 67 | | 67 | |

Table 15 shows the MDS-UPDRS Part II score for the Exablate Neuro study arm through 12-months post-procedure and through 3-months for the sham control study arm. The MDS-UPDRS Part II score provides an overall measure of the impact of PD on motor aspects of the patient's routine daily activities. This questionnaire is completed by the patient or the caregiver regarding the amount of care or support needed to do activities of daily living. In the Exablate Neuro group, the mean slightly improved from 15.1 at baseline to 12.3 at 3-months post-procedure, and 13.6 at 12-months post-procedure. At 6-months and 12-months post-procedure, there was an improvement in the mean score compared to baseline of 1.8 and 1.5 points, respectively.

**Table 15:** Secondary Outcome – MDS-UPDRS Part II through 12-Months Post-Procedure (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 | | | | |

| Visit / Statistics | | Motor Aspects of Experiences of MDS-UPDRS Part II Daily Living | | | | | |
|---|---|---|---|---|---|---|---|
| | | Calculated Score | | Change from Baseline | | Percent Change from Baseline | |
| | | Exablate | Sham | Exablate | Sham | Exablate | Sham |
| Month 1 | Mean | 11.8 | 12.3 | 3.3 | 0.9 | 21.8 | -16.9 |
| | Lower 95% CL | 10.2 | 10.0 | 1.9 | -1.3 | 13.6 | -55.5 |
| | Upper 95% CL | 13.5 | 14.5 | 4.6 | 3.1 | 30.1 | 21.8 |
| | N | 67 | 24 | 67 | 24 | 67 | 24 |
| | Comparison to Baseline | | | | | <.001 | 0.729 |
| | Between Group Difference | | | | | 0.013 | |
| 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 | |

| Visit / Statistics | | Motor Aspects of Experiences of MDS-UPDRS Part II Daily Living | | | | | |
|---|---|---|---|---|---|---|---|
| | | Calculated Score | | Change from Baseline | | Percent Change from Baseline | |
| | | Exablate | Sham | Exablate | Sham | Exablate | Sham |
| Month 6 | Mean | 13.3 | | 1.8 | | 7.5 | |
| | Lower 95% CL | 11.6 | | 0.2 | | -2.9 | |
| | Upper 95% CL | 15.1 | | 3.4 | | 18.0 | |
| | N | 67 | | 67 | | 67 | |
| | Comparison to Baseline | | | | | 0.173 | |
| Month 12 | Mean | 13.6 | | 1.5 | | 4.7 | |
| | Lower 95% CL | 11.8 | | -0.2 | | -6.5 | |
| | Upper 95% CL | 15.4 | | 3.1 | | 15.9 | |
| | N | 67 | | 67 | | 67 | |
| | Comparison to Baseline | | | | | 0.235 | |

Table 16 shows the MDS-UPDRS Part IV assessment of dyskinesias and motor fluctuations collected through 12-months post-procedure for the Exablate Neuro study arm and through 3-months post-procedure for the sham control patients. The percent change from baseline showed that improvement in the MDS-UPDRS Part IV score was maintained and stable in the Exablate Neuro treated patients through 12-months post-procedure: 45% at 1 month, 46% at 3 months, 45% at 6 months, and 38% at 12 months.

**Table 16. Secondary Endpoint - MDS-UPDRS Part IV - Motor Complication Score through Month 12 (mITT)**

| Visit / Statistics | | MDS-UPDRS Part IV- Motor Complication | | | | | |
|---|---|---|---|---|---|---|---|
| | | 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 | | | | |

| Table 16. 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 |
| | Upper 95% CL | 11.4 | 11.8 | | | | |
| | N | 67 | 24 | | | | |
| 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 study arm had a baseline score of "0." The % change from baseline cannot be calculated for patients who have a baseline score of "0."

Table 17 shows the UDysRS Part III Objective Impairment score that assesses four daily activities of communication, drinking from a cup, dressing and ambulation for Exablate Neuro study patients through 12-months post-procedure and through 3-months post-procedure for the sham control patients. The results show that the Exablate Neuro treated patients had a 38% improvement in the UDysRS Part III Objective Impairment score from baseline compared to a worsening of -3.8% from baseline for the sham control patients through 3-months post-procedure. Additionally, the percent change from baseline for the

UDysRS Part III Objective Impairment score in the Exablate Neuro treated patients still showed improvement through 12-months post-procedure, although the amount of improvement seems to decrease over time: 42% at 1 month, 38% at 3 months, 32% at 6 months, and 9% at 12 months after the procedure.

**Table 17:** Secondary Outcome – UDysRS Part III Objective Impairment Score Through Month 12 (mITT)

| Visit / Statistics | | UDysRS Objective Impairment | | | | | |
|---|---|---|---|---|---|---|---|
| | | 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 | |
| | Lower 95% CL | 3.8 | | 0.7 | | -13.3 | |
| | Upper 95% CL | 5.9 | | 3.1 | | 30.7 | |
| | N | 67 | | 67 | | 60* | |

*Some patients had a score of "0" at baseline. The % change from baseline cannot be calculated for patients who have a baseline score of "0."

The PD006 clinical study was also designed to evaluate the following clinical secondary outcomes, although no statistical inference could be made and only descriptive statistics are presented:

- Historical and Objective UDysRS sub-scores at all visits as well at the Total UDysRS score;
- MDS-UPDRS: Total of Parts I, II, III OFF Medication (Treated Side), and IV ON Medication.

The UDysRS evaluates dyskinesias (involuntary movements) associated with PD patients on medication. The UDysRS has two primary sections of Historical (Part 1: On-Dyskinesia, Part 2: Off-Dystonia) and Objective (Part 3: Impairment, Part 4: Disability). Table 18 presents descriptive statistics of the total UDysRS (Historical + Objective) score for Exablate Neuro patients through 12-months post-procedure and sham patients through 3-months post-procedure. The Exablate Neuro treated patients showed a 48% improvement in the total UDysRS score from baseline compared to an improvement of 7% from baseline for the sham control patients at 3-months post-procedure. For the Exablate Neuro treated patients, the percent change from baseline showed improvement of 52% at 1 month, 48% at 3 months, 43% at 6 months, and 32% at 12 months after the procedure.

The overall MDS-UPDRS covers four sections of Part I: Non-Motor Aspects of Experiences of Daily Living, Part II: Motor Aspects of Experiences of Daily Living, Part III: OFF Medication Motor Examination, and Part IV: Motor Complications. Table 19 presents descriptive statistics of the total MDS-UPDRS (Part I + Part II + Part III OFF Medication (extremities treated side) + Part IV) score through 12-months post-procedure for the Exablate Neuro treated patients and through 3-months post-procedure for the sham control patients. The Exablate Neuro treated patients showed a 26% improvement of the total MDS-UPDRS score at 3-months post-procedure compared to baseline while the sham control patients showed a 3% improvement at 3-months post-procedure compared to baseline. The percent change from baseline of the total MDS-UPDRS score for the Exablate Neuro treated patients through 12-months post-procedure was 27% at 1 month, 26% at 3 months, 23% at 6 months, and 20% at 12 months.

**Table 18:** UDysRS Total Score (mITT)

| Visit / Statistics | | Unified Dyskinesia Rating Scale (UDysRS) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 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. The % change from baseline cannot be calculated for patients who have a baseline score of "0."

| Table 2. 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 | |
| | 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 | |

Both Exablate Neuro and sham study patients in the PD006 pivotal trial received adjunctive medication therapy (i.e., levodopa) throughout all study visits. All patients in both study arms were counseled to keep their levodopa dosage unchanged at least during the first 3-months post-procedure. As shown in Table 20, the levodopa medication usage is fairly stable through 12-months post-procedure based on the available data in both study arms.

**Table 20**: Adjunctive Medication Treatment with 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. | | | |

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

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

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The Exablate Neuro group demonstrated a 68.6% responder improvement rate, while the sham group demonstrated 33.3% improvement by 3-months post-procedure. This difference in the responder rate between treatment groups was significant ($p < 0.005$).

## B. Safety Conclusions

The risks of the device are based on nonclinical laboratory, animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above. A total of 149 adverse events were reported based on the safety population of 92 patients (68 patients in the Exablate Neuro group, 24 patients in the sham control group), with a total of 131 adverse events observed in 43 Exablate Neuro treated patients (63.2%) and 18 adverse events reported in 12 sham patients (50%).

Of the total adverse events observed in the PD006 pivotal trial, 91% of adverse events in the Exablate Neuro study group [119/131] and 94% (17/18) of adverse events in the sham group were categorized by the DSMB as mild or moderate. There were a total of 16 serious adverse events observed in the pivotal trial. The DSMB adjudicated 14 of the 15 serious adverse events observed in the Exablate Neuro group as unrelated to the Exablate Neuro device or procedure. Out of the 16 serious adverse events, 15 events occurred in the Exablate Neuro study arm through 12-months post-procedure and 1 event occurred in the sham control arm through 3-months post-procedure.

## C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The response to treatment and primary effectiveness outcome is evaluated by whether a patient improved on either the MDS-UPDRS Part III (OFF medication motor exam on the treated side) or UDysRS Objective Impairment (ON medication) without worsening on the other assessment. The results showed that the Exablate Neuro group demonstrated a 68.6% responder improvement rate, while the sham group demonstrated 33.3% improvement by 3-months post-procedure. This difference in the responder rate between treatment groups was significant ($p < 0.005$).

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Of the total adverse events observed in the PD006 pivotal trial (149), 91% of adverse events in the Exablate Neuro study group [119/131] and 94% (17/18) of adverse events in the sham group were categorized by the DSMB as mild or moderate. There were a total of 16 serious adverse events observed in the pivotal trial. The DSMB adjudicated 14 of the 15 serious adverse events that occurred in the Exablate Neuro group as unrelated to the Exablate Neuro device or procedure. Out of the 16 serious adverse events observed in the PD006 pivotal study, 15 events occurred in the Exablate Neuro study arm through 12-months post-procedure and 1 event occurred in the sham control arm through 3-months post-procedure.

Additional factors to be considered in determining probable risks and benefits for the Exablate Neuro device included that the PD006 pivotal study was designed with three (3) confirmatory effectiveness outcomes of MDS-UPDRS Part IV, MDS-UPDRS Part III OFF Medication for the treated side extremities, and MDS-UPDRS Part II that all showed a statistically significant difference between the Exablate Neuro and sham study groups where greater improvement was observed in the Exablate Neuro group at 3-months post-procedure. These clinical outcomes and the assessment of UDysRS Part III Objective Impairment showed that improvement in the Exablate Neuro treated patients were maintained through 12-months post-procedure.

1. Patient Perspective

   Patient perspectives considered during the review included:

   - A Patient Global Impression of Change (PGIC) assessment, which is a 7-point scale where the patient rates the severity of their condition at the time of assessment relative to before the Exablate Neuro or sham treatment dependent on the treatment assignment of the patient.
   - A patient satisfaction questionnaire that is comprised of 5 questions assessing treatment satisfaction.

   The PGIC and the patient satisfaction questionnaire showed a higher percentage of patients in the Exablate Neuro group felt their condition post-treatment improved or were satisfied with the treatment, respectively, compared to the patients in the sham group.

In conclusion, given the available information above, the data support that for 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, the probable benefits outweigh the probable risks.

### D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Based on the results of the pivotal study, the unilateral thermal ablation of the GPi adjunctive to medication using the Exablate Neuro may provide benefit as an alternative to other existing treatments relative to the risks in selected patients with severe disabling motor complications of advanced, idiopathic Parkinson's disease.

## XIV. CDRH DECISION

CDRH issued an approval order on October 29, 2021. The final clinical conditions of approval cited in the approval order are described below.

PMA Post-Approval Study (PAS): The purpose of the PAS is to provide follow-up on those patients in the "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease with Unilateral Lesioning of the Globus Pallidum using the Exablate Neuro System (PD006)" study and enroll new patients to determine the durability of treatment and whether there are fewer serious adverse events in the newly enrolled patients than occurred in the pivotal study. The PAS will evaluate the safety and long-term effectiveness of the Exablate Neuro 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. The PAS should be a registry study that includes the patients in the PD006 pivotal trial and all eligible patients from multiple sites with a minimum of 60 newly enrolled and treated patients. Newly enrolled patients should be followed at baseline, 6-months, 1-year, 2-years, 3-years, 4-years, and 5-years post-procedure with a missing data rate of 10% or less. The primary effectiveness outcome should be the same primary effectiveness outcome as the PD006 clinical study. The primary safety outcome is the assessment of all adverse events starting on or after the day of treatment through all study follow-up visits.

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

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES

None.