SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Magnetic Resonance Guided Focused Ultrasound Surgery System (MRgFUS)

Device Trade Name: ExAblate Model 4000 Type 1.0 System (ExAblate Neuro)

Device Product Code: 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

Date of FDA Notice of Approval: July 11, 2016

Expedited Access Pathway (EAP): Granted EAP designation status on September 25, 2015 because the device is intended to treat an irreversibly debilitating disease or condition, and addresses an unmet need.

II. INDICATIONS FOR USE

The ExAblate Neuro is intended 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.

III. CONTRAINDICATIONS

The ExAblate treatment is contraindicated for use in:

- Patients with standard contraindications for Magnetic Resonance Imaging (MRI) such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, allergies to MR contrast agent, etc.
- Women who are pregnant.
- Patients with advanced kidney disease or on dialysis.
- Subjects with unstable cardiac status or severe hypertension.
- Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse.
- History of abnormal bleeding, hemorrhage, and/or coagulopathy.

- Subjects receiving anticoagulants or drugs known to increase risk or hemorrhage within one month of focused ultrasound procedure.
- Subjects with cerebrovascular disease.
- Subjects with brain tumors.
- Individuals who are not able or unwilling to tolerate the required prolonged stationary position during treatment (approximately 2 hours).
- Subjects who have an Overall Skull Density Ratio of 0.45 (± 0.05) or less as calculated from the screening Computed Tomography (CT).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ExAblate Neuro labeling (Information for Prescribers and Operator's Manual).

V. DEVICE DESCRIPTION

The ExAblate Model 4000 Type 1.0 System ("ExAblate Neuro" or "the system") is a transcranial, magnetic resonance, image-guided focused ultrasound system ("MRgFUS"). The system combines a multiple-channel phased-array focused ultrasound ("FUS") transducer and magnetic resonance imaging ("MRI") in a closed-loop procedure for the thermal treatment of brain tissue, while monitoring the procedure in real-time.

The treatment effect of the ExAblate Neuro is achieved by guiding the focus of the ultrasound energy to the target region. The energy is then repeatedly transmitted to the target until the desired outcome is achieved. The targeted area is defined based on magnetic resonance ("MR") images taken during the procedure. The treatment procedure is constantly monitored by real-time closed-loop thermal feedback. Once the targeting is complete, the treatment outcome is confirmed with adequate post-treatment MR imaging sequences.

The physician analyzes the feedback information received during the procedure. The physician monitors patient safety and controls and adapts system parameters in order to gain optimal results. This is done via an interactive operator's workstation interface application.

The high-level technological characteristics and principles of operation are summarized below. For detailed descriptions, please refer to the Operator's Manual.

A. Technological Characteristics

The ExAblate Neuro is comprised of three main sub-systems:

1. Patient Table: Contains the FUS transducer with its positioning system.
2. Console/Workstation: Allows the user to run the ExAblate Neuro system through the clinical application software.
3. Supporting Equipment: The supporting equipment is located in 3 separate cabinets:

    - The Front End Cabinet contains the power amplifiers that drive the FUS transducer, as well as the control and monitoring electronics.

- The Equipment Cabinet contains the control Personal Computer (PC), power supplies, and control and data acquisition electronics.
- The Water System Cabinet contains equipment to cool and degas the water that is used as the interface between the transducer and the patient's head.

Each of these sub-systems is comprised of sub-units. They are all connected to each other via power, control and communication cables. The ExAblate Neuro system interfaces to the MRI machine mainly through the Workstation.

1. Hardware

The ExAblate Neuro consists of the following hardware components:

The Magnet Room houses the patient table with the helmet and the Front End Unit (**Figure 1**). The table is a standard MR table on which the patient lies. The helmet contains 1074 transducer arrays and attaches to the patient's head over a stereotactic frame and rubber diaphragm with circulating degassed water.

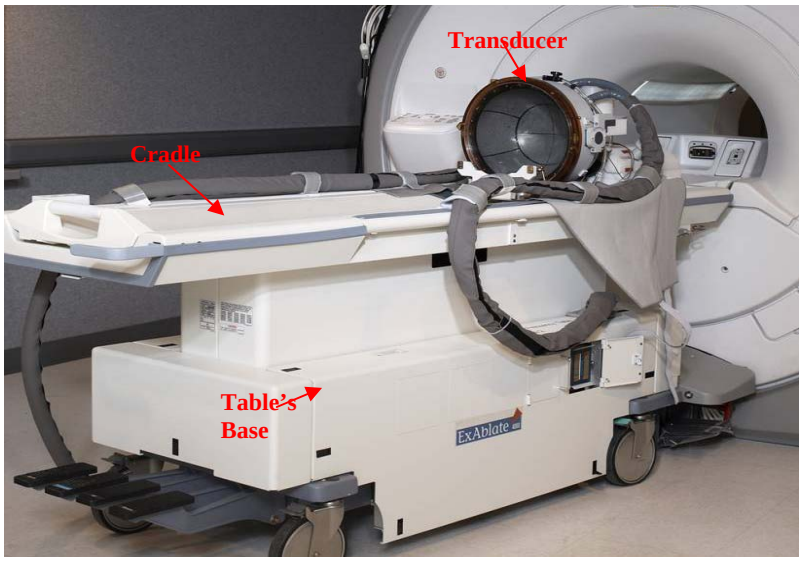

Figure 1: ExAblate Neuro Patient Table

The Front End Unit which is also located in the Magnet Room contains the high power electronic modules to drive and monitor the ultrasound transducer during the treatment, and operate the cooling mechanism.

Within the Equipment Room, the equipment cabinet houses the electronics and amplifiers required to power the system, along with the water cooling system.

Within the Control Room, the Workstation is a PC that has the ExAblate Neuro software installed and is referred to as the Control Personal Computer ("CPC"). The CPC controls the physical motion of the transducer and coordinates the power output and focusing of the transducer, as well as the water cooling system. The operator controls the ExAblate Neuro

using graphical interface-based software which communicates user requests and commands to the rest of the system. The Workstation has a monitor, a mouse and an emergency stop sonication button that cuts the power to the system in case of an immediate need to stop the sonication.

2. Software

The ExAblate Neuro software performs the following principal functions:

- Graphical user interface for system operation;
- MRI communication and remote operation of the MR;
- ExAblate hardware system operation and control;
- MRI image acquisition and viewing;
- Graphical treatment planning tools; and
- Calculations of thermal dose, and graphical monitoring of treatment thermal and acoustical parameters.

3. Accessories

The full list of key accessories needed for ExAblate Neuro operation is displayed below in **Table 1**.

Table 1: List of Accessories for use with the ExAblate Neuro

Name	InSightec P/N	Comments
Long / Short Stereotactic Frame Pins Set*	MPR000444 / MPR000445	For Stereotactic frame fixation.
Stereotactic Frame*	ASM001399	Stereotactic head frame, including adapters to ExAblate 4000 patient interface.
Frame Attachment Strap	MEC001647	Assists with stereotactic frame placement.
Protective Frame Pin Caps	MPR001164	Silicone protective caps used to cover the frame pins, for membrane protection. For single use. Supplied in groups of 5 units.
Silicone Membrane	ASM000355	For coupling of patient head to FUS helmet. Allows multiple uses. For use only with 3.0T MRI ExAblate system.
Helmet Sealant	BUY000180-AA	Tube containing sealant material for water-tight coupling to the transducer. For single-use.
DQA Gel	SET000893	Tissue mimicking phantom gel, used for Daily Quality Assurance (DQA).
Cleaning Kit	SET000870	Bottle filled with Sodium hypochlorite Chloride * based solution, and disinfectant wipes (based on benzalkonium chloride). This is used for cleaning after each treatment. For single-use.

Table 1: List of Accessories for use with the ExAblate Neuro		
Name	**InSightec P/N**	**Comments**
*: Integra Radionics MR-compatible stereotactic head frame with insulated pins and non-metallic posts (K946252 and K944463).		

B. Principles of Operation

When using the ExAblate Neuro, the patient lies on a patient table that fits into a standard MRI scanner as shown in Figure 1 above. The patient is prepared with a head shave, a catheter to empty the bladder, and an intravenous line for hydration and medication delivery. A stereotactic head frame is placed on the patient's head. The patient sits on the side of the table and has a rubber diaphragm placed over the scalp. Then the patient lies on his/her back on the MR table, the head frame is locked to the table and the helmet is attached to the stereotactic head frame and the rubber diaphragm. The patient is awake and responsive during the entire treatment.

Once the patient is in position, the ExAblate Neuro system is registered and aligned. Using a CT scan previously performed within 6 months of the treatment (requiring at least 2 dimensions in ≤ 1.0 mm slices) and loaded into the ExAblate Workstation, the physician calculates phase correction of the focused ultrasound beams as they cross the two bone layers of the skull. The operator takes MR images to align images in 3 axes with the CT images. Markers may be placed on the images, if needed, to indicate no-pass zones. Once the MR images have been attained, and treatment planning has been performed, then cold, degassed water is circulated under the rubber diaphragm, filling the space between the scalp and the transducer. The selected target, the ventralis intermedius ("Vim") nucleus of the thalamus, is unilateral (right or left side of the brain) and contralateral to the affected body side. The target is localized on MR by the treating neurosurgeon at low power.

Once the ExAblate Neuro is aligned, treatment with transcranial focused ultrasound energy is initiated in stepwise increments called sonications. After each sonication, patient feedback is sought regarding what they feel and how they respond to the sonication. The target is confirmed over incremental increases in energy until clinical effect (e.g., reduction of tremor without side effects) is observed. Once the target is confirmed by MR localization and clinical effect, the energy is increased to obtain a temperature rise at the target site for lesion creation. Once the lesion is created, a post-treatment set of MR images is collected in at least 2 planes to evaluate treatment effect. The patient is removed from the MR unit and the stereotactic frame is removed. Subjects are usually observed overnight following treatment.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of idiopathic Essential Tremor (ET) in patients with medication-refractory tremor, including:

- Surgical resection;
- Radiofrequency Thalamotomy;

- Deep brain stimulation; and
- Medication.

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

Outside the United States ("U.S."), the ExAblate system received the CE Mark in December 2012 for use in the treatment of neurological disorders (Essential Tremors, Tremor Dominant Idiopathic Parkinson's Disease – Unilateral) and neuropathic pain. The ExAblate system has also received the CE mark for pain palliation of Metastatic Bone Cancer in January 2009 and treatment of uterine fibroids in October 2002. Furthermore, the ExAblate is now regulatory approved for pain palliation of Metastatic Bone Cancer and treatment of uterine fibroids by Health Canada, Japan Ministry of Health, Labour and Welfare (MHLW), Korean Ministry of Food and Drug Safety (MFDS) and China Food and Drug Administration (CFDA).

In the U.S., the ExAblate system has been approved for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy (P110039). The ExAblate system has also been approved for the ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure (P040003).

The ExAblate is currently in commercial use in the United States, Israel, Europe, Canada, Japan, China, Russia, Korea, Brazil, India, and Australia, among other countries.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Adverse events for the ExAblate Neuro are consistent with those generally reported for thalamotomy, including numbness/tingling of the fingers, imbalance/unsteadiness, ataxia or gait disturbance, and headache.

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

Non-significant side effects of MRgFUS are those which normally resolve without sequelae within 10-14 days of treatment:

- Transient fever.

- Oral temperature > 100.4°F/ 38°C.
- Transient pain on the skin.
- Minor (1° or 2°) skin burns less than 2 cm in diameter.

Significant anticipated treatment side effects of MRgFUS 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 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

A. Bench Studies

Bench testing for the ExAblate Neuro is described in **Table 2** below:

Table 2: Summary of Preclinical Experiments

Category of Testing	Test Design	Acceptance Criteria and Results	Comments
Focusing ability in water, including electronic steering	Hydrophone measurement of focus in water compared to simulated values.	All tests met requirements, including: Spot Dimensions of 1.3 x 1.3 x 2.6 mm; Effective electronic steering of 15 mm around natural target; and Acoustic performance is as predicted by simulation of ideal transducer +/-10%.	Verified that the ExAblate transducer can precisely focus an ultrasound beam at a desired location in water. Verified no significant hot spots or focal intensity drop over various steering ranges, and according to simulation.
Thermal rise in target and MR thermometry	Sonications into tissue mimicking gel. Verified heating with MR thermometry. Verified MR thermometry with thermocouple readings.	All tests met requirements including: Difference within 2 °C.	Verified ExAblate can create the expected thermal spot in tissue mimicking phantom. Verified MR thermometry as used by ExAblate in 1.5 T and 3 T MR environments.
Transducer Power Measurements	Radiation force measurements.	Tests met requirements including: Acoustic power measurement accuracy is better than +/-10%.	Verified that the ExAblate system is delivering the prescribed acoustical energy and verified measurement accuracy.

Table 2: Summary of Preclinical Experiments			
Category of Testing	**Test Design**	**Acceptance Criteria and Results**	**Comments**
Skull aberration correction	Hydrophone measurement of focus in water through ex-vivo skull.	Tests met requirements including: Trans-skull Spot (after correction) has no hot spots; Dimension is +/-10% from no skull.	Verified that the (trans-skull) acoustic field after phase correction, is significantly better versus uncorrected, and maintains desired shape.
Sonication location accuracy	Sonications into tissue mimicking phantom, with MR thermometry to verify spot location	Tests met requirements including: Accuracy less than 1 mm.	Verified that distance from measured peak temperature to prescribed target was according to specifications.
Patient immobilization	Applied expected forces and torques on "patient interface".	Tests met requirements including: Maximal displacement when a load is applied = less than 0.5 mm / 2 mm for static / dynamic displacement.	Verified measured displacement of patient interface when exposed to expected forces/torques is within specification.
Transducer tracking	ExAblate 4000 in MR setup. Compare tracking results with transducer location as measured with standard MR images.	Tests met requirements including: Standard deviation of tracker readings less than 0.2 mm.	Verified that Tracking process yields robust and repeatable results that are accurately aligned with Transducer location, as measured with independent method.
Cavitation detection	Analysis of cavitation levels created by ExAblate, as measured by ExAblate receivers and independent acquisition system.	All tests met acceptance criteria per requirements, including: • System cavitation detectors detects in-vitro cavitation signal. • Cavitation signal meets requirement of being higher (an order of magnitude) than nominal signal. • Calibration procedure is robust and repeatable, and allows detection accuracy of +/-15%.	Verified cavitation calibration process, to ensure that all ExAblate systems have the same sensitivity and criteria with ExAblate unit used during cavitation safety study.

B. Electrical Safety and Electromagnetic Compatibility (EMC) Testing

The ExAblate Neuro passed testing per applicable electrical safety and electromagnetic compatibility testing standards as summarized in **Table 3** below.

Table 3: Electrical and EMC Testing		
Category of Testing	**Test Design**	**Comments**

Table 3: Electrical and EMC Testing		
Category of Testing	**Test Design**	**Comments**
Electrical Safety	Per IEC 60601-1-2	Device meets electrical safety requirements for its intended use and use environment
Electromagnetic Interference/Compatibility (EMI/EMC)	Per IEC 60601-1-3	Device meets EMC requirements for its intended use and use environment

C. Biocompatibility Testing

Biocompatibility testing was performed on the patient contacting portion of the final device. Specifically, the silicone diaphragm, which is a limited contact (< 24 hours) surface skin contacting accessory, was certified to be in accordance with *International Standard Organization (ISO) 10993-1 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing with a Risk Management Process.* The only other patient contacting device is the stereotactic head frame (and pins), which is a commercially available medical device with established biocompatibility (see FDA clearances K946252 and K944463).

D. Software Testing

The following ExAblate Neuro software functions were evaluated and all of the software functions passed the acceptance criteria:

- Operator-machine interface, including:
  - display of images and annotation overlays on the images;
  - display of geometrical structures and data and textual data;
  - status display for the various system components (Hardware & MRI);
  - tools for anatomic measurements and deduction of optimal imaging orientations and planes;
  - support of operator-generated drawing operations; and
  - support of operator command activation;
- ExAblate-MRI interface (activating MR scans and retrieval of MR images);
- Activation and control of system technical operation (energy transmission, sampling of transmitted and reflected energy, and sampling of acoustic spectral activity);
- Interpretation and display of thermometry images and treatment results;
- CT based computation of aberrations and bone warming, and compensation by beam shaping (phase-intensity array computations); and
- Simulation and prediction of sonication results, and sonication planning.

In addition, software documentation was provided to fulfill the recommendations in the Guidance for Industry and FDA Staff titled, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued on May 11, 2005.

E. Animal Studies

Animal studies for the ExAblate Neuro are described in **Table 4** below:

Table 4: Animal Testing

Category of Testing	Test Design	Acceptance Criteria and Results	Comments
Thermal rise in living brain tissue	In vivo experiment in swine model (with craniotomy).	All tests met acceptance criteria per requirements, including: Linear correlation between energy applied and temperature rise: $T_{rise} \sim 40$ °C / KJoule.	Verified that thermal heating and spot sizes are correlated with applied sonication parameters.
Brain tissue ablation	In vivo experiments (with craniotomy).	All tests met acceptance criteria per requirements, including: • Brain tissue ablation according to sonication parameters • Tissue damage is confined to targeted spot.	Verified that FUS thermal ablation in living brain tissue results in well-defined lesions without damage to non-targeted tissue.
Skull heating and cooling	Data analysis from in vivo pre-clinical experiments is used to verify skull heating simulation model.	All tests met acceptance criteria per requirements, including: • Verified all base assumptions used by the simulation model. • No skull heating damage for energy density < 100 J/cm^2 (sonication energy / active skull surface).	Verified adequate cooling time. Verified skull adjacent tissue temperature below thermal dose. Verified simulation with data from primate and pig experiments.
Animal trials for treatment efficacy estimation	Ten pigs underwent bilateral craniotomy to provide a bone window for the ultrasound beams. Later, a predefined, 1-3 cm frontal para ventricular region was treated with multiple sonications. The animals were sacrificed after a follow-up and the brains removed for pathological study.	All tests met acceptance criteria per requirements, including: • Ablation limited to focal point • Level of tissue ablation correlates with delivered energy • Accurate MR thermometry monitoring of temperature change	Verified efficacy and controllability of ablation of brain tissue using MRgFUS. Confirmed tissue ablation limited to targeted areas. Ablation performed with real-time MR thermometry

Table 4: Animal Testing			
Category of Testing	**Test Design**	**Acceptance Criteria and Results**	**Comments**
Animal trials for validation of the safety of the cavitation detection mechanism	Treatment of pigs in multiple treatment modes to locate and verify safety thresholds.	All tests met acceptance criteria per requirements, including: • System cavitation detectors detects in-vivo cavitation signal • Cavitation signal meets requirement of being higher (an order of magnitude) than nominal signal • Tissue damage is confined to targeted area, even when deliberately exceeding cavitation threshold.	Verified safety of ExAblate 4000 Type 1.0 in vivo. Verified system cavitation safety feature, to prevent cavitation and allow effective ablation of desired tissue.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of unilateral thalamotomy with ExAblate Neuro for the treatment of idiopathic Essential Tremor in patients with medication-refractory tremor in the U.S. under Investigational Device Exemption (IDE) G120246. Data from this clinical study were the basis for the Premarket Approval (PMA) decision. A summary of this pivotal clinical study is presented below.

In addition to the pivotal study conducted under G120246, a preliminary feasibility study was conducted under IDE G100169. Fifteen subjects were enrolled and treated at one site. This study has been completed and the full results of this study were published in the New England Journal of Medicine[1].

A. Study Design

Patients were treated between August 12, 2013 and September 30, 2014. The database for this PMA reflected data collected for primary endpoint analyses through Month-3 follow up and included 76 patients. There were 8 investigational sites.

The study was a prospective, multi-center, randomized (3:1), two-arm, sham-controlled, double-blinded, crossover clinical study. The study population was medication-refractory idiopathic essential tremor patients who failed two courses of essential tremor medications and who are functionally impaired as measured on the Clinical Rating Scale for Tremor (CRST) Part B. The duration of the study was 12 months with follow-up visits at 1 week, 1 month, 3 months, 6 months, and 12 months post-operatively.

[1] Elias, W.J., et al., *A pilot study of focused ultrasound thalamotomy for essential tremor.* N Engl J Med. 369(7): p. 640-8.

The control group was subjects who received the same procedure as the ExAblate treatment protocol without an active focused ultrasound being used (sham procedure). Both treatment and control groups received pre-treatment planning and post-treatment MRIs. All subjects were observed over night following treatment. All subjects were followed through the Month 3 follow-up visit and received the same assessments.

At the Month 3 follow-up visit, the subjects and local site assessors and Tremor Core lab assessors were un-blinded. The clinical investigators performing the surgical procedures were not blinded. ExAblate subjects, now un-blinded, had follow-up visits at Month 6 and Month 12 post-treatment. At the Month 3 follow-up visit, control (Sham) subjects were permitted to crossover to the ExAblate treatment group as long as they continued to meet all the inclusion/exclusion criteria in the protocol. Follow-up after crossover treatment was captured at Months 1, 3, 6 and 12 in a manner similar to the main analysis.

An independent group[2] within a professional neurological medical society was contracted to independently score movement disorder videos of study subjects, i.e., a Core Lab independent review. The purpose of the Tremor Core Lab review was to provide a uniform, blinded scoring across all sites.

Analysis Populations

Safety: The Safety population included all randomized subjects who received at least one sonication – ExAblate or Control (Sham) – in the Main stage (see analysis in Section X.D below) of the study.

Intent-to-Treat ("ITT"): The ITT analysis population included all Safety subjects for whom there exists a valid baseline measurement and at least one post-baseline measurement on the primary effectiveness data. The Safety and the ITT populations are identical and will be referred to as the ITT population hereinafter.

Per Protocol ("PP"): The PP analysis population included all ITT subjects who have observed primary effectiveness data at three months and have no major protocol violations likely to affect outcome.

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

[2] http://www.tremorresearchgroup.org/index.php/en/

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the G120246 study was limited to patients who met the following 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.
   a) The 1-Month stability period visit will be 1-month post consent date.

6) 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.

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).

Patients were <u>not</u> permitted to enroll in the G120246 study if they met any of the following exclusion criteria:

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; and
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 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (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); and
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 blood pressure (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/1.73 m^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 (cerebrovascular accident or stroke) or CVA within 6 months).

13) Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, or 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 (PD). 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 Patient Health Questionnaire (PHQ-9)
    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; and
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, International Normalized Ratio (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.

2. Follow up Schedule

All patients were scheduled to return for follow-up examinations at Day 1 (i.e., prior to discharge), Week 1 (± 3 days), Month 1 (± 7 days), Month 3 (± 14 days), Month 6 (± 21 days), and Month 12 (± 1 month) postoperatively. The study's primary endpoint was at Month 3, at which time all subjects were un-blinded. Sham subjects were then given an opportunity to crossover to the ExAblate treatment. Sham subjects who crossed over were scheduled to return for follow-up examinations at Month 1 (± 7 days), Month 3 (± 14 days), Month 6 (± 21 days), and Month 12 (± 1 Month) post ExAblate treatment.

The key time points are shown below in **Table 5** summarizing safety and effectiveness with the preoperative and postoperative objective parameters measured during the study. Adverse events and complications were recorded on all visits.

Table 5. Summary of Study Schedules 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. Clinical Endpoints

With regard to safety, the safety endpoint analyzed the incidence and severity of device-related adverse events (AEs)/serious adverse events (SAEs) from treatment day through the Month 12 post-treatment time point.

With regards to effectiveness, the primary endpoint (PE) is comparing the percent improvement (between Month 3 and Baseline) of the CRST scores between the ExAblate and Sham study groups using the following formula:

$$\mathbf{PE} = \%\ Improvement = \frac{CRST_{[contralateral\ \ Baseline]} - CRST_{[contralateral\ \ 3\ month\ FU]}}{CRST_{[contralateral\ Baseline]}} \text{ x } 100\%$$

Where the CRST score implemented for this study is the average of 8 components, this study combined the 3-components of the CRST Part A (tremor localization/severity rating) with the 5-components of the CRST Part B (specific motor tasks/function rating) from the *treated* side of the body, and it is referred to as the "Composite Tremor/Motor Function Score":

$$CRST_{[Contralateral]} = \frac{PART\_A + PART\_B}{Max\_Score}$$

Where: **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).

With regard to success/failure criteria, success for the primary effectiveness endpoint was defined 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.*

Statistical Analysis

Primary effectiveness analyses were conducted on the ITT analysis population and tested the following hypothesis:

H_0: $M3_{ExAblate} \leq M3_{Sham}$

H_1: $M3_{ExAblate} > M3_{Sham}$

Where, $M3_{ExAblate}$ and $M3_{Sham}$ are the means of primary endpoint (PE) in the ExAblate and Control (Sham) groups, respectively. This hypothesis was analyzed using independent group t-test with two-sided alpha=0.05, should the data not differ appreciably from normal theory. Otherwise, the Wilcoxon rank-sum test was applied. Based on the hypothesis testing, the study would be considered successful if the Null is rejected and the mean PE is higher in the ExAblate group than in the Sham group.

Secondary confirmatory endpoints evaluated during the study included the following:

- Questionnaire for Essential Tremor (QUEST) outcome (upper extremity questions) at Months 3 change from Baseline as compared between treatment groups;
- Durability (as measured by CRST upper arm extremity questions) of the procedure as reflected by the effectiveness data through change from baseline measures through Month 12 follow up;

- Subject daily functionalities as measured by CRST Part C (subscales), within group Month 12 as compared to baseline, and between treatment groups at Month 3, 6, and 12;
- Crossover cohort treatment outcome (perform secondary endpoints 1-3 above for the Crossover cohort).

B. Accountability of PMA Cohort

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 patients received treatment (i.e., 56 patients with ExAblate and 20 patients with Sham), of which 74 (97.4%) patients are available for analysis at the completion of the study, the Month 3 post-operative visit for the primary endpoints. There were two ExAblate patients who withdrew from the study prior to the Month 3 post-operative visit and did so for reasons unrelated to their participation in the study. All 20 Sham patients completed the primary endpoint post-operative visit (Month 3).

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

At the Month 3 follow-up visit, Sham patients were given the option of crossing over to the ExAblate treatment if they still met the enrollment criteria. Of the 20 Sham patients, 19 became Crossover patients. One Sham patient was undecided for several months, then withdrew from the study. In addition, as stated above, 2 non-responding ExAblate patients 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 patients. Of the Crossover patients, 21 out of 21 (100%) have completed their follow up visits through Month 6.

A subject accountability table (**Table 6**) and study flowchart (**Figure 2**) are provided below.

Table 6. 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							
Screening Failures 1, SF1[1]	33							
Discontinued for Reasons Other than SF (not yet randomized)	7							
Randomized[2]	61	20						
Screening Failures 2, 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.

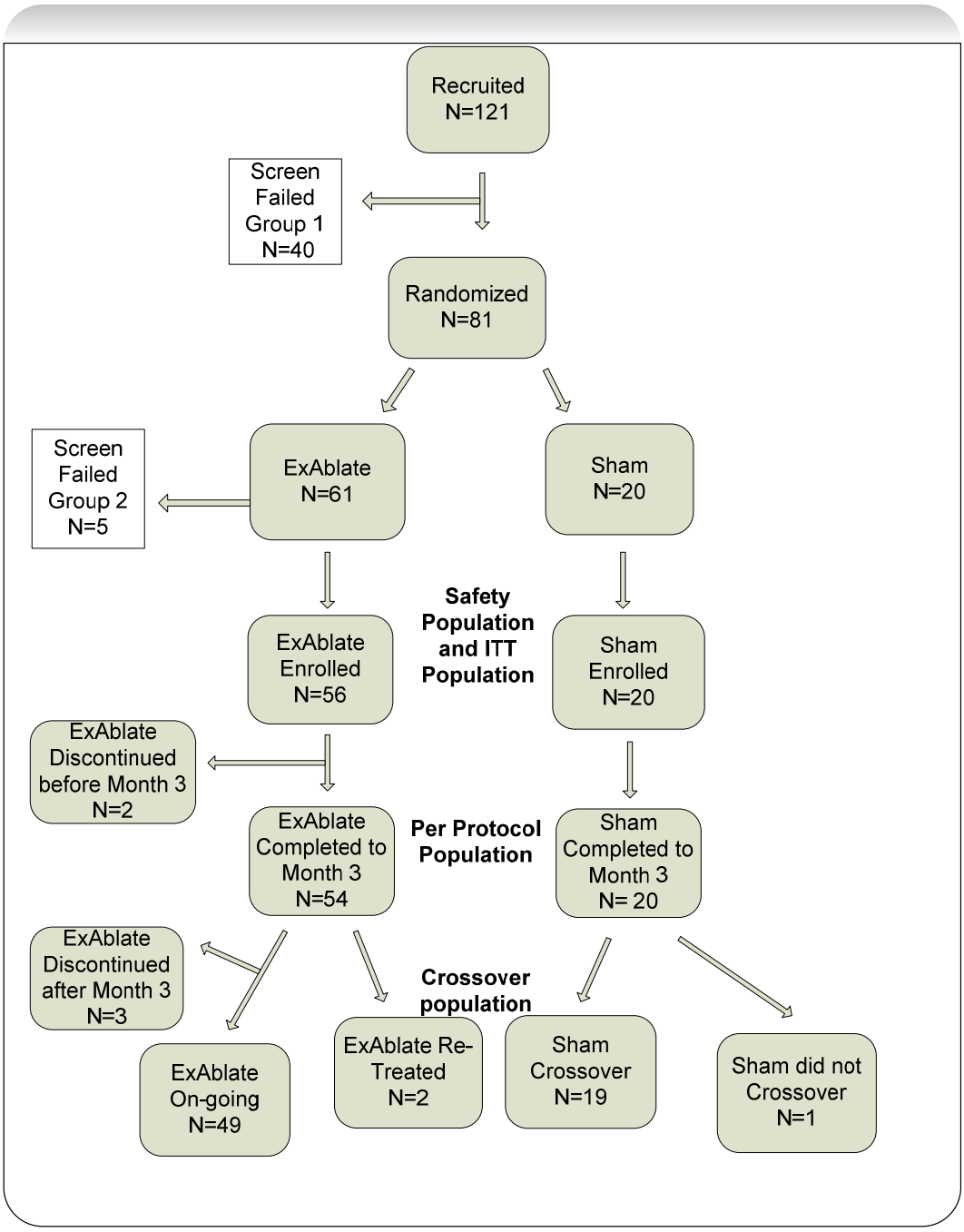

Figure 2: G120246 Study Flow Chart

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an ET study performed in the U.S. The Caucasian ethnicity reflects the general condition across the population in that Caucasians are 5 times more likely to report ET than Blacks. It should be noted that the Hispanic population epidemiology is between that of Caucasian and Black. The demographics, baseline, and operative characteristics were similar between the two treatment (ExAblate and Sham) groups, as shown in **Table 7** below.

Table 7. Baseline and Demographic Information by Treatment Group			
Demographic Characteristics		Treatment Group	
		ExAblate N=56	Sham N=20
Age [Years]	Mean	70.8	71.4
Body Mass Index (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	Mean	13.9	14.7
Skull Density Ratio "SDR"	Mean	0.6	0.5
Treated (Contralateral Upper Extremity (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.			

D. Safety and Effectiveness Results

Main Analysis

1. Safety Results

The analysis of safety was based on the ITT/Safety cohort of 76 patients (56 ExAblate patients and 20 Sham patients) available for the Month 12 evaluation. The Sham patients' AE data was only collected out to the Month 3 post-operative visit (i.e., primary endpoint), after which all Sham patients either crossed over to the ExAblate treatment or withdrew. **Table 8** below reflects the adverse effects data through the Month 12 follow-up visit for the ExAblate group and data through the Month 3 follow-up visit for the Sham group. **Table 9** 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.

In summary, the key safety outcomes for the study is that a total of 210 AEs in 76 patients were reported, 209 (99.5%) of which were either Mild or Moderate. There was also 1 (0.5%) unrelated Severe AE. In the ExAblate group, 184 AEs were reported by 49 ExAblate patients: 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 AEs or deaths. In the Sham group, which underwent all the procedural preparations, a total of 26 AEs in 14 patients were reported, and all (100%) of them were Mild or Moderate: 18 (70%) of these events were Mild, and 8 (30%) were Moderate. There were 6 patients in the Sham group who reported no AEs.

Table 8. 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 (0.5%)	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	Tinnitis	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
	Imbalance	7 (4%)	7 (13%)	3 (2%)	3 (5%)	0	0	1 (4%)	1 (5%)	0	0
	Muscukoskeletal Weakness	1 (0.5%)	1 (2%)	1 (0.5%)	1 (2%)	0	0	0	0	0	0
	Other Muskuloskeletal 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

Table 8. 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 # (%)**
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
	Dysgeugia	3 (2%)	2 (2%)	0	0	0	0	0	0	0	0
	Dysnogia	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
	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%)
	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

Table 8. 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 # (%)**
	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%)**	**10 (50%)**	**8 (31%)**	**6 (30%)**

Table 9. Adverse Events Onset versus Adverse Event Duration by Treatment Group												
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	Incidence N=56	Freq N=184	Incidence N=56	Freq N=184	Incidence N=56	Freq N=27	Incidence N=20	Freq N=27	Incidence N=20	Freq N=27	Incidence N=20
<30 days	88 (48%)	43 (77%)	2 (1%)	2 (4%)	4 (2%)	3 (5%)	24 (92%)	13 (65%)	0	0 (0%)	0	0 (0%)
31-90 days	14 (8%)	12 (21%)	2 (1%)	1 (2%)	1 (1%)	1 (2%)	2 (8%)	2 (10%)	0	0 (0%)	0	0 (0%)
> 90 days	25 (14%)	19 (34%)	2 (1%)	2 (4%)	4 (2%)	4 (7%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Ongoing	35 (20%)	21 (38%)	2 (1%)	2 (4%)	5 (3%)	3 (5%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
TOTAL	**162 (88%)**	**49 (88%)**	**8 (4%)**	**2 (20%)**	**14 (8%)**	**11 (9%)**	**26 (96%)**	**14 (70%)**	0	0 (0%)	0	0 (0%)

The safety profile indicates that 94% of the AEs were observed within 30 days after the procedure. About half of these AEs resolved within the first month. However, about half of the AEs following the ExAblate procedure persisted beyond 30 days and 23% were ongoing at 12 months. 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 10 presents the AEs that 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. Sixteen events were categorized as procedure-related (e.g., fatigue, weakness, headache, and sonication-related head pain) and lasted longer than 3 days. Fifty-eight events were listed as thalamotomy related and are similar to the types of events that have been reported in the literature as with radiofrequency lesioning or even DBS stimulation. Events with the greatest frequency were Numbness/Tingling (20), Imbalance (10), and Unsteady (7). There were 2 Sham procedure-related events including 1 generalized weakness, and 1 imbalance.

Table 40. Frequency of Adverse Events Categorized as Related to the Procedure or to Device/Thalamotomy by Treatment Group.

Relation/Body System, AE Coded Term			**ExAblate Arm N=184**		**Sham Arm N=26**	
			N	**%**	**N**	**%**
Procedure-related	ENT	Tinnitis	3	2%	0	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%
Procedure Related Subtotal			**16**	**9%**	**2**	**8%**

Table 40. Frequency of Adverse Events Categorized as Related to the Procedure or to Device/Thalamotomy by Treatment Group.						
Relation/Body System, AE Coded Term			**ExAblate Arm N=184**		**Sham Arm N=26**	
			N	**%**	**N**	**%**
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%
		Dysgeugia	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%
	Vestibular disorder	Dizziness	1	0.5%	0	0%
Subtotal Thalamotomy related			**58**	**32%**	**0**	**0%**
TOTAL			**74**	**100%**	**3**	**12%**

Serious Adverse Events

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 Data Safety Monitoring Board (DSMB) and adjudicated and FDA was notified of the occurrence of these events. The first ExAblate subject reported a Moderate event of numbness/tingling immediately following the procedure and the event was determined to be a SAE due to impairment. The DSMB adjudicated the event and agreed that it was thalamotomy-related. 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.

Mental Status Assessment - PHQ-9

An additional safety measure that was captured in this study was mental status of patients using the Patient Health Questionnaire (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 was counted as a SAE. The follow-up PHQ-9 scores showed that no study subject scoring a 20 or higher on the PHQ-9 (**Table 11**) at any time during the study. This outcome indicates that the ExAblate treatment does not induce depression.

Table 11. 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

2. Effectiveness Results

The primary analysis of effectiveness was based on the ITT population, i.e., the 76 evaluable patients at the Month 3 time point, while some secondary confirmatory effectiveness endpoints continued to Month 12. Key effectiveness outcomes are presented in **Table** to **Error! Reference source not found.**.

Primary Endpoint (PE)

As shown in **Table 12**, the ExAblate group demonstrated a 46.9% 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 12. Primary Endpoint (Composite Tremor/Motor Score): Mean Score and Percent Change from Baseline at Three Months by Treatment Group (ITT)					
	Treatment Group				
	ExAblate N =56		Sham N = 20		
	Mean Score	% Change	Mean Score	% Change	P-Value*
Primary Endpoint (PE)	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. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100 and reported as the mean for the ITT cohort 2. Lower PE values represent improvement *p-value reflects testing between groups.					

Confirmatory Secondary Endpoints

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 13** 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.

Table 13: Confirmatory Endpoint: Percent Change in the Composite Tremor/Motor Function in ExAblate Arm by Visit (ITT)			
		Treatment Group	
Visit	SE2	ExAblate	P-Value*
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	

Table 13: Confirmatory Endpoint: Percent Change in the Composite Tremor/Motor Function in ExAblate Arm by Visit (ITT)			
		Treatment Group	
Visit	SE2	ExAblate	P-Value*
	Upper 95% CI	45.3	
	N	56	
*p-value reflects testing vs. baseline Notes: 1. SE2 was calculated as Percent Change ({(Baseline - Visit)/Baseline}*100) 2. Higher SE2 values represent improvement			

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 (see **Table 4**).

Table 14. 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		Change from Baseline		ExAblate % change from baseline*	Sham % change from baseline*
			Treated Side		Treated Side			
			ExAblate N=56	Sham N=20	ExAblate (N=56)	Sham (N=20)		
/Part A - Posture Only	Baseline	Mean	2.13	1.65	N/A	N/A		
		Lower 95% CI	1.82	1.08	N/A	N/A		
		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	N/A	1.41	N/A	62.5% (n=52)	N/A
		Lower 95% CI	0.44		1.08		50.8%	
		Upper 95% CI	0.99	N/A	1.74	N/A	74.2%	N/A
	12 Months FU	Mean	0.68	N/A	1.45	N/A	65.5%	N/A
		Lower 95% CI	0.42	N/A	1.14	N/A	54.7%	N/A

Table 14. 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		Change from Baseline		ExAblate % change from baseline*	Sham % change from baseline*
			Treated Side		Treated Side			
			ExAblate N=56	Sham N=20	ExAblate (N=56)	Sham (N=20)		
		Upper 95% CI	0.94		1.76		76.3%	

* Calculated from means, not from individual subject scores.

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).

CRST Overall 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 15**). 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 15**, the improvement in the patient overall Functional Disability (CRST Part-C) when compared to baseline was 64%, 62% and 64% at Months 3, 6 and 12. This improvement was observed across all Functional Disability components for ExAblate-treated patients. However, little/no change to slight worsening was observed in the Sham-treated group for all Functional Disabilities.

Table 15. Confirmatory Endpoint - CRST Part C Overall Functional Disabilities Score /% Change from Baseline by Treatment Group and by Visit (ITT)

	ExAblate N=56		Sham N=20			
SE3	Change from Baseline *	% Change from Baseline**	Change from Baseline	% Change from Baseline	Between groups P Value+	Within groups p-value ExAblate Arm
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%				
Lower 95% CI	8.42	64.3%				
Upper 95% CI	11.69	81.8%				
Month 12	10.20	64.0%				
Lower 95% CI	8.66	55.2%				
Upper 95% CI	11.74	72.7%				

* Change from Baseline was calculated as: (Baseline - Visit).

**: % change calculated as: 100*(Baseline - Follow-up Visit)/Baseline

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

Note:

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

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

From the results reported in **Table 16**, 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 significant ($p < 0.001$).

Table 16. Confirmatory Secondary Efficacy QUEST Summary of Dimensions Score % Change from Baseline at Month 3 by Treatment Group (ITT)

	Treatment Group				
SE1	ExAblate N=56		Sham N=19**		P-Value*
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%	

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

In summary, the primary endpoint and all confirmatory secondary endpoints were met and were highly statistically significant (see **Table 17**).

Table 17. Effectiveness Analysis Summary

	% of Improvement At Month-3 – ITT			**% of Improvement At Month 12 – ITT**
	ExAblate (N=56)	**Sham (N=20)**	**Between Groups p-value**	**ExAblate (N=56)**
Primary Endpoint – Composite Tremor/Motor Function	46.9%	- 0.1%	p< 0.001	39.6%
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)		65.5 %
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%		64.0%
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%
Lower 95% CI	34.3%	-14.9%		36.5%
Upper 95% CI	56.3%	36.2%		62.1%
Note: A negative sign "-" indicates worsening condition.				

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.

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 $p < 0.001$.

Crossover Cohort Analysis

A total of 21 subjects were included in the Crossover Arm (19 Sham patients + 2 ExAblate patients that were re-treated). All data for Crossover patients was entered into a separate database, which included all safety and effectiveness data points. For all patients, the baseline value was taken from the original baseline visit for that patient. The Core Lab scored the CRST videos for the Crossover Arms as in the blinded portion of the study. Similar descriptive analysis and within-group statistics were performed on this cohort of patients. At the time of this PMA submission, not all patients had completed the 12 month follow up evaluation. All 21 patients completed the 1 week, 1, 3 and 6 month post-operative visits. Sixteen (16) of the 21 patients had completed the 12 month follow up.

1. Safety Results – Crossover Cohort

Similar to the Main Analysis population, the primary analysis of safety was based on 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. The Crossover safety profile shows no new AEs, and further re-affirms the safety profile of the Main population (see **Table 19**).

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 (see **Table 20**). Events with the highest frequency included headache (7), sonication-related headache (6), nausea/vomiting (4), and pin site pain (4).

Table 18 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 18. 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%)

Table 19. Frequency and Incidence of Adverse Events for ExAblate Crossover by Severity ExAblate							
Body System	**Preferred Term**	**Mild**		**Moderate**		**Severe**	
		Frequency N (%)	**Incidence # (%)**	**Frequency N (%)**	**Incidence # (%)**	**Frequency N (%)**	**Incidence # (%)**
Cardiovascular	Hypertension	1 (1%)	1 (5%)	1 (1%)	1 (5%)		
	Preventricular Contractsions	1 (1%)	1 (5%)				
	Sick Sinus Syndrome					1 (1%)	1 (5%)
Gastrointestinal	Dry mouth	1 (1%)	1 (5%)				
	Dysgeusia	2 (3%)	2 (10%)				
	Nausea/Vomiting	3 (4%)	3 (14%)	1 (1%)	1 (5%)		
General	Fatigue	1 (1%)	1 (5%)	1 (1%)	1 (5%)		
	Musculoskeletal Weakness	1 (1%)	1 (5%)	1 (1%)	1 (5%)		
Infections	Flu	1 (1%)	1 (5%)				
Musculoskeletal	Musculoskeletal Weakness	2 (3%)	2 (10%)				
	Dysmetria	2 (3%)	2 (10%)				
	Imbalance	2 (3%)	2 (10%)	1 (1%)	1 (5%)		
	Unsteady	1 (1%)	1 (5%)	1 (1%)	1 (5%)		
Nervous	Ataxia	2 (3%)	2 (10%)	2 (3%)	2 (10%)		
	Cognitive Disturbance	1 (1%)	1 (5%)				
	Dizziness	1 (1%)	1 (5%)				

Table 19. Frequency and Incidence of Adverse Events for ExAblate Crossover by Severity ExAblate							
Body System	**Preferred Term**	**Mild**		**Moderate**		**Severe**	
		Frequency N (%)	**Incidence # (%)**	**Frequency N (%)**	**Incidence # (%)**	**Frequency N (%)**	**Incidence # (%)**
	Dysarthria	2 (3%)	2 (10%)	1 (1%)	1 (5%)		
	Grogginess	1 (1%)	1 (5%)				
	Dysmnesia	1 (1%)	1 (5%)				
	Hand Tremor (untreated side)	1 (1%)	1 (5%)				
	Numbness/Tingling	10 (13%)	7 (33%)				
	Paresthesia	2 (3%)	2 (10%)				
	Slow Movements	1 (1%)	1 (5%)				
Pain/Discomfort	Headache	5 (7%)	5 (24%)	2 (3%)	2 (10%)	1 (1%)	1 (5%)
	Sonication-related head pain	4 (5%)	4 (19%)	2 (3%)	2 (10%)		
Stereotactic Head Frame	Pin Site Bleeding	1 (1%)	1 (5%)				
	Pin Site Edema	1 (1%)	1 (5%)				
	Pin Site Pain	4 (5%)	4 (19%)				
	Ptosis	1 (1%)	1 (5%)				
Vestibular Disorder	Dizziness	3 (4%)	3 (14%)				
	Vertigo	1 (1%)	1 (5%)				
TOTAL		**60**	**16 (76%)**	**14**	**8 (38%)**	**2**	**2 (10%)**

Table 20. 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%
		Parasthesia	1	1%
	Pain/Discomfort	Headache	7	9%
		Sonication-Related Head Pain	6	8%
	Vestibular Disorder	Dizziness	3	4%
		Vertigo	1	1%
Unrelated	Cardiovascular	Hypertension	2	3%
		PVC	1	1%
		Sick Sinus Syndrome	1	1%
	Gastrointestinal	Dry mouth	1	1%
		Dysgeusia	1	1%
	Infections	Flu	1	1%
	Nervous	Dysarthria	1	1%
		Dysmnesia	1	1%
		Hand Tremor	1	1%
	Stereotactic Frame	Pin Site Bleeding	1	1%
		Pin Site Edema	1	1%
		Pin Site Pain	4	5
		Ptosis	1	1
Total			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 21**). These events lasted longer than 72 hours. The most frequent events include numbness/tingling (8) and ataxia (4).

Table 21. 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%
		Parasthesia	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 22**). All of these events are either Mild or Moderate.

Table 22. Ongoing Adverse Events from the First 30 Days in ExAblate Crossover Arm.			
Body system	**Preferred term**	**Frequency N=**	**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 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.

2. Effectiveness Results – Crossover Cohort

As in the Main Analysis, the Primary Effectiveness Endpoint for the Crossover Arm is a composite of 3 tremor measurements and 5 motor function measurements (i.e., Composite Tremor/Motor Function score) that characterize the impact of Essential Tremor on the clinical "disability" level of an ET patient.

Primary Effectiveness Endpoint

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 23**). 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, which demonstrates a treatment response that is slightly better than that of the Main analysis (46.9% ExAblate, $p<0.01$). Data available through Month 12 follow-up demonstrate the CRST Composite

Tremor/Motor Function was 50% or greater as calculated from the Baseline at Month 3, 6, and 12 (N = 21 for Month 3 and 6, N=16 for Month 12, p<0.001). The percent improvement of CRST Composite Tremor/Motor Function Score for Crossover ExAblate is similar or slightly better than that experienced by the ExAblate Arm in the Main Analysis (47% ExAblate at Month 3; 43% at Month 6; 40% at Month 12; p<0.001 at all visits).

Table 5. Crossover Arm - Primary Endpoint (Composite Tremor/Motor Function % Improvement): Three Months Post-Treatment Analyses

	Treatment Group	
	ExAblate Crossover N =21	
$PE_{crossover}$	Mean Score	% Change
Mean	0.24	53.1%
Lower 95% CI	0.18	43.4%
Upper 95% CI	0.30	62.8%

Notes:
1. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100.
2. Higher SPE values represent improvement

Confirmatory Endpoint – CRST Overall Part C Comparison to Baseline

The CRST Part C is a Composite score across 8 activities of daily living and measures the level of disability experienced by a patient with ET. Low scores (Higher Percent Change) represent improvement. **Table 24** shows all available data shown through Month 12 for the ExAblate Crossover group. While not all the patients have completed the Month-12 follow up visits, the p-value at Month-12 shows high significance (p=0.004). The result for the ExAblate Crossover Arm compares favorably with that of the Main Analysis where the ExAblate group experienced mean improvement in activities of daily living of 62% to 64% at all visits (p<0.001 at all visits). The ExAblate Crossover Arm surpassed this level of improvement to almost 75% (p<0.001).

Table 24. 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
3 Months FU Mean N=21	4.29	74.6%
Lower 95% CI	1.00	66.2%
Upper 95% CI	7.00	82.9%
6 Months FU Mean, N=21	4.62	72.1%
Lower 95% CI	2.00	62.4%
Upper 95% CI	6.00	81.8%
12 Months FU Mean, N=16	5.17	68.9
Lower 95% CI	0.00	55.0
Upper 95% CI	9.00	82.9
Notes: 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.		

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 25**. **Table 25** shows 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). Similar to the primary endpoint, the "Posture" CRST outcomes for the ExAblate Crossover group are favorable and similar to what was seen in the Main Analysis ExAblate group.

Table 25. CRST Part A Posture for Treated Arm by Treatment Group by Visit Through Month 3				
		CRST Posture Calculated Scores[1]	Change from Baseline[2]	Percent Change from Baseline
		Treated Side	Treated Side	Treated Side
		ExAblate Crossover	ExAblate Crossover	ExAblate Crossover
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)).

QUEST Endpoint Analysis 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% ($p<0.001$) (see **Table 26** below). 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%).

Table 26. Crossover QUEST Analysis - Improvement from Baseline at 3 Months Post-Treatment		
	Treatment Group	
$SE1_{crossover}$	ExAblate Crossover N=21	
Mean	19.20	59.2%
Lower 95% CI	3.54	38.16
Upper 95% CI	30.28	94.94
Notes: 1. QUEST Summary of Dimensions was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher QUEST Summary of Dimension values represent improvement.		

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 8 principal investigators (PIs). None of the PIs had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided did not raise any questions about the reliability of the data.

XI. 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, and in particular the results of the pivotal clinical trial, supported the safety and effectiveness of the ExAblate device when used according to the prescribed intended use.

XII. CONCLUSION DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the present analysis provide reasonable assurance of effectiveness and meet the pre-specified criteria for success. The ExAblate group demonstrated a 46.9% (N=56) improvement in the Composite Tremor/Motor Function score compared to baseline ($p<0.001$), while the Sham group (N=20) demonstrated no improvement in this measure by Month 3. Furthermore, patients in the ExAblate group showed an improvement in the tremor "Posture" score of 64% (N=56) at 3 months , whereas the Sham group experienced a worsening of 4% (N=17).

When looking at the secondary confirmatory end points, the ExAblate treatment performed significantly better ($p<0.001$) on all 3 secondary confirmatory endpoints. The confirmatory secondary endpoints were the Composite Tremor/Motor Function Score at months 3, 6 and 12, the CRST Part C Overall Functional Disabilities Score, and the QUEST (Summary of Dimension Score) at three months.

The effectiveness results for the Crossover portion of the study (unblinded) were very similar to the results seen in the Main Analysis (blinded). For the primary effectiveness endpoint, the ExAblate Crossover group reported a mean percent improvement of 53.1%, compared to 46.9% for the ExAblate group in the Main Analysis.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

Overall, the summary of safety demonstrated that no Severe or Life-threatening events related to the device or procedure occurred and no worsening depression occurred during the course of the study. Of the 210 AEs that were reported in this study, 99.5% were categorized as Mild or Moderate and many resolved within 3 months.

For the ExAblate treatment group, a total of 184 AEs were reported in this study (N=56, 3.3 AEs per ExAblate patient). There was only 1 Severe event, and 183 out of 184 of the events were either Mild or Moderate. Of the 184 AEs, 8 events (8/184 = 4%) began between 30 to 90 days post-procedure and 14 events (14/184 = 8%) began more than 90 days post procedure. 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. Sixteen (16, 9%) were categorized as procedure related and 58 were related to the device/thalamotomy. Of procedure and device/thalamotomy related AEs (n=74),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. Overall, the study shows a very favorable safety profile.

The safety profile of the ExAblate Crossover group mirrored that of the ExAblate group in the Main Analysis with no new AEs observed from 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 with 1 SAE (i.e., the patient was diagnosed with sick sinus syndrome 8 months after the ExAblate procedure and underwent a medical procedure to have a pacemaker implanted). The SAE 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.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Probable benefit, as shown in the clinical study, is demonstrated by a highly significant improvement (i.e., reduction) in the tremor scores that included not only an objective measure of the tremor reduction, but also an improvement in the functional activities of writing, drawing and pouring. For the Main Analysis primary endpoint, the mean percent change between baseline and Month 3 in the ExAblate group was 46.9% (i.e., improvement) compared with a mean of "-0.1%" (i.e., deterioration) in the Sham group ($p<0.001$). Also, an improvement of higher magnitude (approximately 70%) was observed in the activities of daily living (drinking, eating, dressing, hygiene, writing and social activities). The QUEST also showed significant improvements in the physical and psychosocial domains. These improvements were reported through the Month 12 follow-up visit.

The effectiveness results of the Main Analysis were supported by comparable, or better, results in the ExAblate Crossover group, which reported a 53.1% improvement in the primary endpoint compared to 46.9% improvement for the ExAblate group in the Main Analysis. The ExAblate Crossover group also showed significant improvement in all secondary analyses, compared to baseline.

Additional factors to be considered in determining probable risks and benefits for the ExAblate Neuro device included: numbness/tingling of the fingers, imbalance/unsteadiness, ataxia or gait disturbance and headache. All adverse events related to procedure/device/thalamotomy were Mild to Moderate in nature. One patient in the Main Analysis experienced an unresolved moderate numbness of his dominant hand that impaired his ability to use a pen and write at work.

In comparison with alternative electrical stimulation therapies, the safety profile for ExAblate is without infections, intracranial hemorrhages, seizures, dead batteries, or skin erosion (approximately12% serious adverse events for Deep Brain Stimulation (DBS)[3]), and patients are not subjected to a permanent implant. In addition, the recovery period and hospital stay is much shorter for an ExAblate procedure (i.e., overnight hospital stay) as

[3] http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140009b.pdf

compared to more invasive surgical alternatives that require a much longer hospital stay and recovery period. Events that are unique to ExAblate Neuro include sonication-related head pain that is transient (seconds to 24 hours).

1. Patient Perspectives

Patient perspectives considered during the review included:

- Patient perspective data was collected using the quality of life assessment as measured by the Questionnaire for Essential Tremor (QUEST) assessment at the 3 month time point. An improvement of 43.2% in the mean score in the ExAblate group compared to baseline was demonstrated. The Sham group had only a 5% improvement compared to baseline.

- Data from the patient perspective was also collected using the Patient Health Questionnaire (PHQ-9) that is for screening, diagnosing, monitoring and measuring the severity of depression. This data was collected as part of the safety assessment of the ExAblate System. This outcome indicates that the ExAblate treatment does not induce depression.

- This ExAblate treatment is performed inside an MR suite in about 2-3 hours in the awake subject who communicates with the physician throughout the procedure helping to drive the treatment. Treatment effect is immediate and distinguishable by the patient as a decrease in tremor severity.

In conclusion, given the available information above, the data supports that for the treatment of idiopathic ET patients with medication-refractory tremor, the probable benefits outweigh the probable risks.

D. Overall Conclusion

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.

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 results from the pivotal study demonstrate that the device is effective as the primary and secondary endpoints were met and statistically significant and the safety profile is reasonable as the majority of adverse events were minor or moderate, and were transient. In conclusion, the treatment benefits of the device for the target population outweigh the risks when used in accordance with the directions for use.

XIII. CDRH DECISION

CDRH issued an approval order on July 11, 2016.

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

XIV. 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.

XV. REFERENCES

Elias, W.J., et al., *A pilot study of focused ultrasound thalamotomy for essential tremor.* N Engl J Med. 2013. **369**(7): p. 640-8.