SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

GENERAL INFORMATION

Device Generic Name:	Magnetic Resonance Guided Focused Ultrasound Surgery System (MRgFUS)
Device Trade Name:	Exablate Model 4000 Types 1.0 and 1.1 System (Exablate Neuro)
Device ProCode:	POH
Applicant's Name and Address:	InSightec, Inc. 4851 LBJ Freeway Suite 400 Dallas TX, 75244
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P150038

Date of FDA Notice of Approval: December 16, 2018

The original PMA (P150038) was reviewed as a "breakthrough device" and approved on July 16th 2016. It is indicated for:

> *The Exablate Model 4000 ("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*

The SSED to support the indications is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indications for use for the Exablate Models Type 1.0 and 1.1.

INDICATIONS FOR USE

The Exablate Model 4000 ("Neuro") is intended in the unilateral Thalamotomy (ventralis intermedius) treatment of Tremor-dominant Parkinson's Disease with medication-refractory tremor. Patients must be at least age 30.

CONTRAINDICATIONS

The Exablate treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, allergies to MR contrast agent, etc.;
- Pregnant Women;
- 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 are unwilling to tolerate the required prolonged stationary position during treatment (approximately 2 hours); and,
- Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening Computed Tomography (CT).

WARNINGS AND PRECAUTIONS

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

DEVICE DESCRIPTION

The Exablate Neuro (both the PMA approved Type 1.0 and Type 1.1) is a transcranial magnetic resonance image-guided focused ultrasound ("MRgFUS") system. 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. As approved in P150038 & P150038/S005, the Exablate Neuro is comprised of three main sub-systems: the front-end unit, equipment cabinet and water system.

The Exablate system platform is intended to ablate brain tissue with focused ultrasound and operates in conjunction with an MRI scanner that is used for guidance and treatment monitoring and control. As approved in PMA P150038 and its supplements, the Type 1.0 (SW version 7.0) operates in conjunction with GE Medical Systems ("GE") 3T MR scanners or 1.5T MR scanners with a dedicated Exablate 1.5T MR Head Coil. Type 1.1 (SW version 7.2) has the same approved intended use utilizing the Siemen's 3T MRs.

The treatment effect using Exablate Neuro Type 1.0 and Type 1.1 is achieved by accurately 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.

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 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 system interfaces to the MRI machine mainly through the Workstation.

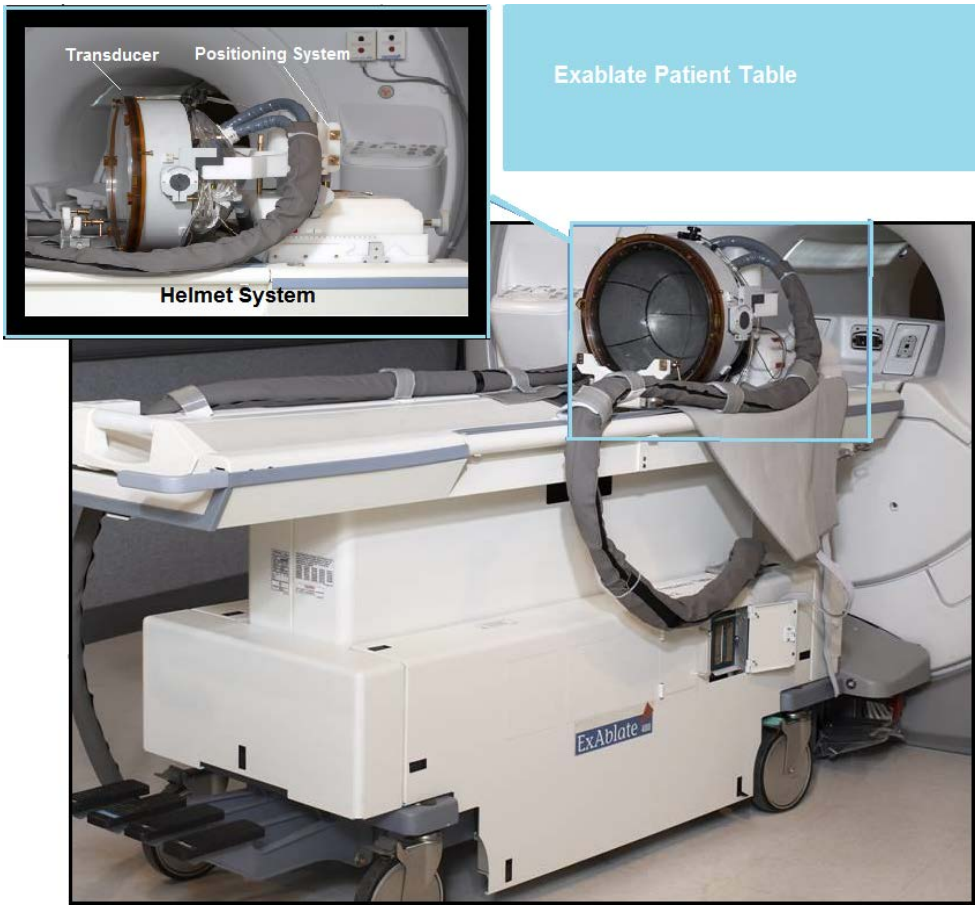
1. Hardware

As approved in P150038, the Exablate Neuro is comprised of three main sub-systems.

Exablate Helmet System

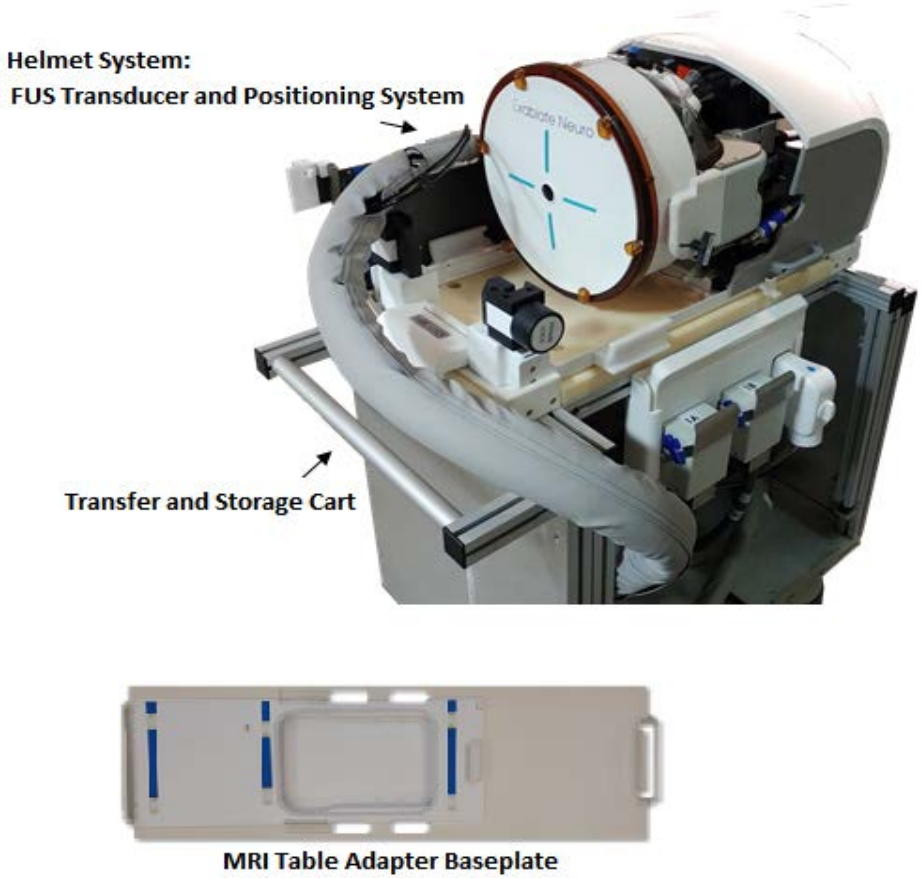
The Exablate Model 4000 Type 1.0 Helmet System (contains the FUS transducer with its positioning system) and Cradle sit atop a standard MR table. This configuration is provided as an Exablate Patient Table (**Figure 1**).

Figure 1: Exablate Neuro Patient Table



In the Exablate Neuro Type 1.1, The Helmet System (FUS Transducer and its positioning system) (**Figure 2**) is no longer integrated with the MR patient table. To improve usability and of the Exablate Neuro system with a fixed MR table, the Helmet System is provided on a dedicated cart. The cart serves as a storage and transfer of Helmet System to and from a standard MR table using the MR Table Adapter Baseplate. These modifications did not alter the existing basic principles of operation of the Helmet System, electrical and technical characteristics or the interface between the patient and the Helmet System.

Figure 2: Exablate Neuro Type 1.1 Helmet System



Console / Workstation

The Workstation (WS) is a personal computer (PC) that serves as the operator application interface for both the MRI and the Exablate. It communicates with both the MR and the Exablate hardware for both control and data acquisition. The user defines and executes the treatment plan from the WS Software GUI (Graphical User Interface). Commands to the various system hardware components are transmitted by the WS via the Control PC (CPC, part of the Equipment cabinet). The CPC manages all control functions required for timing, planning and monitoring of sonications. The WS also controls the MR, executing dedicated scans and displaying processed results to the operator.

Front End Unit or Cabinet (FE)

The Front-End (FE) 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.

The FE contains 1024 power amplifiers to drive the desired signal in each of the elements in the Exablate 4000's Type 1.0 and 1.1 Phased array transducer. The FE also contains control and monitoring electronics for the power amplifiers, as well as filters-amplifiers for acquisition of acoustic feedback for cavitation monitoring purposes. The electronic blade cards are located at the Front-End cabinet at the MR room. The cards drive the 1000 channels that feed the piezoelectric crystals at the transducer. The cards are cooled by air flow, using ribbed heat sinks.

The FE still contains the 1024 power amplifiers, the filters-amplifiers and corresponding control and monitoring electronics.

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 Type 1.0 and Type 1.1 software perform 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 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.
1.5T Head Coil with Silicone Membrane	ASM002258	The Head Coil is used with a 1.5T MRI.
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 ammonium

Table 1: List of Accessories for use with the Exablate Neuro		
Name	InSightec P/N	Comments
		chloride*). This is used for cleaning after each treatment. For single-use.
∫: Integra Radionics MR-compatible stereotactic head frame with insulated pins and non-metallic posts (K946252 and K944463). *: In full compliance with FDA recommendations: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=178.1010		

B. Principles of Operation

The Exablate Neuro principles of operation approved in PMA P150038 remain the same for the Type 1.0 and 1.1 configurations:

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 MR table and has a rubber diaphragm placed over the scalp. Then the patient lies on the MR table, the head frame is locked in on 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 previously performed and loaded into the Exablate Workstation. The CT is used for 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.

ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of Tremor Dominant Idiopathic Parkinson's Disease in patients with medication-refractory tremor, including:

- Medication;
- Surgical resection;
- Radiofrequency Thalamotomy; and
- Deep brain stimulation.

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.

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). More recently, the system was approved for the treatment of Essential Tremor (ET) in July, 2016

The Exablate 4000 is currently in commercial use in the United States, Israel, Europe, Canada, Japan, Russia, Korea, and Taiwan among other countries.

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 Exablate Neuro.

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 possible 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 skin pain.
- 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 1.14.1.1 below.

SUMMARY OF NONCLINICAL STUDIES

C. Bench Studies

Bench testing for the Exablate Neuro (PMA P150038) is described in **Table 2** below:

Table 2: Summary of Preclinical Testing			
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 • 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 3T 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.
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 1mm	Verified that distance from measured peak temperature to prescribed target was according to specifications.

Table 2: Summary of Preclinical Testing			
Category of Testing	**Test Design**	**Acceptance Criteria and Results**	**Comments**
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.

D. Electrical Safety and Electromagnetic Compatibility (EMC) Testing

Per PMA P150038, 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**
Electrical Safety	Per IEC 60601-1-2	Device meets electrical safety requirements for its intended use and use environment
Electromagnetic Compatibility (EMI/EMC)	Per IEC 60601-1-3	Device meets EMC requirements for its intended use and use environment

E. Biocompatibility Testing

Per PMA P150038, the 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 ISO 10993. The only other patient contacting device is the stereotactic head frame (and pins), which is a commercially available medical device with established biocompatibility (K946252 and K944463). InSightec utilizes these accessories according to their intended use.

F. Software Testing

The following software functions were tested satisfactorily (see also Table 4):

- 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 (HW & 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.

Table 4: Software Testing

Category of Testing	Test Description	Testing Criteria	Comments
Pre-treatment preparation related features	Preparation session, DQA flow and Water system control.	Pass/Fail	Pass
Calibration and positioning operations	New flow of calibration and calibration calculations, Focal and Target points position, Reset or preserve geometrical adjust after recalibration and Central frequency determination scan – B0 scan.	Pass/Fail	Pass
Planning images scans and images loading	Guided planning images scan based on Ac-Pc points, Anatomical Atlas display, New load form (including GUI, MR/CT/ Sessions loading, automatic loading of planning images, and images replacement), Exam identification and MR data synchronization.	Pass/Fail	Pass
Planning stage	Button for calcifications calculations, Transformations between the MR live – MR pre-op and CT worlds and Treatment protocols.	Pass/Fail	Pass
Treatment stage	Movement detection, Options to treat with/without ROT, Automatic spot generation, Sonication controls, Spot coordinates field and option to lock spots, Temperature-Energy prediction flow and algorithm and Transducers Masks.	Pass/Fail	Pass
Sonication and Thermometry	ARFI flow and ACT calculations, comparison of Thermometry to previous 6.4 version, Multi-echo thermometry, Heat detection, Failures in sonication flow and Cooling time proportional to the transmitted energy.	Pass/Fail	Pass
Other features	Scans state machine, GUI and general changes, and Replay	Pass/Fail	Pass

G. Animal Studies

Per PMA P150038, Animal Studies for the ExAblate Neuro are described in Table-5 below:

Table 5: Software 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} ~ 40C / KJoule.	Verified that thermal heating and spot size 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 < 100J/cm^2 (sonication energy / active skull surface).	Verified adequate cooling time (Sim). Verified skull adjacent tissue temperature far below thermal dose (Sim). 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

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.

SUMMARY OF PRIMARY CLINICAL STUDIES

1.1 Summary of Primary Clinical Studies

Primary clinical studies performed with the Exablate Neuro were conducted under G120017. This IDE study used the same device that was approved under P150038. The study was designed to assess the safety and effectiveness of Exablate for unilateral thalamotomy in the treatment of medication-refractory idiopathic Tremor Dominant Parkinson's Disease (TDPD).

1.2 Investigational Objectives

The purpose of this study is to demonstrate the safety and effectiveness of the Exablate Neuro to treat medication-refractory, idiopathic TDPD. This was a randomized, sham-controlled, prospective, blinded, multi-center study. Sham subjects were permitted to crossover to active treatment after completion of month 3. This study design is exactly the same as the study used to support PMA approval for P150038 for the treatment of idiopathic Essential Tremor patients with medication-refractory tremor.

For all subjects, a unilateral thermal lesion was created in the *ventralis intermedius* (*Vim*) nucleus of the thalamus. Like the PMA study under P150038, the effectiveness endpoints were obtained at month 3 and then all subjects were unblinded and sham-treated subjects were invited to crossover to an actual treatment. The effectiveness data of thalamotomy for TDPD (P150038) is compared to ET thalamotomy.

*Treated (contralateral) upper limb **CRST** applicable subscores of Part-(A & B) as compared to baseline for the Exablate Group and Sham Group at month 3. Percent of change from baseline is also presented for each cohort.

*CRST Part-C is similarly presented at month 3, and change from baseline within group at month 3. Percent of change from baseline is also presented for each cohort.

*Summary of Dimensions (from QUEST) measure is similarly presented at month 3 for TDPD compared to ET Pivotal data. Percent of change from baseline is also presented for each cohort.
*Safety profile is presented by treatment group comparing the Exablate TDPD group to the ET Pivotal data.

1.2.1 Study Design

This was a prospective, multi-center clinical trial. The protocol was very similar to the ET002 study (IDE G120246) protocol. This study population was medication-refractory TDPD patients who failed tremor medications. The data from this study has been published by Bond *et al*.[1]

1.2.2 Clinical Report Sample Size

The report sample size includes the 27 subjects treated using the Exablate Neuro system (20 Exablate-treated subjects; 7 Sham-treated subjects). The following table (**Table 5**) provides information regarding the enrollment status at each of the participating centers. University of Virginia (UVa) enrolled 25 subjects (92.5%) and Swedish Hospital enrolled 2 subjects (7.5%).

Table 5. Number and Percentage of Subjects by Center by Group

Center	**Exablate Group**		**Sham Control Group**	
	N	**%**	**N**	**%**
University of Virginia	18	90	7	100
Swedish Hospital	2	10	0	0
Total	**20**	**100**	**7**	**100**

1.2.3 Selection of Study Population

Subjects met all the below inclusion/exclusion criteria.

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 3 months;
- Subjects with a diagnosis of idiopathic PD as confirmed from clinical history and examination by a movement disorder neurologist at the site; and,
- All subjects included in this study will have a TD/PIGD ratio $\geq$ 1.5 in the *medicated* [ON] state as calculated from the UPDRS formula as described by Jankovic, *et. al*., [2].

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

- Subject demonstrates a resting tremor severity score of greater than or equal to 3 in the hand/arm as measured by the medicated (*ON*) UPDRS question #20 or a postural/action tremor greater than or equal to a 2 for question #21;
- Subject exhibits a significant disability from their PD tremor despite medical treatment. A significant disability is defined as a PD tremor with at least a score of 3 on #16 of the medicated (*ON*) UPDRS or as identified by a score of 2 or more on any item in Part C of the CRST;
- Tremor remains disabling when medical therapy is optimal or not tolerated for the treatment of other cardinal signs of PD (bradykinesia, rigidity, etc), as determined by a movement disorders neurologist at the site;
- Subjects should be on a stable dose of all PD medications for 30 days prior to study entry;
- The thalamus must be apparent on MRI such that targeting of the Vim nucleus can be performed indirectly by measurement from a line connecting the anterior and posterior commissures of the brain; and,
- Subject is able to communicate sensations during the Exablate Neuro procedure.

Exclusion Criteria

- 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
- Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within the preceding 12 month period;
- Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household);
- Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use);
- Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct);
- Continued substance use despite having persistent or recurrent social or interpersonal; problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights);
- Severe hypertension (diastolic BP > 100 on medication);
- Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.;
- Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease or severely impaired renal function (estimated glomerular filtration rate < 45ml/min/1.73 m^2) or receiving dialysis;
- Significant claustrophobia that cannot be managed with mild 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 or 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 INR coagulation studies exceeding the institution's laboratory standard;
- History of intracranial hemorrhage;

- History of multiple strokes, or a stroke within past 6 months;
- Subject who weigh more than 285 lbs (130 kg) as this is the upper weight limit of subjects who will fit into the MR scanner;
- Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment;
- Are participating or have participated in another clinical trial in the last 30 days;
- Subjects unable to communicate with the investigator and staff;
- Presence of central neurodegenerative disease, including but not limited to Parkinson-plus syndromes, suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and Alzheimer's diseas;
- Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications;
- Presence of significant cognitive impairment as determined with a score ≤ 21 on the Montreal Cognitive Assessment (MoCA);
- Unstable psychiatric disease, defined as active uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation. Subjects with stable, chronic anxiety or depressive disorders may be included provided their medications have been stable for at least 60 days prior to study entry and if deemed appropriately managed by the site neuropsychologist;
- Subjects with significant depression as determined following a comprehensive assessment by a neuropsychologist. Significant depression is being defined quantitatively as a score of greater than 14 on the Beck Depression Inventory;
- Legal incapacity or limited legal capacity as determined by the neuropsychologist;
- 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;
- Any illness that in the investigator's opinion preclude participation in this study;
- Pregnancy or lactation; and,
- Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia.

1.2.4 Study Conduct

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

This was a randomized, sham-controlled study. Both the subject and the neurologist who performed the CRST assessments were unaware of the treatment assignment. The neurologist was not in the MR suite during the Exablate procedure. Care was taken and training was provided regarding the means to keep the blind through month 3.

1.2.5 Pre-Treatment Data Collection and Procedures

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

1.3 Study Treatment

In this study, subjects were treated in the same manner and using the same software version as subjects in the pivotal study (G120246).

Subjects in both treatment arms were blinded to the treatment assignment (Exablate or Sham). Subjects randomized to Sham had all the patient prep for the procedure and all the MRs as the Treatment Arm subjects, except that for the Exablate procedure the energy was turned to 0 output. All follow-up procedures were the same. After the month 3 visit, the subject and the Neurologist were unblinded and Sham subjects were offered Crossover to an actual treatment.

1.4 Study Follow-up

Subjects were discharged at day 1 and safety was checked at week 1. All safety and efficacy assessments were performed at months 1, 3, and 12 using the same assessments as collected in the pivotal study. A phone call for safety assessment was performed at month 6. Patients returned to clinic for their month 12 assessment. Data analysis was modeled after the same method of statistical analysis as performed for the ET002 pivotal Statistical Analysis Plan.

1.4.1 Study Endpoints

The first effectiveness endpoints for the study utilized 8 components of the CRST (Part A +B) which measured the treated arm tremor in 3 conditions (rest, posture, action/intention) as well as the ability to perform five daily tasks. Effectiveness for TDPD tremor was assessed for each treated TDPD patient at month 1, 3, and 12. Baseline was compared to the post-treatment

interval at months 3 for each subject. These data were reported in 2 ways: 1) Using the actual calculated score sums, and 2) Calculations based on percent change from Baseline. All values are reported as a mean for each reporting method across the cohort.

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

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

The safety profile included all adverse events collected for all 20 subjects in the Exablate TDPD Arm. These events were evaluated and compared to the types and frequency of events that were observed in the ET PMA Exablate cohort.

1.4.2 Results

1.4.2.1 Demographics

The baseline and demographic characteristics (See **Table 6. Baseline and Demographic Information by Treatment Cohort**) of the patients showed differences between the pivotal study population and the Exablate TDPD cohort in the proportions of gender, race, and year of tremor history. None of these differences has an effect on the thalamotomy procedure or outcome.

Table 6. Baseline and Demographic Information by Treatment Cohort

Demographic Characteristics		**Exablate ET Pivotal N=56**	**Exablate TDPD N=20**
Age [Years]	Mean	70.8	67.9
BMI [kg/m²]	Mean	26.9	27.1
Height [3]	Mean	171.9	175.6
Weight [kg]	Mean	79.6	83.3
Gender	Male	37 (66%)	19 (95%)
	Female	19 (34%)	1 (5%)
Race	Caucasian	41 (73%)	18 (90%)
	Black	0	2 (10%)
	Asian	14 (25%)	0
	Hispanic	0	0
	Other	1 (2%)	0
Average Years History of Tremor	Mean	13.9	5.2

Table 6. Baseline and Demographic Information by Treatment Cohort			
Demographic Characteristics		**Exablate ET Pivotal N=56**	**Exablate TDPD N=20**
Baseline CRST score	Mean	20.2	19.0

1.4.2.2 Safety Assessment

The primary analysis of safety was based upon the collection of adverse events during the study as collected by the investigators at each site. Similar to the Exablate Pivotal cohort, 95% of all adverse events were Mild/Moderate, 50% of all the events were Transient, and 21% of all these events were Unrelated to the device or procedure.

As shown in **Table 7**, most events were Mild or Moderate in the Exablate TDPD cohort (95/100, 95%). Of the 5 Severe events, two of these events were totally unrelated to the Exablate device or procedure (cholecystitis; degenerative knee disease with total knee surgery; one event was categorized as worsening PD condition (cognitive impairment in one domain); one patient had no treatment effect in the treated arm (worsening arm tremor); one subject reported a transient sonication-related head pain, lasting seconds to minutes and resolving; and one subject reported ataxic gait disturbance/hemiparesis side effects immediately after the procedure which completely resolved (categorized as an SAE and described below Table 8).

Table 7. Number of Exablate Arm Adverse Events by Severity Compared to ET P150038 Pivotal Trial Data				
Severity	**Exablate ET Pivotal**		**Exablate TDPD**	
	Frequency N=184	Incidence N=56	Frequency N=100	Incidence N=20
Mild	137 (74%)	46 (82%)	72 (72%)	19 (95%)
Moderate	46 (25%)	28 (50%)	23 (23%)	14 (70%)
Severe	1 (1%)	1 (2%)	5 (5%)	4 (20%)
Life	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	184 (100%)	49 (88%)	100 (100%)	20 (100%)

Table 8. Adverse Events by Severity for Exablate Arm TDPD Subjects below lists all the events that occurred by severity and treatment cohort in the PD001 study by coded relation term, coded body system and coded term. In this study, there were no Serious or Life-threatening events, nor new or unexpected events as compared to ET Pivotal study. The overall safety profile is very similar to what was reported in the PMA study.

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

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

- In this study, there were 33 Mild events in 17 subjects; 16 Moderate events in 11 subjects and one Severe event (sonication-related head pain lasting seconds) in one subject.

UNRELATED to Exablate: These are events that are captured and determined by Investigator(s) to be unrelated to the treatment device (Exablate) or procedure.

There were 15 Mild events in 9 subjects, 4 Moderate events in 4 subjects, and 2 Severe events in 2 subjects (1 cholecystitis; 1 Other musculoskeletal pain).

PD PROGRESSION refers to disease related events that are unrelated to the Exablate procedure and would occur normally within the TDPD population.

In this study, there were two events related to symptom worsening: 1 event of Mild Sleep disorder and 1 Severe event of Tremor worsened.

PROCEDURE-RELATED adverse events refer to events that do not resolve within 3 days post-procedure, but are not related to the Exablate device and may be considered incidental to the procedure.

There were 5 Mild events in 4 subjects which included 2 events of fatigue, and one event each of muscle weakness, dizziness and dysgnosia.

THALAMOTOMY-RELATED adverse events are related to the ablation procedure and may be reported in the literature with other methods of creating a thalamotomy.

There were 18 Mild events in 9 subjects, 3 Moderate events in 2 subjects, and one Severe (Ataxia) event in one subject that was categorized as a serious event (SAE) and is described below.

Table 8. Adverse Events by Severity for Exablate Arm TDPD Subjects

Relation to Device	Body System	Preferred Term	Exablate (N events = 100; # subjects = 20)					
			Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
PD Disease Progression	General	Sleep disorder	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysgnosia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Tremor worsened	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)
PD Disease Progression Subtotal			1 (1%)	1 (5%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)
Procedure Related	General	Fatigue	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Musculoskeletal	Musculoskeletal weakness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysgnosia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Vestibular Disorder	Dizziness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Procedure Related Subtotal			5 (5%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamotomy Related	Musculoskeletal	Dysmetria	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Gait disturbance	2 (1%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Hemiparesis	0 (0%)	0 (0%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)
		Imbalance	4 (4%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Dysmetria	1 (1%)	1 (5%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
		Ataxia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)
		Numbness/tingling	7 (7%)	6 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 8. Adverse Events by Severity for Exablate Arm TDPD Subjects								
Relation to Device	**Body System**	**Preferred Term**	**Exablate (N events = 100; # subjects = 20)**					
			Mild		**Moderate**		**Severe**	
			Freq N (%)	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**
	Neurological	Numbness/tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Unsteady	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamotomy Related Subtotal			18 (18%)	9 (45%)	3 (3%)	2 (10%)	1 (1%)	1 (5%)
Transient	Cardiovascular	Hypertension	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Syncope	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Dematologic	Sonication related flushing	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
	Eye	Visual Field Defect	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Gastrointestinal	Nausea/Vomiting	3 (3%)	3 (15%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)
	Musculoskeletal	Imbalance	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Positional pain	2 (2%)	2 (10%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
	Nervous	Imbalance	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Anxiety	0 (0%)	0 (0%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)
		Dysgnosia	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Numbness/tingling	7 (7%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Pain/Discomfort	Headache	5 (5%)	5 (25%)	6 (6%)	6 (30%)	0 (0%)	0 (0%)
		Sonication-related scalp pain	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
		Sonication-related head pain	3 (3%)	2 (10%)	2 (2%)	2 (10%)	1 (11%)	1 (5%)

Table 8. Adverse Events by Severity for Exablate Arm TDPD Subjects								
Relation to Device	**Body System**	**Preferred Term**	**Exablate (N events = 100; # subjects = 20)**					
			Mild		**Moderate**		**Severe**	
			Freq N (%)	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**
	Stereotactic Frame	Pin site pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Vestibular Disorder	Dizziness	6 (6%)	6 (30%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
Transient Subtotal			33 (33%)	17(85%)	16 (16%)	11 (55%)	1 (1%)	1 (5%)
Unrelated	Eye	Pigment change in eye	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Vision change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Gastrointestinal	Cholecystitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (%)	1 (5%)
		Stomach Pain	0 (0%)	0 (0%)	1 (%)	1 (5%)	0 (0%)	0 (0%)
	General	Vocal change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Worsening Depression	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
	Musculoskeletal	Musculoskeletal weakness	2 (2%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other musculoskeletal pain	0 (0%)	0 (0%)	1 (1%)	1 (5%)	1 (%)	1 (5%)
		Positional pain	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Nervous	Cerebellar Infarct	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Dizziness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		TIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Facial edema	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 8. Adverse Events by Severity for Exablate Arm TDPD Subjects								
Relation to Device	**Body System**	**Preferred Term**	**Exablate (N events = 100; # subjects = 20)**					
			Mild		**Moderate**		**Severe**	
			Freq N (%)	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**	**Freq N (%)**	**Incidence # (%)**
	Stereotactic Frame	Pin site numbness/tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Pin site pain	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Stereotactic frame-Bruising	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)
Unrelated Subtotal			15 (15%)	9 (45%)	4 (3%)	4 (20%)	2 (2%)	2 (10%)

Serious Adverse Events

Three patients experience 1 or more SAEs. All SAEs were adjudicated by the DSMB. Only 2 subjects experienced a SAE that were judged to be thalamotomy related (transient hemiparesis). The others were considered to be Unrelated to Exablate..

Please note that as a result of these two hemiparesis events, all Exablate Physician training since 2013 emphasizes the need for physicians to view the sonications in 2 axes to verify the heat signature of the lesion in 3 dimensions prior to making the final lesion and confirming the shape of the lesion to mitigate these incidents.

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

In the following **Figure 2**, the actual values of the tremor/motor function subscores of Parts-(A+B) are displayed. The Baseline value was 19.0 which improved to 9.6 by Month 3. This compares favorably to Exablate ET Pivotal (-20.2 at Baseline; 9.5 at Month 3). At the Month-3 post-treatment, equivalent improvements in clinical outcomes were observed between the pivotal cohort and the Exablate TDPD cohort. This improvement was maintained at Month 12.

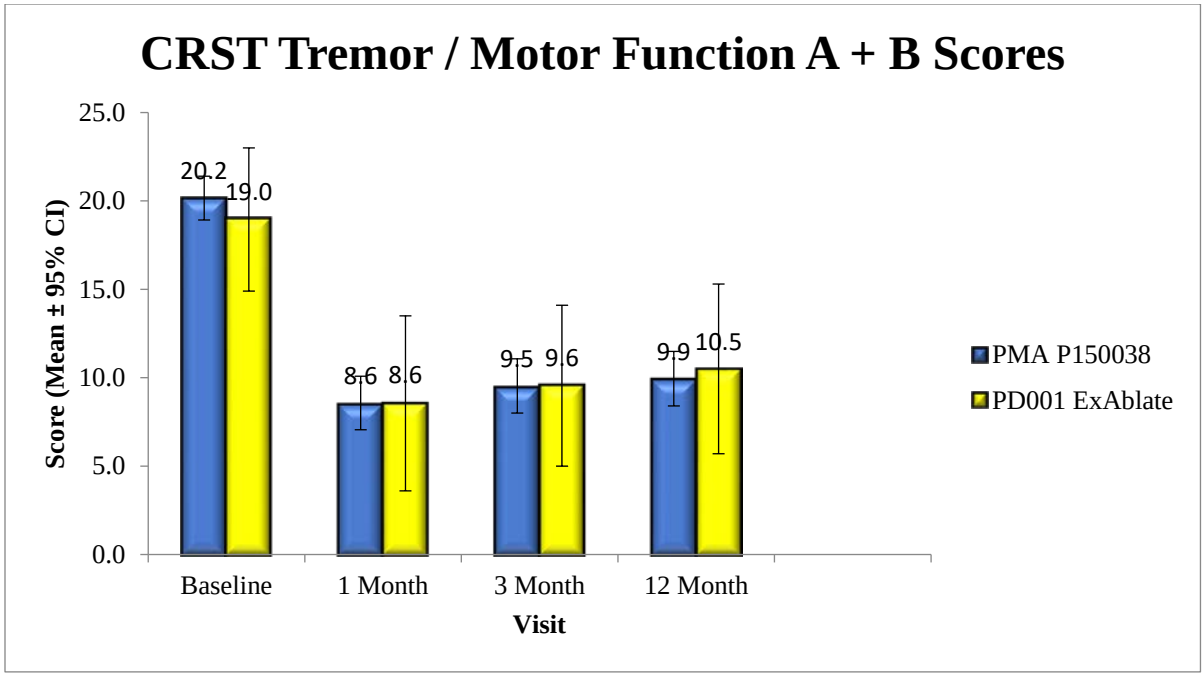


Figure 2: Tremor / Motor Function CRST Actual Subscore (Part A + Part B) for the ET Pivotal Cohort and the Exablate TDPD Cohort through Month 12.

1.4.2.4 Percent Tremor / Motor Function

Percent Change from Baseline of the primary endpoint Parts-(A + B) was also calculated. By Month-3 post-treatment, the Exablate TDPD cohort demonstrated a 51.9% improvement compared to the Exablate ET Pivotal cohort which demonstrated a 46.9% improvement compared to Baseline.

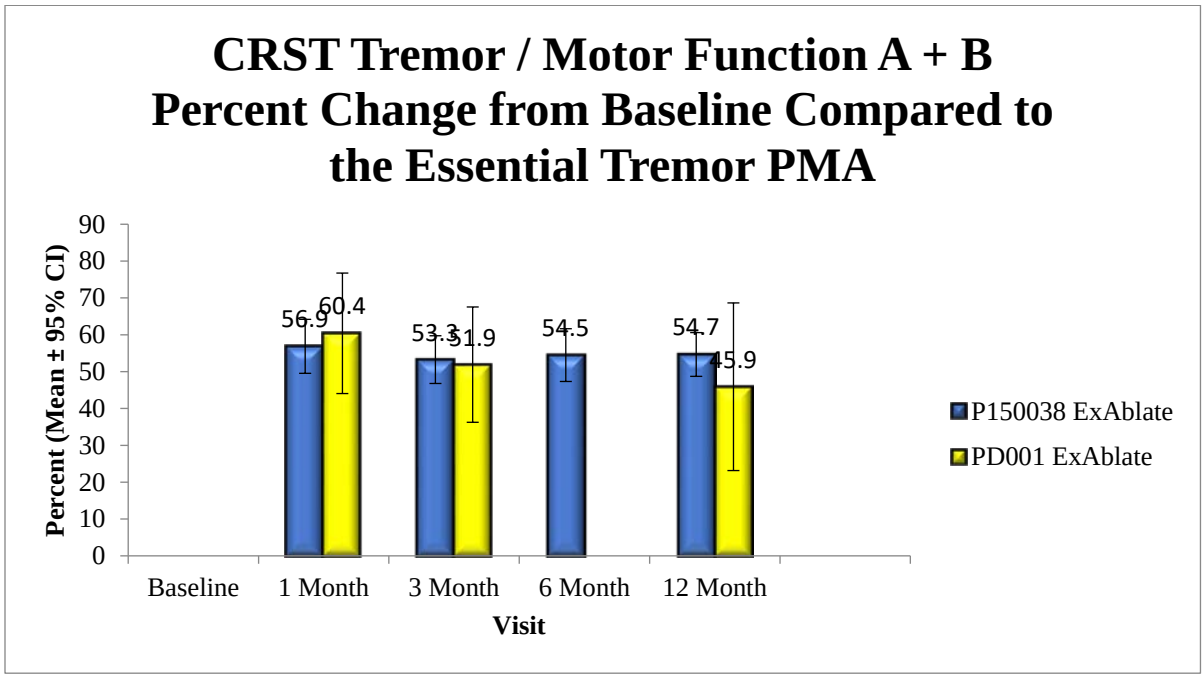


Figure 3 : Tremor / Motor Function percent of change from Baseline between the ET Pivotal Cohort and the Exablate TDPD Cohort through Month 12.

1.4.2.5 Safety Assessment CRST Part A Posture and Rest Upper Extremity Only Exablate TDPD

The Part A Posture component (score of 0-4) is an important single indicator of tremor for ET subjects. For this reason, the Part A was evaluated as a lone measure in the ET Pivotal cohort. For Parkinson's Disease, resting tremor is the cardinal symptom. For the purposes of this measure, we have included the Rest component (score of 0-4) for the TDPD along with the Posture component score for comparison of effect. **Figure 4** and **Table 9** show the actual Postural and Rest component score values in the TDPD cohort.

- Posture: The Exablate TDPD cohort improved from 3.20 at Baseline to 1.6 at month 3 and maintained at 1.8 at month 12.
- Rest: The Exablate TDPD cohort improved from 3.4 at Baseline to 2.1 at month 3 and to 1.9 at month 12.

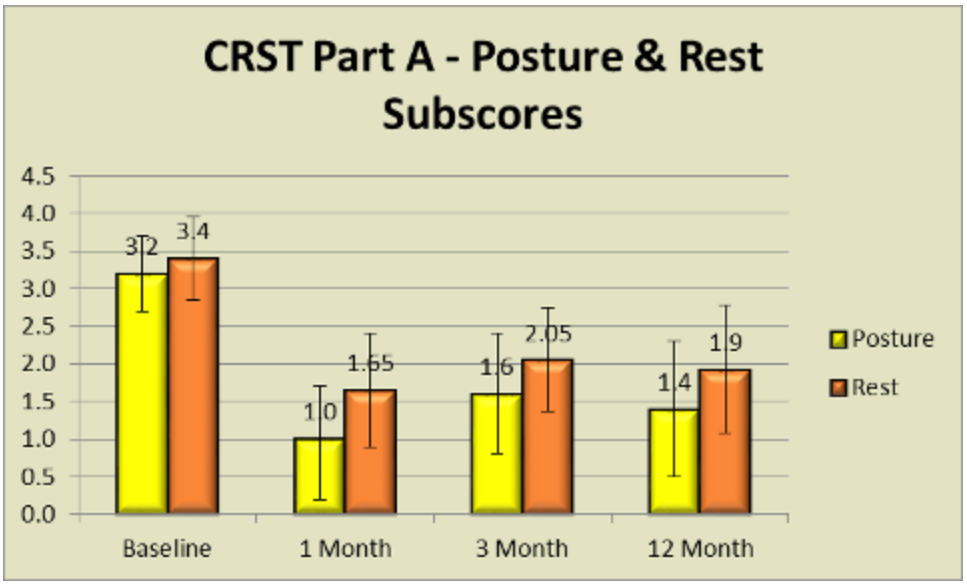


Figure 4. Component scores for Posture (cardinal ET symptom) and Rest (cardinal PD symptom) for the TDPD Cohort.

Table 9. CRST Part A – Posture & Rest - Treated Arm by Treatment Group Scores by Visit Through Month 12

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

Table 9. CRST Part A – Posture & Rest - Treated Arm by Treatment Group Scores by Visit Through Month 12								
Visit / CRST, Part A – Posture calculation	**Posture Observed scores**		**Posture Percent Change from Baseline**		**Rest Observed scores**		**Rest Percent Change from Baseline**	
	Treated Side		**Treated Side**		**Treated Side**		**Treated Side**	
	Exablate	**Sham**	**Exablate**	**Sham**	**Exablate**	**Sham**	**Exablate**	**Sham**
Notes 1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100). 2. For cases of baseline value of 0 (where percent change cannot be defined, if the visit of comparison also had a value of 0, percent change was imputed as 0; otherwise, the percent change was not calculated. 2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).								

Using the Posture component of the CRST, the Exablate TDPD Cohort showed similar improvement as that of the Exablate ET Pivotal Cohort.

The Exablate ET Pivotal Cohort improved from 3.0 at Baseline to 1.1 at month 3. The Exablate TDPD cohort improved from 3.2 at Baseline to 1.6 at month 3 (Error! Reference source not found.).

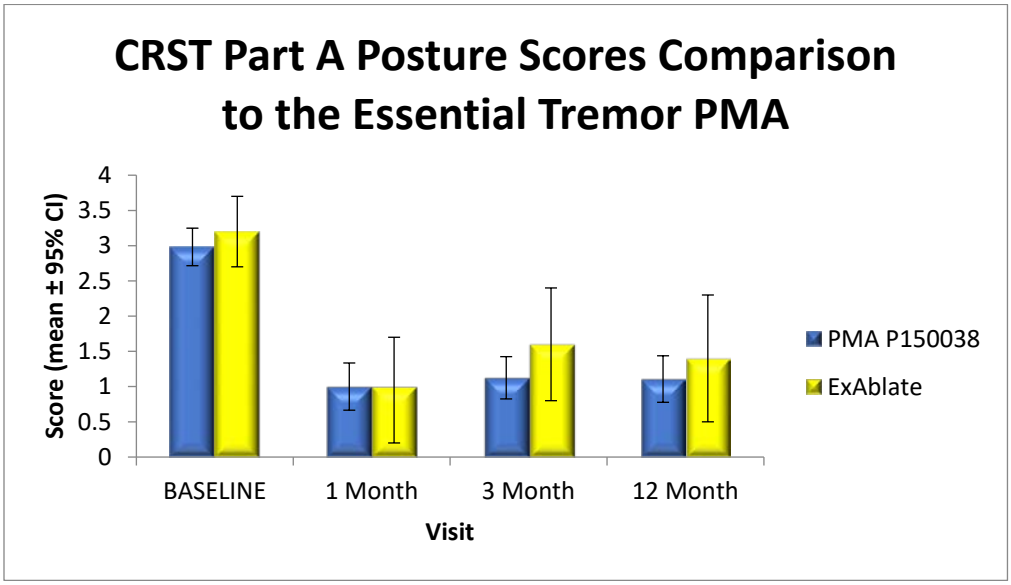


Figure 5. CRST Part A Posture Component Scores over Time for Exablate TDPD Cohort and the Exablate ET Pivotal Cohort.

1.4.2.6 CRST Part C Total Score

In addition to the primary endpoint, the overall CRST Part C total score for the percent improvement in functional disabilities was assessed at month-3 as part of the study endpoints. The Part C is another composite score encompassing speaking, eating, drinking, hygiene, dressing, writing, working and activities. The Exablate TDPD Cohort improved from 14.1 at Baseline to 6.4 at month 3. The Exablate Treatment cohort

improved from 16.5 at Baseline to 6.2 at month 3 (**Figure 6**: Overall CRST Part-C scores for the Exablate TDPD Cohort and the Exablate ET Cohort through Month-12.).

The Mean Percent Change from Baseline was 52.9% in the Exablate TDPD cohort and 63.8% in the Exablate Treatment cohort. Results of the ExAblate TDPD Cohort was very similar to that of the Exablate ET Cohort.

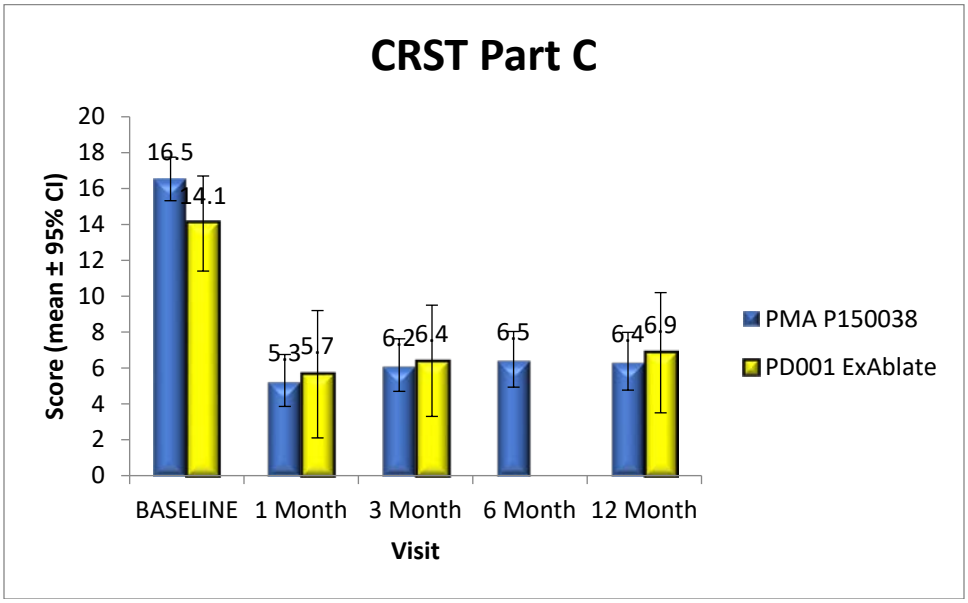


Figure 6: Overall CRST Part-C scores for the Exablate TDPD Cohort and the Exablate ET Cohort through Month-12.

1.4.2.7 QUEST – Quality of Life

Quality of Life scores at the Month-3 were also equivalent between Exablate treatment cohort and Exablate TDPD treatment cohort. This QUEST Patient Reported Outcome (PRO) was completed by the patients and was meant to confirm the measured reduction in tremor with an improvement in daily physical and social activities. **Table 10. QUEST Summary of Dimensions Score and % Change from Baseline by Treatment Cohort** shows improvement in the mean scores of the Summary of Dimension in the Exablate TDPD cohort was 39.6% and 43.2% in the Exablate ET Pivotal Cohort.

Table 10. QUEST Summary of Dimensions Score and % Change from Baseline by Treatment Cohort				
	Treatment Cohort			
	Exablate ET N=56		Exablate TDPD N = 20	
Month 3	23.11	43.2%	25.5	39.6%
Month 12	21.68	47.1%	26.1	28.0%
1. SE1 was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher SE1 values represent improvement				

1.4.2.8 Discussion

Specific targets in the brain have been found to be most effective for treating the various movement disorder disease symptoms. For example, thalamotomy is an effective procedure for the control of tremor of various etiologies. The most common indication is essential tremor (ET), where numerous studies have demonstrated that ablation of the Vim nucleus of the thalamus is associated with dramatic improvements in tremor [4-7]). Thalamotomy and thalamic procedures have also been found to be effective for other types of tremor, including Holmes Tremor [8], Wilson's Disease [9], tremor associated with multiple sclerosis [10-12], Fragile X-associated tremor/ataxia syndrome [13], and the tremor of Parkinson's Disease in patients who have tremor-dominant forms of the condition [5]. The ventralis intermediate nucleus (Vim) of the thalamus has been the preferred surgical target for the treatment of parkinsonian tremor for many years. Recently, a review paper by Anderson et al. [1] summarized the importance of the Vim target for TDPD

In comparison, pallidotomy, a surgical procedure that targets the internal segment of the globus pallidus, has been found to be highly effective at controlling movement disorder symptoms. For example, in Parkinson's Disease, pallidotomy has a prolonged effect on contralateral dyskinesia associated with long-term use of dopaminergic agents (i.e. levodopa induced dyskinesias [14-16] [17] [18, 19] [20-23] [10, 24-26] [27-29] with reported benefit lasting up to 13.5 years [27]. Numerous reports have described the safety profile, and short and long-term outcomes associated with pallidotomy in Parkinson's Disease, a procedure that has been a part of PD management for several decades [14-16]). Other conditions for which pallidotomy has been found to be effective include the dyskinesias of Wilson's Disease [17], Huntington's Disease [18, 19], and Dystonia [primary and secondary] [20-23]. Pallidotomy procedure have been found to be effective in controlling the dyskinesias of PD associated with long-term use of dopaminergic agents (i.e. levodopa induced dyskinesias) [27-29]. Pallidotomy has also been used to

[1] Anderson, D., G. Beecher, and F. Ba, *Deep Brain Stimulation in Parkinson's Disease: New and Emerging Targets for Refractory Motor and Nonmotor Symptoms.* Parkinson's Dis, 2017. **2017**: p. 5124328.

treat other forms of dyskinesias, such as orofacial as well as tardive dyskinesias [10, 24-26].

Tremor in Parkinson's Disease Patients

The classic tremor of PD is reported as a resting tremor of 4-7 Hertz that abolishes with volitional movement.[30] PD tremor can also include a postural or action component, but the combination of a pathological resting tremor with bradykinesia qualifies as a necessary criteria for the clinical diagnosis of idiopathic PD.[31]

Even though tremor may frequently represent the initial manifestation of PD, its occurrence during the course of the disease varies, and it has been demonstrated to occur independently of the other cardinal motor symptoms.[32] Such a variation in symptomatology led to the proposal of clinical subtypes of the disease with "tremor dominance" representing one of the major categories [2]. Tremor-dominant PD tends to present at a younger age and progresses more slowly to the disabling stages [33] or to dementia. [34]

Improved imaging with MRI and refined electrophysiological localization over the past two decades have revealed that the *Vim* nucleus of the thalamus is an effective target, integrating the inflow of cerebellothalamic projections with proprioceptive and kinesthetic sensory information. Furthermore, an abundance of tremor cells which fire synchronously with the limb tremor can be recorded in this region.[35] With electrophysiological confirmation and identification of these cells, only small volumes of *Vim* (~40 mm^3) are required to be targeted for effective treatment.[36]

Both stereotactic radiofrequency thalamotomy and DBS targeted to the *Vim* have proven effective for the treatment of PD tremor and other tremors. [4] Numerous studies of *Vim* ablation and stimulation have demonstrated dramatic improvements of appendicular tremors in PD and ET, and prospective and retrospective comparisons of the two report similar control rates of tremor with 69-90% improvement in appendicular symptoms.[7, 37] Most importantly, quality of life for subjects with tremor, whether due to ET or PD, improves with both unilateral and bilateral therapies targeted to the *Vim*.[38-40]

This study evaluated Exablate Vim thalamotomy in a blinded, sham-controlled fashion, using the same study design as the ET Pivotal study. The same endpoints were evaluated in the same manner as the ET Pivotal Study. The results of the Vim thalamotomy mimicked in all respects the results of the Pivotal Et study even though the sample size was small. Using the measure of Percent Change from Baseline to month 3 for all variables, **Figure 7** and **Table 11** show that there is equivalent improvement in all 4 efficacy measures across the ExAblate treated cohorts.

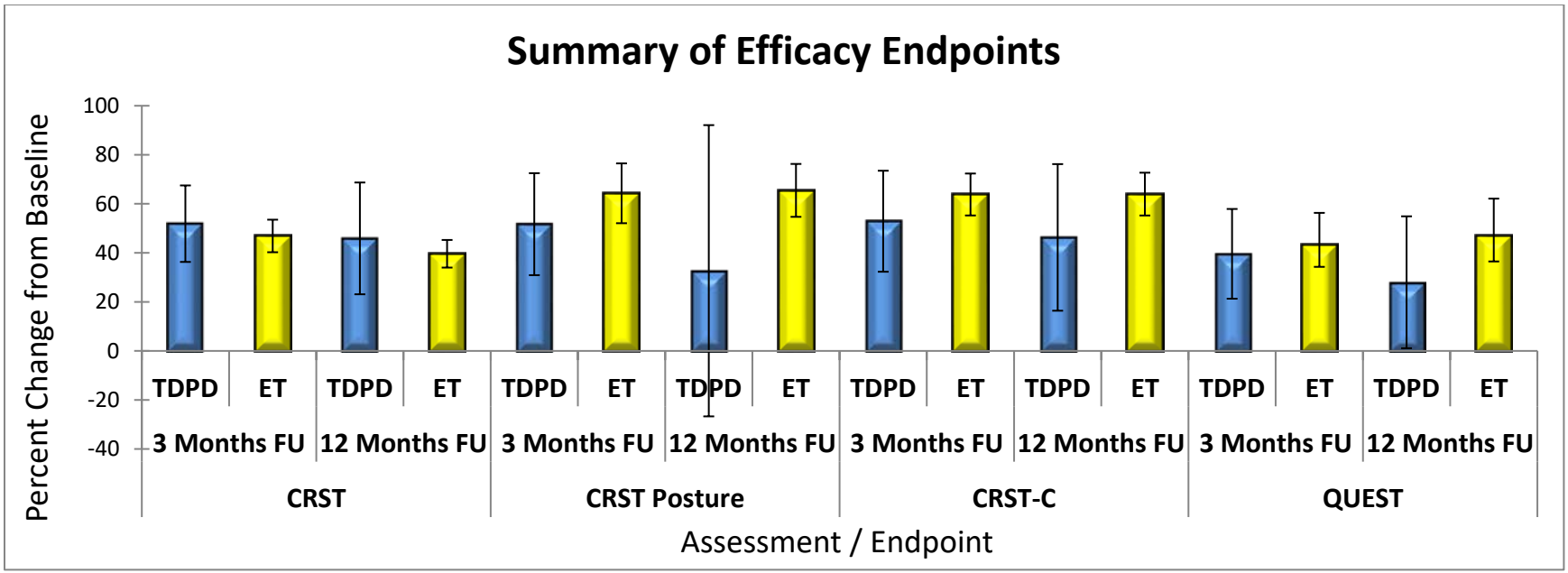


Figure 7: Summary of Percent Change from Baseline for All Effectiveness Endpoints

Table 11. Summary of Efficacy Endpoints		
	Exablate Pivotal N=56	Exablate TDPD N=20
Primary Endpoint – Composite Tremor/Motor Function	46.9%	51.9%
CRST, Part A Tremor "Posture"	64.3%	51.7%
CRST, Part C	63.8%	52.9%
QUEST Summary of Dimensions	43.2%	39.6%

1.5 Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 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 of which none were full-time or part-time employees of the sponsor and 1 principal investigator had disclosable financial interests/arrangements as defined in 21 CFR § 54.2(a), (b), (c) and (f) and described below:

- Significant payment of other sorts (i.e., compensation for advising on the study design and study analysis plan, and acting as a consultant): none.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

1.6 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.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

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, 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.

XIII. CONCLUSION DRAWN FROM PRE-CLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the present analysis provide reasonable data demonstrating the efficacy of the treatment of TDPD using the Exablate Neuro. The Exablate TDPD Cohort- showed an improvement of 51.9%. at 3 months in the Composite Tremor/Motor Function score compared to baseline and 45.9% over baseline at 12 months.. Furthermore, the study showed an improvement over baseline of approximately 51.7% in the "Posture" score of the Clinical Rating Scale for Tremor tremor at 3 month and 32.9% at 12 months.

B. Safety Conclusions

The risks of the device when used for the treatment of tremor in TDPD are no different from the risks for the treatment of tremor in ET. Overall, the summary of safety demonstrated that only two subjects each reported one serious adverse event (SAE) related to the device or procedure (hemiparesis; ataxia) and no Life-threatening events related to the device or procedure occurred. Of the 100 AEs, 14 (95/100 = 95%) were categorized as Mild or Moderate. There were 50 (50/100 = 50%) AEs that were transient (resolved within 72-hours) in this study, whereas the Pivotal study main population registered 29% (53 out of 184) AEs that were Transient

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

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study conducted to support this PMA supplement approval as described above. Probable benefit, as shown in the clinical study, is demonstrated by a statistically significant reduction (i.e., improvement) 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 Study Analysis primary endpoint, the mean percent change between baseline and Month 3 in the Exablate group was 51.9% (i.e., improvement) compared with a mean of 46.9% improvement in the Essential Tremor study group that received the similar thalamotomy procedure with the Exablate Neuro (FDA Approved Essential Tremor indication under PMA P150038). Also, an improvement of similar magnitude (52.9%) 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.

Additional factors to be considered in determining probable risks and benefits for the Exablate Neuro device included: the majority (95%) of adverse events related to procedure/device/thalamotomy were Mild to Moderate in nature. Two patients experienced Moderate and Severe hemiparesis, respectively, and only the Moderate event that remained unresolved.

In comparison with alternative electrical stimulation therapies, the safety profile for Exablate is without infections, intracranial hemorrhages, seizures, dead batteries, or skin erosion (approximately 12% serious adverse events for Deep Brain Stimulation (DBS) for Vim), 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., outpatient procedure with overnight hospital stay as needed) as 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).

i. 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 Tremor (QUEST) assessment at the 3 month time point. An improvement of 39.6% in the mean score compared to baseline was demonstrated. BY comparison, the Essential Tremors study showed a similar improvement of 43.2%.

- This ExAblate Neuro 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 Tremor Dominant Parkinson's Disease patients, the probable benefits outweigh the probable risks.

D. Overall Conclusion

The data in this application shows that the safety and effectiveness of this Exablate Neuro treatment for tremor in TDPD is similar to that of the essential tremor population approved.

For this population of patients suffering from TDPD, the Exablate Neuro treatment is a reasonable alternative to existing treatments. The result from the TDPD study demonstrates that the Exablate Neuro treatment is efficacious and the safety profile is reasonable and does not cause any increased for this population who are at high risk due to the treatment location.

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

E. Pediatric Extrapolation

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

XIV. CDRH DECISION

CDRH issued an approval order on December 16, 2018.

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

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